mately 30% by weight). Analyses were conducted at 113° at a flow rate of 86 cc/min. The retention volume of *exo*-5,6-trimethylene-2-norbornene was 11,000 ml and that of *endo*-5,6-trimethylene-2-norbornene was 11,524 ml.

The isomeric olefins were separated from *endo*-dicyclopentadiene on a 2 m by 0.25 in. copper column packed with Apiezon L on Chromosorb W 60–80 mesh (approximately 30% by weight). Analyses were conducted at 125° at a flow rate of 78 cc/min. The retention volume of dicyclopentadiene was 3634 ml, and that of the mixture of monoolefins was 4056 ml.

Registry No.—I, 2826-19-9; II, 10466-50-9; IIIb, 14362-73-3; IVb, 14362-74-4; acetic acid, 64-19-7.

The Partial Synthesis of 18,19-Dinor Steroids

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The synthesis of 18-norestrone and the 18,19-dinor analogs of testosterone, progesterone, and desoxycorticosterone is described starting from 3-methoxy-17-acetylgona-1,3,5(10),16-tetraene (**4a**). Reduction of the carbonyl group of 18-nor-13α-estrone methyl ether (**3a**) with lithium aluminum hydride gave preponderantly the axial (17β) alcohol **3b**, with sodium–propanol the equatorial (17α) epimer **3c**, and with sodium borohydride–sodium hydroxide the 17β alcohol of the *trans*-C/D series (**2b**).

The preparation of 18-nor steroids, both with and without the 19-methyl group, has been reported by several groups of investigators, using either partial or total syntheses.[1] The present communication describes the partial synthesis of the 18,19-dinor steroids from the 17-acetylgonatetraene **4a**, an intermediate available from estradiol methyl ether by an eight-step reaction sequence.[2,3] (See Scheme I.)

The first phase of the investigation, the synthesis of several gonane derivatives, was initiated by Beckmann rearrangement[4] of the oxime **4b**. To preclude isomerization at C-13 in the expected *trans* ketone **2a**, the phosphorous oxychloride reaction mixture was poured directly into cold aqueous acid. Instead of ketonic product, the intermediate enamide **1** was isolated. Although the enamide showed the expected NH absorption in the infrared (3.02 μ), overlapping aromatic absorptions in both ultraviolet[5] and nmr spectra precluded further support for this structure as opposed to the alternative imine structure.

Hydrolysis of the purified enamide **1** was accompanied by isomerization at C-13. In contrast, direct acid hydrolysis of the phosphorous oxychloride reaction mixture at room temperature afforded in good yield the *trans* ketone, 18-norestrone methyl ether (**2a**). The configuration of the 13 proton in **2a** was assigned from mechanistic considerations: lithium–ammonia reduction of the 13,17a double bond in its chrysenone antecedent[3b] would afford the *trans* (13-β) isomer; no change in this configuration would occur in the subsequent production of **2a**. In agreement with this expectation, the ORD curve of the *trans* ketone (**2a**)[6] (as well as of its D-homo precursor) shows a strong positive Cotton effect, analogous to the *trans*-hydrindan-1-ones. Esr data are also in accord with this assignment.[7] Since the configuration of the 14-hydrogen (α) remains unchanged in the synthesis, the transfusion of the C/D ring juncture is established.

Base-catalyzed equilibration of the *trans* ketone ([α]D +188°) gave a mixture ([α]D +11°) from which the *cis* ketone **3a** ([α]D −66°) could be isolated. The *cis* ketone, obtained previously from ozonolysis of a mixture containing the exocyclic olefin **3d**,[3a] exhibits a negative Cotton effect in its ORD spectrum as expected for a *cis*-hydrindanone structure.[6b] In addition, the *cis* ketone was readily converted with acid or base to the same mixture of ketones obtained from the *trans* ketone, establishing that the two compounds are an epimeric pair. The ratio of 13β/13α epimers at equilibrium calculated from the specific rotations is approximately 7:3.[8]

