54, developed with a mixture of 1-propanol and 1% ammonium hydroxide in proportions 7:3, it moved with an R_f 0.66. With the same mixture, the R_f of D-glucosamine was 0.50, D-galactosamine 0.46, synthetic and natural D-gulosamine 0.55 and 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose 0.57.[17] The natural and the synthetic XIV migrated at the same speed, either developed with the same mixture of solvents, or with the mixture *sec*-butyl alcohol–acetic acid–water in proportions 4:1:1.

Methyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gulopyranoside (XVII). (a) **From Synthetic D-Gulosamine Hydrochloride (XV).**[18]—A solution of 215 mg. of crude synthetic sirupy D-gulosamine hydrochloride[5] (XV) was dissolved in 19 ml. of methanol. After addition of 0.5 g. of silver acetate and 1 ml. of acetic anhydride, the mixture was left overnight at room temperature. After heating to boiling, the silver salts were filtered off and the filtrate evaporated *in vacuo*. The residual sirup was dissolved in 20 ml. of a 2% solution of hydrogen chloride in absolute methanol and refluxed for 2 hours. After cooling, the solution was neutralized with lead carbonate, the filtrate then treated with hydrogen sulfide, filtered through a double layer of Darco G-60 and Celite, and evaporated *in vacuo*. The residual sirup was acetylated overnight with 2 ml. of absolute pyridine and 2 ml. of acetic anhydride. Both reagents were removed by codistillation with dry toluene, and the residue was dissolved in chloroform and chromatographed on silicic acid. Elution with mixtures of ether and ethyl acetate 1:1, and with pure ethyl acetate, gave 163 mg. of crystalline fractions. Recrystallization from a mixture of acetone and ether afforded 116 mg. (32%) of needles, with a double m.p. at 118–119° and 124–125°, $[\alpha]^{23}D$ −54 ±2° (in chloroform, *c* 0.66). *Anal.* Calcd. for $C_{15}H_{23}O_9N$: C, 49.86; H, 6.42. Found: C, 49.69; H, 6.58.

(b) **From Natural D-Gulosamine Hydrochloride (XV).**[18]—This experiment was carried out on 14 mg. of natural D-gulosamine hydrochloride[3] in an identical way as described above with the exception that the first step consisted in a total acetylation with 0.3 ml. of anhydrous pyridine and 0.2 ml. of acetic anhydride, instead of the *N*-acetylation. In the final chromatography, 13 mg. of crystalline fractions was isolated, giving, by recrystallization from a mixture of methanol and ether, 8 mg. (30%) of needles with a double m.p. at 118° and 124–125°, $[\alpha]^{23}D$ −53 ± 2° (in chloroform, *c* 0.56). The product showed no depression of the m.p. in admixture with the compound described under (a).

(c) **From XII.**—To a solution of 50 mg. of XII in 1.2 ml. of acetic anhydride and 0.8 ml. of glacial acetic acid was added 0.02 ml. of concentrated sulfuric acid.[19] After 15 minutes, the solution had $[\alpha]^{25}D$ +77°, after 3 hours +50°, after 24 hours +35°, after 48 hours +32°. The solution was then diluted with 50 ml. of chloroform, washed two times with saturated sodium bicarbonate, three times with water and dried over sodium sulfate. The residual sirup, weighing 92 mg., had $[\alpha]^{28}D$ +54 ± 2° (in chloroform, *c* 1.03). It was dissolved in 5 ml. of a 2% solution of hydrogen chloride in absolute methanol, refluxed, then acetylated as described above. From the chromatography, 78 mg. of crystalline fractions were isolated, giving after recrystallization, 38 mg. (43%) of needles, with double m.p. 117–118° and 124–126°; $[\alpha]^{27}D$ −51 ±2° (in chloroform, *c* 1.02); and showing no depression of the m.p. in admixture with the compound described under (a). When the same reaction was carried out with a higher concentration of XII (10%) for 24 hours, only the starting compound could be recovered as crystalline material.

Action of Hydrochloric Acid on Synthetic D-Gulosamine Hydrochloride (XV).—A solution of 0.5 mg. of XV in 0.1 ml. of 6 *N* HCl was heated in a sealed tube at 100° for 20 hours. After removal of the solvent, the product was chromatographed on Whatman No. 1 and No. 54 paper with a mixture 1-propanol and 1% ammonium hydroxide, in proportions 7:3. After revelation with ninhydrin and silver nitrate, a spot with R_f 0.67, corresponding to XIV, appeared in an amount estimated at one-fourth to one-half the amount of the original material. When XV was heated with 2 *N* hydrochloric acid for 7 hours,[5] no such spot appeared.