Lithium aluminum hydride reduction of the *trans* ketone **2a** provided mainly a single compound, 18-norestradiol methyl ether (**2b**, [α]D +76°). The configuration of the 17-hydroxyl was assigned in analogy to the comparable reduction in the 13-methyl steroids[9] and was supported by rotational data.[10] The axial character of the 17 proton in the nmr, masked by the 3-methoxyl signal in the free alcohol, was seen clearly in the corresponding 17-acetate and supported the configurational assignment.[11] The anal-

(1) W. L. Meyer, D. D. Cameron, and W. S. Johnson, *J. Org. Chem.*, **27**, 1130 (1962), and references cited therein; D. H. R. Barton, A. da S. Campos-Neves and A. I. Scott, *J. Chem. Soc.*, 2698 (1957); L. Velluz, G. Amiard, R. Heymes, and B. Goffinet, *Bull. Soc. Chim. France*, 2166 (1961); R. Anliker, M. Muller, M. Perelman, J. Wohlfahrt, and H. Heuser, *Helv. Chim. Acta*, **42**, 1071 (1958); G. Stork, H. N. Khastgir and A. J. Solo, *J. Am. Chem. Soc.*, **80**, 6458 (1958).

(2) See W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958), for an initial report of this work.

(3) (a) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961); (b) *ibid.*, **28**, 1856 (1963).

(4) Application of this rearrangement to pregnane degradation as well as isolation and characterization of the intermediate enamide was reported by G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956). See also E. Testa and F. Fava, *Gazz. Chim. Ital.*, **87**, 971 (1957).

(5) The acetamidoandrostene was reported in footnote 4 to exhibit λ_{max} 240 mμ (ϵ 6600).

(6) (a) This ORD allows calculation of the insertion value of the 13-methyl group: $\Delta a = -31$. We are indebted to Professor W. Klyne, Westfield College, University of London, for both the ORD curve and the insertion value. (b) For a discussion of the ORD values of the hydrindanones, see C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963), and references cited.

(7) E. R. Talaty and G. A. Russell, *J. Am. Chem. Soc.*, **87**, 4867 (1965).

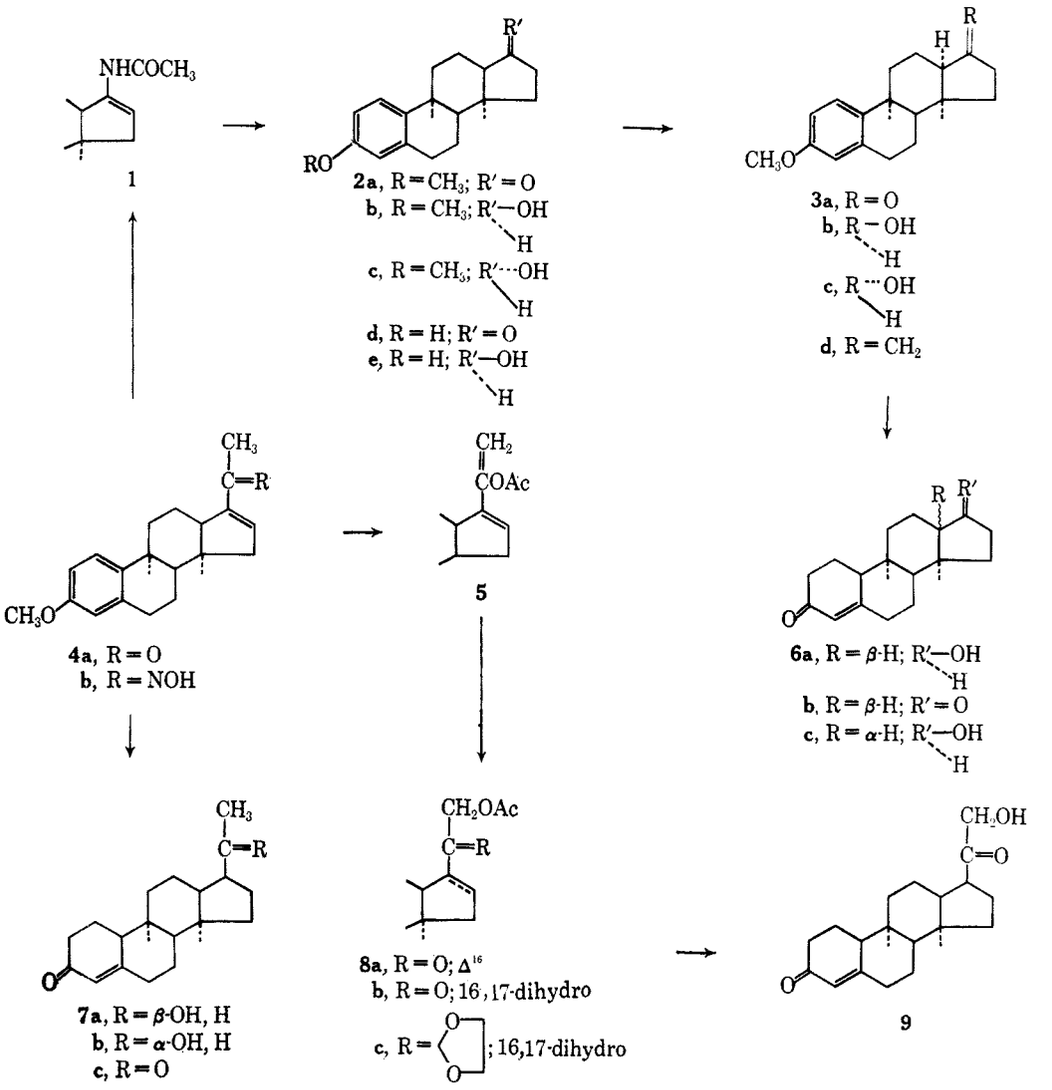
(8) For a discussion of hydrindan-1-one stabilities, see H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963), and references cited therein; N. L. Allinger, R. B. Hermann, and C. Djerassi, *ibid.*, **25**, 922 (1960). The latter report a different equilibrium value (55/45) for this equilibrium mixture, the discrepancy presumably being due to the inherently greater accuracy of the ORD method employed by them.

(9) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 467.

(10) For the values of estrone methyl ether (+169°) and estradiol methyl ether (+78°), see J. Jacques, H. Kagan, and G. Ourisson, "Pouvoir Rotatoire Naturel," Pergamon Press Inc., New York, N. Y., 1965.

(11) E. L. Eliel, M. H. Gianni, and Th. H. Williams, *Tetrahedron Letters*, 741 (1962); Y. Kawazoa, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963).

SCHEME I



lysis of the total reduction product showed *ca.* 5% of a minor component, presumably the 17α epimer of **2b**, since it was clearly different from either of the 13α derivatives (see below). The amount of the 17α epimer was not significantly different from the amount of 17α-estradiol 3-methyl ether produced in a comparable reduction of estrone methyl ether (tlc analysis); this similarity in product ratios demonstrates the minor directive effect of the angular methyl group in this reduction.

Lithium aluminum hydride reduction of the *cis* ketone **3b** afforded two new alcohols in a 2:1 ratio. The preponderant compound **3b**, eluted first from a chromatographic column, showed in its nmr spectrum a narrow signal for the 17 proton (W_h = 6 cps) suggestive of a 17-axial hydroxyl.[11] The minor isomer (**3c**) showed a broad signal (W_h = 10 cps) upfield from the signal of the first epimer, which implies that the hydroxyl is equatorial. This assignment agrees with the result of the sodium–alcohol reduction of the *cis* ketone **3a** (see below) from which alcohol **3c** was the major product. The equatorial isomer is in the α configuration on the basis of conformational analysis of 13α steroids.[12a]