Acknowledgments.—The author is very grateful to Dr. J. R. Dyer for providing samples of natural D-gulosamine hydrochloride and natural 2-amino-1,6-anhydro-2-deoxy-β-D-gulopyranose.

(17) In the previous communication,[4] the $R_{glucosamine}$ of this compound has been erroneously reported at 1.45.

(18) This experiment was performed by Dr. Z. Tarasiejska.

(19) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 662 (1945).

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Synthesis of A-Norsteroids

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Ozonolysis of the 2-hydroxymethylene derivatives of testosterone and progesterone gave unsaturated 2,3-seco acids which were converted by pyrolysis to A-nortestosterone and A-norprogesterone. Catalytic reduction of the 3,4-double bond of A-nortestosterone gave only the A/B *cis* fused system whereas reduction with lithium in liquid ammonia yielded approximately equal amounts of A/B *cis* and A/B *trans* fused products. The structure of a by-product from the ozonolysis of hydroxymethylenetestosterone was elucidated and a number of A-nor-derivatives are described.

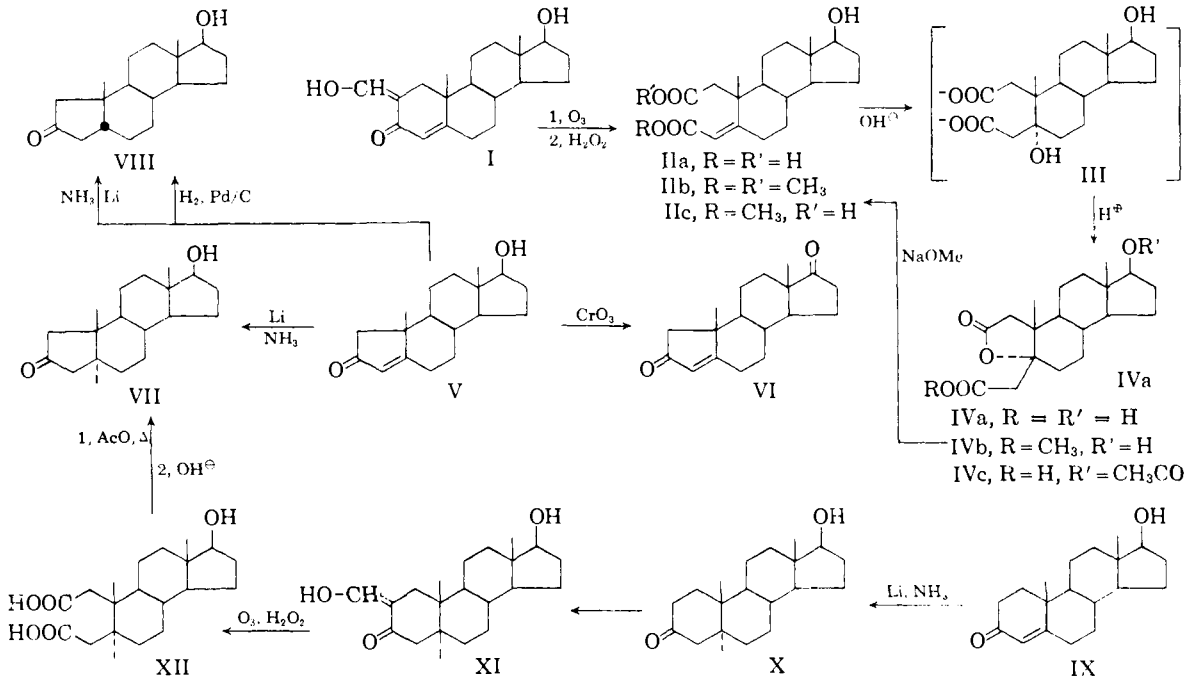
Although a number of A-norsteroids have been described in the literature,[1a] none having a 2-keto-Δ^3 system has been reported.[1b] The synthesis of the A-nor analogs of testosterone and progesterone appeared attractive in order to study the effect of this change in structure on physiological activity.

The unsaturated diacid IIa was reported[2] previously to be one of the products obtained from the ozonization of 2-hydroxymethylenetestosterone (I). This diacid was considered a convenient starting material since on distillation the compound should cyclize with loss of carbon dioxide to form A-nortestosterone, a reaction analogous to that used to prepare saturated A-norsteroids.[1a]

When 2-hydroxymethylenetestosterone (I) was treated with one equivalent of ozone followed by hydrogen peroxide and the acidic products esterified, there was isolated, in addition to the diester IIb, a monoester having the formula $C_{20}H_{30}O_5$, corresponding to a loss of one carbon atom from the parent hydroxymethylene compound. The substance showed no specific ultraviolet absorption and did not form a carbonyl derivative with either semicarbazide or 2,4-dinitrophenylhydrazine. The corresponding free acid ($C_{19}H_{28}O_5$) which could

(1) (a) For a summary see Elsevier's "Encyclopedia of Organic Chemistry," Supplement I, Vol. 14; (b) T. L. Jacobs and N. Takahashi (THIS JOURNAL **80**, 4865 (1958)) has recently reported the synthesis of A-norcholestenone.