Comparison of the optical rotations of the pair of epimeric 13α-androstan-17-ols with those of the corresponding 13α-norestratrienes shows a qualitative agreement of values.[12] Correlation of rotations with the 13α-estrone 3-methyl ether series[13] is difficult since only a single isomer was isolated; this isomer, according to current theory, should have an α- (equatorial) hydroxyl rather than the β-hydroxyl depicted.[12]

Sodium–propanol reduction of the *cis* ketone afforded a product containing *ca.* 5% of the axial alcohol **3b** (tlc analysis). Although the remainder of the product was homogeneous by tlc, the spectral data indicated it to be a mixture. Precise nmr analysis was foiled by the overlapping signals of the 3-methoxyl and the 17 proton. However, on acetylation of the mixture the signals were cleanly separated; integration of the nmr showed the product to consist of a 3:1 mixture of *cis*-C/D isomer **3c** and *trans*-C/D **2b**, the latter arising by prereduction isomerization of the 13-hydrogen.

The preponderant formation of the 17α-hydroxy derivative by hydride reduction of the 13α-androstan-17-ones presents a clear contrast with the present case.

(12) (a) L. J. Chinn, *J. Org. Chem.*, **30**, 4165 (1965); **27**, 54 (1962). The hydride reduction of 3β-hydroxy-13α-androst-5-en-17-one ([α]D −175°) gives a 3:1 ratio of 17α ([α]D +50°)/17β ([α]D +91°) alcohols. (b) M. Fétizon and J.-C. Gramain, *Bull. Soc. Chim. France*, 1003 (1967), report a similar reduction of 13α-androstan-17-one ([α]D −103°) to give a 3:2 ratio of 17α ([α]D −54°)/17β ([α]D −9°) alcohols.

(13) A. Butenandt, A. Wolff, and P. Karlson, *Chem. Ber.*, **74**, 1308 (1941), prepared this isomer ([α]D +15°) by sodium–alcohol reduction of the ketone ([α]D −28°).

This difference must arise because of the steric effects involved since the relative product stabilities are approximately the same (as judged by the product ratios from the sodium–alcohol reduction) and suggests that the reduction is controlled by steric approach rather than product development.[14] In the 18-nor steroid the attack is relatively nonspecific, favoring approach from the α face of the molecule. In contrast, the 13-methyl group of 13α-androstanone hinders this mode of reduction, and the favored frontal approach of the reagent produces proportionately more of the α hydroxyl.

The much slower rate of hydride reduction of the *cis* ketone compared with that of the *trans* made possible the formation in high yield of the *trans*-C/D alcohol from the *cis*-C/D ketone by use of sodium borohydride–sodium hydroxide.[15] A continuous equilibration of the *cis* to the *trans* ketone followed by rapid reduction of the latter is effected, providing about 85% of the pure *trans*-C/D alcohol **2b** as shown by tlc and nmr analysis of the corresponding acetate mixture. This reductive method has clear utility in syntheses which would produce the *cis* ketone.

Lithium–ammonia reduction of the *trans* alcohol **2b** followed by acid hydrolysis gave dinortestosterone **6a** in good yield. The configuration of the 10-hydrogen is assigned by analogy to the comparable reduction of the 13-methyl series, an assignment in agreement with the ORD data obtained.[16] Oxidation of the 17 alcohol gave 18,19-dinorandrostenedione (**6c**). Lithium–ammonia reduction was also used to produce the 13α-dinortestosterone **6b** from the corresponding 13α-estradiol **3b**.

Preparation of 18-norestradiol and 18-norestrone proceeded through 18-norestradiol methyl ether (**2b**) to preclude isomerization at C-13 during cleavage of the C-3 ether function. Hydrolysis of this group was accomplished with potassium hydroxide in diethylene glycol at 200° and furnished the desired phenol **2e**. Chromic acid oxidation of the 17-hydroxyl group afforded 18-norestrone (**2d**).

The second phase of the synthetic program dealt with the preparation of several dinor pregnanes. Treatment of the acetylgonatetraene **4a** with lithium–ammonia effected reduction of both the unsaturated ketone group in the D ring and the aromatic A ring. Fractional crystallization of the product led to the isolation of a single C-20 epimer which was hydrolyzed to a lower melting unsaturated ketone **7a**. The remainder of the reduction product on acid hydrolysis gave a higher melting epimer, **7b**. The two were distinguishable not only on the basis of their melting points but also from slight differences in the nmr absorption for both the 20 and the 21 protons. The C-21 proton signals were separated to such a small degree (1.1 cps at 100 Mc) that a tentative configurational assignment is suggested only on the basis of the smaller splitting constant for the 20α-ol (higher melting isomer) as compared to its epimer.[17] Each of the 20-hydroxy derivatives was oxidized to *d*-18,19-dinorprogesterone. This material was correlated with the *dl* compound described in the total synthesis of Nelson and Garland[18] by spectral comparison of the *d*- and *dl*-16,17-dihydro derivatives of **4a**. Dinorprogesterone shows a positive ORD curve, but with an amplitude less than that exhibited by progesterone. This effect has been previously noted in the other 18-nor compounds and is ascribed to the freer rotation of the acetyl side chain compared with the 13-methyl analogs.[19]

Attempts to compare the relative stability of the β (equatorial) side chain in dinorprogesterone with that of progesterone were complicated by the difficulty in separating or even detecting a second component in the dinor system under conditions (gas chromatography, tlc) which cleanly separated 17-isoprogesterone from progesterone. Conceivably, the amount of the 17α-acetyl (axial) derivative is very small in the dinor series owing to the lack of 13-methyl and 17-acetyl group interaction here.

Introduction of the 21-oxygen function in the dinor pregnanes was initiated by preparation of the enol acetate **5**. This derivative was halogenated with N-iodosuccinimide and the resulting 21-iodide was displaced with acetate.[20] Reduction of the 16,17 double bond of the resulting unsaturated ketone **8a** proceeded readily to provide the saturated derivative **8b**. The corresponding 20-ketal **8c**, prepared readily with ethylene glycol, was reduced with lithium in ammonia. Acid-catalyzed hydrolysis of the product gave the desired 18,19-dinorcorticosterone (**9**).

Experimental Section[21]

3-Methoxygona-1,3,5(10)-trien-17-one (18-Norestrone Methyl Ether) (2a).—A solution of 1.0 g of the **3-methoxy-17-acetylgona-1,3,5(10),16-tetraene (4a)**[3b] and 0.6 g of hydroxylamine hydrochloride in 10 ml of pyridine was boiled for 45 min, was cooled, and was diluted with water, yielding 1.05 g of the oxime **4b**, mp 186–188°, λ_{max} 3.05 μ.

A cold solution of 10 ml of phosphorous oxychloride in 50 ml of pyridine was added very slowly (*ca.* 2 ml in 5 min) to a solution of 3.02 g of the oxime **4b** in 70 ml of pyridine at 0°. This addition caused a pronounced exothermic effect. Additional increments generated little further heat and the remainder of the reagent was added over 10 min. After a total of 30 min the solution was poured slowly onto a stirred mixture of 225 ml of concentrated hydrochloric acid and 300 g of ice. After 1 hr at room temperature the mixture was filtered and the crystalline material was washed with water and air dried. The product was dissolved in benzene, the insoluble material filtered, and the filtrate washed with water. The resulting solution was dried and concentrated, yielding a residue which was crystallized from acetone–hexane to give 0.90 g of product, mp 155–159°. Recrystallization of this material from methanol yielded pure 18-norestrone methyl ether **2a**, mp 161–163°, as lustrous platelets: λ_{max} 5.73 μ; λ_{max}

(14) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 30, presents a recent discussion of these factors.

(15) This reagent was first employed in a similar reduction of the 18-nor androstanes by Dr. R. Pappo, of these laboratories, U. S. Patent 3,080,360 (1963).

(16) 19-Nortestosterone has a weak negative ORD curve (see C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362, 6377 (1956)) whereas 10α-testosterone shows a positive curve (see R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 2420 (1962)).