(2) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, *ibid.*, **76**, 552 (1954).



be isolated by fractional crystallization of the crude acidic fraction titrated as a monobasic acid and formed a monoacetate on acetylation with acetic anhydride in pyridine. The infrared spectrum of the acid showed broad carbonyl absorption at 5.65–5.80 μ. Formation of the monosodium salt shifted the carbonyl absorption associated with the carboxyl group to 6.3 μ leaving a sharp band at 5.67 μ which indicated the presence of a 5-membered lactone ring. On the basis of the above evidence structure IVa was derived for this substance. Presumably this compound was formed during isolation of the acidic fraction by a Michael-type addition of water to the α,β-unsaturated system of the diacid (IIa) to give the intermediate III which lactonized on acidification of the basic solution. The structure IVa was subsequently confirmed by the observation that treatment of the ester IVb with methanolic sodium methoxide resulted in β-elimination of the carboxylate anion to give IIc. Esterification of the acid IIc then gave a diester identical with the diester IIb.

The crude acidic fraction obtained from the ozonolysis reaction contained approximately 40% of the desired diacid IIa as estimated from the extinction value at 222 mμ in the ultraviolet spectrum. Although the pure diacid could be obtained by fractional crystallization of the mixture, it was found more expedient to use the total acidic fraction for the subsequent acetylation and cyclization steps to give crude A-nortestosterone 17-acetate. Pure A-nortestosterone (V) was then easily obtained by basic hydrolysis of the acetates since the contaminants were converted back to acidic substances. A-Nortestosterone showed the characteristic ultraviolet absorption for a cyclopentenone, λ_{max} 234 mμ (log ϵ 4.18). Oxidation of A-nortestosterone (V) with chromic acid in acetone yielded A-norandrost-3-ene-2,17-dione (VI) in good yield. Catalytic reduction of A-nortestosterone with palladium-on-carbon and hydrogen gave a single dihydro derivative in good yield, presumably either A-norandrostane-2-one-17β-ol (VII) or A-noretiocholane-2-one-17β-ol (VIII). Although the melting point (196.5–197°) of the product obtained was close to that reported by Marker[3] for A-norandrostane-2-one-17β-ol it appeared desirable to prepare an authentic sample of this A/B *trans* compound. The following method was found to be most convenient.

Androstane-3-one-17β-ol[4](X), obtained by reduction of testosterone (IX) with lithium in liquid ammonia, was condensed with ethyl formate in benzene using sodium hydride to give 2-hydroxymethyleneandrostane-3-one-17β-ol (XI). The latter compound was ozonized and the resulting saturated diacid[3] XII after acetylation was cyclized by distillation to the A-nor-17β-acetate. Basic hydrolysis then gave the desired A-norandrostane-2-one-17β-ol (VII), m.p. 195-196.5°. This compound, however, was not identical with the palladium–hydrogen reduction product of A-nortestosterone described above, thereby indicating that the catalytic reduction product of A-nortestosterone must have the A/B *cis* configuration and correspond to A-noretiocholane-2-one-17β-ol (VIII). This was confirmed by the isolation of both VII and VIII when A-nortestosterone was reduced with lithium in liquid ammonia. It is interesting to note that the metal–ammonia reduction of this particular indenone system gives approximately equal amounts of A/B *cis* and A/B *trans* fused products indicating that there is very little difference in thermodynamic stability between the two forms, whereas in the re-

(3) R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, THIS JOURNAL, **59**, 1363 (1937).

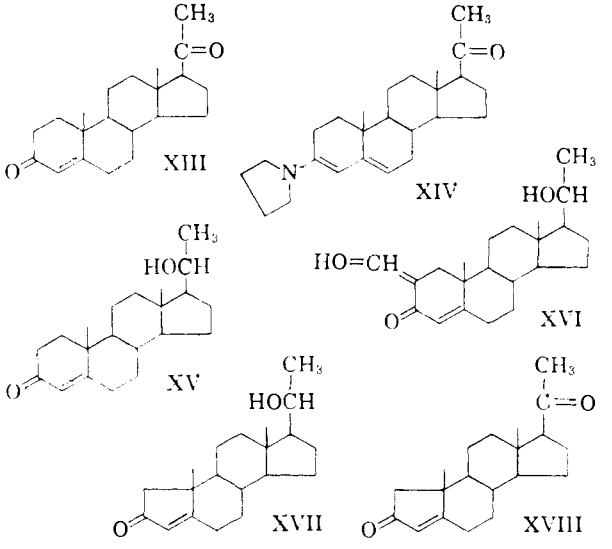
(4) Butenandt, Tscherning and Hanisch (*Ber.*, **68**, 2097 (1935)) prepared this compound by catalytic reduction of testosterone. In our hands catalytic reduction always gave substantial amounts of the A/B *cis* isomer. Only the A/B *trans* compound was found, however, by reduction of testosterone with lithium in ammonia.

duction of testosterone with lithium in ammonia only the A/B *trans* fused product was isolated.

Further, it was observed that catalytic reduction of the unsaturated diacid IIa with palladium and hydrogen gave the *trans* saturated diacid XII.

An attempt was made to cyclize the diester IIb by way of a Dieckmann-type condensation using sodium hydride in benzene, but the starting material was recovered unchanged.

A-Norprogesterone was prepared from progesterone (XIII) following closely the (same) pattern used to prepare A-nortestosterone. In order to protect the 21-position during condensation with ethyl formate, progesterone was first reduced to the 20β-ol[5] XV with lithium aluminum hydride by way of the pyrrolidine derivative[6] XIV. Pregn-4-ene-3-one-20β-ol (XV) was condensed with ethyl formate and the product, 2-hydroxymethylene-pregn-4-ene-3-one-20β-ol, ozonized with one molar equivalent of ozone. When base was used in isolating the acidic products from the ozonolysis reaction, the yield of unsaturated diacid (determined by ultraviolet absorption) was 15%. When the use of base was avoided, however, the yield rose to 53% presumably because lactonization of the type found with the corresponding testosterone derivative (IIa) was prevented. The crude diacid obtained was cyclized to A-norpregn-3-ene-2-one-20β-ol (XVII) which was then ozidized with chromic acid in acetone to give A-norprogesterone (XVIII).



The physiological properties of certain of these A-nor derivatives will be discussed elsewhere.

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Experimental

Ozonization of Hydroxymethylenetestosterone (I). (A) Preparation of Diester IIb and Lactone IVb.—Hydroxymethylenetestosterone[2] (3.00 g.) was dissolved in 30 ml. of ethyl acetate and 30 ml. of acetic acid and treated with one molar equivalent of ozone at −10 to −15°. The resulting solution was diluted with 30 ml. of water and 7.5 ml. of 30% hydrogen peroxide and allowed to stand 24 hours. The colorless solution was then diluted with 400 ml. of ether and the organic layer washed eight times with 75-ml. portions of water to remove the acetic acid. The ether solution was extracted with three 30-ml. portions of 1 *N* sodium hydroxide, the basic extracts acidified with 20 ml. of 6 *N* hydrochloric acid and the precipitate again extracted with ether. The combined ether extracts were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 2.1 g. of amorphous acidic product. This material showed a maximum in the ultraviolet spectrum at 222 mμ (4,500) (the pure diacid[2] absorbs at 222 mμ (11,500) indicating that about 40% of the acidic fraction consisted of the diacid IIa. The acidic fraction (1.7 g.) was dissolved in 20 ml. of ether and treated with an excess of ethereal diazomethane. The ether solution was then concentrated to dryness dissolved in benzene, and chromatographed on 45 g. of Merck acid-washed alumina. The diester IIb was eluted with 2–10% chloroform–benzene and crystallized from ether–hexane 274 mg., m.p. 123–124°, $[\alpha]_D$ +89° (alcohol); λ_{max}^{alc} 222 mμ (14,200); λ_{max}^{Nujol} 5.80, 5.85, 6.15, 2.88 μ.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; CH_3O, 17.00. Found: C, 69.46; H, 8.98; CH_3O, 17.02.

The lactone IVb was eluted with 1:1 chloroform–benzene and crystallized from ether in colorless rosettes, 212 mg., m.p. 183–183.5°, $[\alpha]_D$ +82° (chlf.); λ_{max}^{Nujol} 2.85, 5.66–5.80 μ.

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; CH_3O, 8.85. Found: C, 68.46; H, 8.51; CH_3O, 8.58.