(17) The nmr data for the saturated pregnan-20-ols is given by H. Lee, N. S. Bhacca, and M. E. Wolff, *J. Org. Chem.*, **31**, 2692, 192 (1966), and C. H. Robinson and P. Hofer, *Chem. Ind.* (London), 377 (1966).

(18) N. A. Nelson and R. B. Garland, *J. Am. Chem. Soc.*, **79**, 6313 (1957).

(19) K. M. Wellman and C. Djerassi, *ibid.*, **87**, 60 (1965); W. Klyne and J. C. Danilewicz, *J. Chem. Soc.*, 1306 (1965).

(20) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **76**, 1722 (1954).

(21) We wish to thank Dr. R. T. Dillon and staff for the analyses and spectra reported. The infrared spectra were determined in chloroform, ultraviolet spectra in methanol, and rotations in chloroform (1%). Nmr spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., at 60 Mc, using tetramethylsilane as an internal standard ($\Delta\nu$ = 0); W_h denotes peak width at half-height. Log ϵ values are given in parentheses.

278 mμ (3.82), 286 (3.25); ORD (*c* 1.0, CH_3OH), $[\phi]_{307}$ 9900° pk, $[\phi]_{270}$ −7150 tr, $a = +171.^5$

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.87; H, 8.36.

A comparison of the nmr spectra of 18-norestrone methyl ether with estrone methyl ether showed the former to have relatively sharper signals in both the CHC=O region (centered at 136 cps) and in the methylene region (centered at 85 cps).

Another 0.60 g of pure **2a** was obtained by chromatography of the mother liquors;[22] the product was eluted with 3% ethyl acetate–benzene.

If the acid hydrolysis time was shortened or the temperature kept below 10°, the pure enamide **1** was obtained in 35% yield from chromatography of the product. Recrystallization from acetone–hexane of this material, eluted at 10% ethyl acetate–benzene, afforded the **17-acetamidogona-1,3,5(10),16-tetraen-3-ol 3-methyl ether** (**1**): mp 177–179°; λ_{max}^{KBr} 3.07, 5.89, 6.02 μ; λ_{max} 220–231 mμ (plateau) (4.26), 278 (3.38), 286 (3.29); Δν 122 ($COCH_3$) cps.

Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09. Found: C, 76.88; H, 8.02.

The enamide **1** was hydrolyzed to an equilibrium mixture of ketones **2a** and **3a** by boiling it in methanol containing a little aqueous acid. Hydrolysis to yield only the *trans* ketone **2a** was not achieved.

Equilibration of 13α- and 13β-18-Norestrone Methyl Ether (3a, 2a).—A solution of 40 mg of the 13α derivative **3a**[3a] and 0.6 g of potassium carbonate in 15 ml of methanol and 3 ml of water was boiled under nitrogen for 30 min. The solution was cooled, diluted with water, and extracted with benzene, yielding 40 mg of semicrystalline material, $[\alpha]_D$ +11°. A similar run using potassium hydroxide–methanol at reflux for 1 hr gave the same mixture, $[\alpha]_D$ +14°. By reference to the rotations of the pure components (−66°, +188°) the mixture is a 7:3 mixture of **3a** and **2a**. Paper chromatography and infrared analysis agreed with these values and showed no other components.

A similar potassium carbonate treatment of 50 mg of the 13β isomer **2a** gave the same mixture. Chromatography of the product afforded fractions eluted with 1% ethyl acetate–benzene which were combined and recrystallized from hexane to yield 15 mg of the pure 13-iso derivative **3a**: mp 121–122°; identical in the infrared with the material obtained earlier;[3a] ORD (*c* 1.0, CH_3OH), $[\phi]_{312}$ −2950° tr, $[\phi]_{298}$ 0°, $a = -45$![23]