(B) **Preparation of the Diacid IIa and the Lactone IVa.**—In another run in which 3.00 g. of hydroxymethylenetestosterone (I) was ozonized with one equivalent of ozone as described above, 2.41 g. of total acidic material was obtained. The mixture was dissolved in a small amount of hot methanol and on standing the solution deposited 0.740 g. of diacid IIa, m.p. 256–257°. On recrystallization from methanol 515 mg. of colorless needles was obtained, m.p. 260–262°, reported[2] m.p. 262–263°. This diacid IIa on treatment with ethereal diazomethane–methanol gave the diester IIb.

The mother liquor from which IIa was obtained was diluted with ether and on standing, 0.509 g. of the acid-lactone IVa crystallized out, m.p. 259–261°. Recrystallization from methanol–ether gave an analytical sample, m.p. 263–265°, $[\alpha]_D$ +36° (ethanol); λ_{max}^{KBr} 3.00, 5.76, sh 5.68 μ.

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.72; H, 8.30.

The lactone IVa (10 mg.) was titrated with sodium hydroxide in ethanol and the resulting solution taken to dryness. An infrared spectrum in Nujol on the resulting sodium salt showed carbonyl absorption associated with the carboxylate anion at 6.30 μ in addition to a strong band at 5.67 μ (5-membered lactone).

17-Acetate IVc of the Lactone-acid IVa.—The lactone-acid IVa (23 mg.) was dissolved in 2 ml. of dry pyridine and 1 ml. of acetic anhydride and the solution allowed to stand at room temperature overnight. The solvents were removed under vacuum and the residue taken up in chloroform, washed with water, dried over sodium sulfate and concentrated to dryness. Crystallization of the residue from methanol–water gave 18 mg. of the acetate IVc, m.p. 267–268°, $[\alpha]_D$ +49° (ethanol); λ_{max}^{Nujol} 5.59, 5.78, 5.88 μ.

Anal. Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.95; H, 8.17.

Conversion of the Lactone IVb to the Diester IIb.—The ester-lactone IVb (40 mg.) was heated under reflux for two hours in methanolic sodium methoxide solution (67 mg. of sodium 30 ml. of methanol). The resulting solution was acidified with a few drops of acetic acid and concentrated to dryness. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate and concentrated. Two recrystallizations of the residue from ether–hexane gave 25 mg. of the acid-ester IIc, m.p. 194–195°, $[\alpha]_D$ +91° (ethanol), λ_{max}^{EtOH} 223 μ (12,700).

Anal. Calcd. for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.43; H, 8.48.

(5) H. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1923 (1949).

(6) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl. THIS JOURNAL, **78**, 430 (1956).

The acid-ester IIc (14 mg.) was dissolved in 5 ml. of methanol and esterified by the addition of ethereal diazomethane. The solution was evaporated to dryness and the residue crystallized from ether–hexane in colorless needles, m.p. 121–122°. The infrared spectra of this substance and the diester IIb described previously were identical.

A-Nortestosterone (V).—The diacid IIa (600 mg.) was dissolved in 5 ml. of acetic anhydride and the solution heated under reflux for one hour. The acetic anhydride was then allowed to distil off as the temperature was raised to 250°. At this temperature carbon dioxide was eliminated. When the evolution of gas ceased the residue was placed under vacuum (0.01 mm.) at 250° and A-nortestosterone 17-acetate distilled as a yellow viscous oil, 433 mg. This oil was dissolved in 12 ml. of ethanol and 1.5 ml. of 40% sodium hydroxide and the solution heated under reflux for 45 minutes. Water (10 ml.) was added and the alcohol removed under vacuum. The resulting basic solution was extracted with ether, and the combined extracts washed with water, dried over sodium sulfate, and concentrated to dryness leaving 241 mg. of colorless solid, m.p. 169–170°. Two recrystallizations from ethyl acetate–hexane gave an analytical sample of A-nortestosterone (V), m.p. 175–176°, $[\alpha]_D$ −22° (ethanol); λ_{max}^{EtOH} 234 mμ (15,200); λ_{max}^{Nujol} 2.90, 5.94, 6.15 μ.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.93; H, 9.43.

When the total crude acidic fraction, obtained by the ozonization of hydroxymethylenetestosterone, was used instead of the pure diacid IIa in the cyclization step, approximately the same yield of A-nortestosterone was obtained (based on the amount of IIa present).

A-Norandrost-3-ene-2,17-dione (VI).—A-Nortestosterone (62 mg.) was dissolved in 6.0 ml. of acetone and treated dropwise with stirring with a solution prepared by dissolving 20 mg. of chromic oxide and an equivalent amount of sulfuric acid in 2.0 ml. of acetone. When the reaction was complete (5 minutes), the chromic sulfate was centrifuged off and washed with acetone. The combined acetone washings were evaporated to dryness, the residue taken up in chloroform, washed with water, dried over sodium sulfate and the chloroform solution concentrated. The residue crystallized from ethyl acetate–hexane yielding 45 mg. of A-norandrost-3-ene-2,17-dione, m.p. 165–165.5°. A second recrystallization from ethyl acetate–hexane gave an analytical sample, m.p. 166–166.5°, $[\alpha]_D$ +55.9° (ethanol); λ_{max}^{EtOH} 232 mμ (15,600); λ_{max}^{Nujol} 5.78, 5.94, 6.18 μ.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.98.

A-Noretiocholane-2-one-17β-ol (VIII) from A-Nortestosterone (V).—A-Nortestosterone (66 mg.) was hydrogenated at room temperature and pressure over 165 mg. of 5% palladium-on-charcoal catalyst for 24 hours. The reaction ceased after the absorption of one molar equivalent of hydrogen. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was recrystallized from ethyl acetate–hexane to give 48 mg. of A-noretiocholane-2-one-17β-ol, m.p. 196.5–197°, $[\alpha]_D$ −72° (ethanol); λ_{max}^{Nujol} 2.92, 5.80 μ.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.60; H, 10.19.

Androstane-3-one-17β-ol (X).—A solution of 5.0 g. of testosterone in 60 ml. of dioxane and 60 ml. of ether was added dropwise with stirring to a solution of 600 mg. of lithium in 500 ml. of liquid ammonia over a period of 10 minutes. An additional 70 mg. of lithium was then added to maintain the blue color for another 30 minutes. The sodium amide formed was neutralized by the addition of 12 g. of ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in chloroform, washed with water, dried over sodium sulfate and concentrated. The solid remaining was recrystallized from ethyl acetate–hexane to give 4.6 g. of androstane-3-one-17β-ol, m.p. 184–185°, reported[4] m.p. 178°.

2-Hydroxymethyleneandrostane-3-one-17β-ol (XI).—Sodium hydride (450 mg.) was added to a solution of androstane-3-one-17β-ol (1.50 g.) in 60 ml. of benzene and 3.0 ml. of ethyl formate and the reaction mixture allowed to stand under nitrogen for 5 days. Methanol (2 ml.) was added to decompose the excess hydride and the solution was then diluted with 100 ml. of benzene and 125 ml. of water. The layers were separated and the basic solution extracted with benzene to remove neutral material. The aqueous layer was then acidified with dilute hydrochloric acid and the liberated enol extracted with ether. The combined ether extracts were washed with water, saturated sodium chloride solution, dried over sodium sulfate, and concentrated to dryness leaving 1.20 g. of crystalline solid, m.p. 212–213.5°. Two recrystallizations from methanol gave an analytical sample of 2-hydroxymethyleneandrostane-3-one-17β-ol (XI), m.p. 217–218°, $[\alpha]_D$ +49° (ethanol), λ_{max}^{EtOH} 275 mμ (11,200); λ_{max}^{Nujol} 2.93, 6.00, 6.40 μ.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.92; H, 9.32.

Preparation of the Saturated Diacid XII. (A) By Ozonization of 2-Hydroxymethyleneandrostane-3-one-17β-ol.—2-Hydroxymethyleneandrostane-3-one-17β-ol (XI) (1.20 g.) was dissolved in 12 ml. of ethyl acetate and 12 ml. of acetic acid and ozonized with one molar equivalent of ozone at −10 to −15°. The resulting solution was diluted with 12 ml. of water and 3 ml. of 30% hydrogen peroxide and on standing overnight the solution deposited 455 mg. of colorless crystalline diacid XII, m.p. 270–273°. The solution was concentrated to remove the ethyl acetate and a second crop of 236 mg. of diacid was obtained. Two recrystallizations from methanol gave an analytical sample of XII, m.p. 280.5–281°, $[\alpha]_D$ +11° (ethanol), reported[3] m.p. 273°.

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94; neut. equiv., 169. Found: C, 67.70; H, 8.54; neut. equiv. (sodium hydroxide), 173.

(B) By Catalytic Reduction of the Unsaturated Diacid IIa.—The unsaturated diacid IIa (100 mg.) was dissolved in 10 ml. of methanol and reduced over 25 mg. of 5% palladium-on-charcoal catalyst. One molar equivalent of hydrogen was absorbed during 16 hours. The catalyst was filtered off and the filtrate concentrated, whereupon 45 mg. of the saturated diacid precipitated, m.p. 275–276°. Recrystallization from methanol gave a pure sample of XII, m.p. 280–281°, $[\alpha]_D$ +7.5° (ethanol). A mixed melting point of this substance with the diacid obtained by ozonolysis of 2-hydroxymethyleneandrostane-3-one-17β-ol showed no depression and their infrared spectra in Nujol were identical.

A-Norandrostane-2-one-17β-ol (VII) from the Diacid XII.—The diacid XII (485 mg.) was heated under reflux with 5 ml. of acetic anhydride for one hour. The acetic anhydride was then distilled off and the temperature of the residue raised to 250° to effect decarboxylation. When the evolution of carbon dioxide ceased the system was placed under 25 μ pressure and the crude A-nor 17-acetate distilled at 220–230°. The distillate weighed 346 mg. and crystallized on cooling. This solid was dissolved in 10 ml. of 5% alcoholic sodium hydroxide and the mixture heated under reflux in a nitrogen atmosphere for one hour. The alcohol was then removed under vacuum, the residue diluted with water and extracted with ether. The combined ether extracts were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated leaving 252 mg. of crystalline product. Recrystallization from ethyl acetate–hexane gave pure A-norandrostane-2-one-17β-ol, m.p. 195–196.5°, $[\alpha]_D$ +174° (ethanol), λ_{max}^{Nujol} 2.92, 5.79; reported[3] m.p. 197°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.91; H, 10.00.

A-Noretiocholan-2-one-17β-ol (VIII) and A-Norandrostane-2-one-17β-ol (VII) from A-Nortestosterone.—A solution of A-nortestosterone (V) (200 mg.) in 10 ml. of tetrahydrofuran and 10 ml. of ether was added dropwise with stirring to a solution of 175 mg. of lithium in 50 ml. of liquid ammonia. After 30 minutes the blue color of the solution was discharged by the addition of 3.0 g. of ammonium chloride and the ammonia was allowed to evaporate. The residue was distributed between chloroform and water and the chloroform extract washed with water, saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness leaving 189 mg. of product. The ultraviolet spectrum of this material showed that only about 3% of A-nortestosterone remained unreduced. The specific rotation of the mixture was found to be +45° (ethanol). Assuming that only two products were formed in this reduction, the mixture contained approximately 53% of A-noretiocholan-2-one-17β-ol (VIII, $[\alpha]_D$ −72°) and 47% A-norandrostane-2-one-17β-ol (VII, $[\alpha]_D$ +172°). A comparison of appropriate bands in the infrared spectra of pure VII and VIII with those of the mixture also showed

that approximately equal amounts of the two isomers were present.

This product (165 mg.) was then chromatographed on 10 g. of Merck acid-washed alumina. Elution of the column with benzene first removed A-norandrostane-2-one-17β-ol which gave the constants, m.p. 192–193°, $[\alpha]_D$ +161° (ethanol) after two recrystallizations from ethyl acetate–hexane. A mixed melting point of this substance with an authentic sample of VII showed no depression and their infrared spectra in chloroform were identical. Further elution of the column with benzene gave impure A-noretiocholan-2-one-17β-ol (VIII), difficult to further purify by fractional crystallization. Five recrystallizations from ethyl acetate–hexane gave a sample, m.p. 188–190°, $[\alpha]_D$ −55° (ethanol). A mixed melting point with an authentic sample of VIII was not depressed and the infrared spectra of the two substances were nearly identical.

3-(N-Pyrrolidinyl)-3,5-pregnadiene-20-one (XIV) was prepared according to the method of Johnson, *et al.*[6] Progesterone (XIII) (10.0 g.) was dissolved in 40 ml. of hot methanol and treated with 2.70 ml. of pyrrolidine. The product crystallized almost immediately and after cooling the mixture was filtered yielding 11.7 g. of the derivative XIV. Recrystallization from ethyl acetate and then ether gave an analytical sample, m.p. 188–190°.

Anal. Calcd. for $C_{25}H_{37}ON$: C, 81.69; H, 10.15; N, 3.81. Found: C, 81.52; H, 9.94; N, 4.04.

Pregn-4-ene-3-one-20β-ol (XV).—The method used for the reduction of the pyrrolidine derivative was essentially that of Herr and Heyl.[7] The pyrrolidine derivative XIV (43.7 g.) was dissolved in 400 ml. of tetrahydrofuran and treated with 25 g. of lithium aluminum hydride in small portions with stirring. The mixture was stirred one hour after addition of hydride and then the complex was decomposed by the cautious addition of 125 ml. of water. The mixture was diluted with 1200 ml. of methanol and a buffer consisting of 260 ml. of water, 212 g. of sodium acetate and 200 ml.. of glacial acetic acid. The solution was heated under reflux for 2.5 hours and then concentrated under vacuum to remove the methanol. The resulting aqueous suspension was made strongly acidic with 3 *N* hydrochloric acid and thoroughly extracted with chloroform. The combined chloroform extracts were washed with 5% sodium bicarbonate solution, water, dried over sodium sulfate and concentrated. The residue crystallized from ethyl acetate–hexane to give 31.1 g. of impure pregn-4-ene-3-one-20β-ol (XV), m.p. 161–164°, probably contaminated with the 20α-ol isomer. This material was chromatographed on Merck acid-washed alumina. The 20β-ol was eluted with 1% chloroform–benzene. Recrystallization of the combined eluates gave pure pregn-4-ene-3-one-20β-ol, m.p. 173–174°, $[\alpha]_D$ +80° (ethanol); reported[5] m.p. 171–172°, $[\alpha]_D$ +84° (chloroform).

2-Hydroxymethylenepregn-4-ene-3-one-20β-ol (XVI).—Sodium hydride (13.4 g.) was added to a solution of pregn-4-ene-3-one-20β-ol (XV) (27.7 g.) in 550 ml. of benzene and 28 ml. of ethyl formate and the reaction mixture was allowed to stand under nitrogen for two days. Methanol (30 ml.) was added to decompose the excess sodium hydride and the solution was then diluted with 50 ml. of water. The layers were separated and the basic aqueous solution extracted with ether to remove neutral material. The aqueous layer was then acidified with 280 ml. of 3 *N* hydrochloric acid and the liberated enol extracted with ether. The ether extracts were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated. The residue of 2-hydroxymethylenepregn-4-ene-3-one-20β-ol (XVI) was obtained as a light yellow, amorphous solid weighing 29.9 g. Recrystallization from methanol–water gave an analytical sample, m.p. 86–88°; $\lambda_{max}^{alc.}$ 251 (10,000), 307 mμ (4,500).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.31; H, 9.59.

Ozonization of 2-Hydroxymethylenepregn-4-ene-3-one-20β-ol (XVI).—2-Hydroxymethylenepregn-4-ene-3-one-20β-ol (24.8 g.) was dissolved in 240 ml. of acetic acid and 240 ml. of ethyl acetate and ozonized at −10° with one molar equivalent of ozone. The resulting solution was diluted with 240 ml. of water and 60 ml. of 30% hydrogen peroxide and allowed to stand overnight. The solution was diluted with 1500 ml. of water and extracted three times with 700-ml. portions of ethyl acetate. The combined extracts were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to dryness under vacuum leaving 23.4 g. of a colorless amorphous residue of crude diacid. This material showed a maximum in the ultraviolet spectrum at 224 mμ (ε 6,400) indicating a 53% yield of unsaturated acid. It was used without further purification in the succeeding cyclization step.

A-Norpregn-3-ene-2-one-20β-ol (XVII).—The crude diacid (26.5 g.) prepared as described above was dissolved in 100 ml. of acetic anhydride and the solution heated under reflux for one hour. The acetic anhydride was then allowed to distil off as the temperature was raised to 250°. When the evolution of carbon dioxide was complete the resulting acetate of A-norpregn-3-ene-2-one-20β-ol was distilled at 0.01 mm. at 250°. The crystalline acetate (17.1 g.) so obtained was hydrolyzed with 500 ml. of 4% aqueous alcoholic sodium hydroxide solution held at the boiling point for 45 minutes. Water (650 ml.) was added and the alcohol removed under vacuum. The resulting solution was extracted with ether to give 8.6 g. of XVII, m.p. 209–211°. Recrystallization from ethyl acetate–hexane raised the melting point to 213–214°, $[\alpha]_D$ −22° (ethanol); $\lambda_{max}^{alc.}$ 234 mμ (15,000); λ_{max}^{Nujol} 2.85, 5.91, 6.18 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.57; H, 9.81.

A-Norprogesterone (XVIII).—A-Norpregn-3-ene-2-one-20β-ol (XVII) (500 mg.) was dissolved in 50 ml. of acetone and treated dropwise with stirring with an equivalent amount of chromic acid–sulfuric acid in acetone solution. The precipitate of chromic salts was centrifuged off and the supernatant solution concentrated to dryness. The residue was dissolved in chloroform, washed with 5% sodium bicarbonate solution, water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to dryness. The residue of A-norprogesterone (XVIII) crystallized from ethyl acetate–hexane in colorless prisms, m.p. 150–151°, $[\alpha]_D$+76° (ethanol); $\lambda_{max}^{alc.}$ 233 mμ (15,800); λ_{max}^{Nujol} 5.85, 5.92, 6.15 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.75; H, 9.02.

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(7) M. E. Herr and F. W. Heyl, THIS JOURNAL, **75**, 5927 (1953).