Gona-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether (18-Norestradiol Methyl Ether) (2b). A. From the *trans* Ketone.—A solution of 1.2 g of norestrone methyl ether (**2a**) in 20 ml of tetrahydrofuran was added to a solution of 0.3 g of lithium aluminum hydride in 30 ml of ether, and the mixture was stirred at room temperature for 2 hr. Cautious dilution of the reaction with water and then with aqueous hydrochloric acid was followed by extraction and chromatography of the product. (Tlc showed the presence of *ca.* 5% of a faster running impurity, presumably the 17α epimer.) Fractions eluted with 5% ethyl acetate in benzene were combined (0.59 g) in a small volume of benzene. Addition of hexane caused precipitation of a gelatinous precipitate which was dried in a stream of air, giving 0.14 g of norestradiol methyl ether: mp 158–161°; λ_{max} 3.11 μ; $[\alpha]_D$ 76°. The 17α-H signal was centered near 225 cps, obscured in part by the methoxyl signal (226 cps).

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.41; H, 9.12.

Spectral examination of the mother liquors showed it to be largely pure **2b**, implying the poorly crystalline nature of the compound was the chief factor in lowering the apparent yield.

The acetate was prepared with acetic anhydride–pyridine and was recrystallized from aqueous methanol to give a sample: mp 91–95°; Δν 284 cps (multiplet; W_h = 12 cps).

Lithium aluminum hydride reduction of estrone methyl ether under the same conditions gave the same relative ratio of epimers as did **2a** (tlc analysis).

B. From the *cis* Ketone 3a.—To a solution of 35 mg of the 13-iso ketone **3a** and 0.1 g of sodium hydroxide in 1 ml of 2-propanol was added 0.1 g of sodium borohydride in 4 ml of 2-propanol. After 16 hr at 25°, the solution was diluted with 20 ml of water and concentrated in a stream of nitrogen. A crystalline product formed and, after recrystallization, afforded 29 mg of **2b**, mp 145–149°, identical with an authentic sample by comparison of infrared and nmr spectra. The crude product (before recrystallization) by thin layer chromatography showed two 5% spots corresponding to the alcohols **2c** and **3b**. The product composition was confirmed by acetylation of the crude material and subsequent nmr analysis.

13α-Gona-1,3,5(10)-triene-3,17α-diol 3-Methyl Ether (3c) and 13α-gona-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether (3b). A. Hydride Reduction.—A solution of 1.10 g of 13-isoestrone methyl ether (**3a**) in 20 ml of tetrahydrofuran was added over a 5-min period to a stirred solution of 0.5 g of lithium aluminum hydride in 110 ml of ether at room temperature. After an additional 10 min the solution was diluted cautiously with water and then with dilute hydrochloric acid. The semicrystalline product (1.2 g) was isolated by benzene extraction and was seen by tlc to contain 65% of a less polar and 30% of a more polar derivative (estimated by visual comparison to pure standards). Chromatographic separation afforded fractions, eluted with 1% ethyl acetate–benzene, which were combined and recrystallized from acetone–hexane to yield 0.14 g of the pure β-diol **3c**: mp 117–118°; λ_{max} 2.95 μ; Δν 253 cps (multiplet; W_h = 6 cps); $[\alpha]_D$ 96°.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.20; H, 8.86.

Continued elution of the above column with 2% ethyl acetate in benzene afforded fractions which were recrystallized from acetone–hexane and then from aqueous methanol to afford 0.15 g of the α-diol **3b** as cottony rods: mp 153–155°; λ_{max} 3.06 μ; Δν 246 cps (multiplet; W_h = 10 cps); $[\alpha]_D$ 21°.

Anal. Found: C, 79.19; H, 9.24.

13α-Gona-1,3,5(10)-triene-3,17β-diol 3-Methyl Ether 17-Acetate, after recrystallization from aqueous acetone, had mp 68–72°; Δν 316 cps (multiplet; W_h = 7 cps).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.43. Found: C, 76.26; H, 8.47.

13α-Gona-1,3,5(10)-triene-3,17α-diol 3-Methyl Ether 17-Acetate was amorphous. The signal for the 17β proton was seen as a multiplet centered at 302 cps (W_h = 11 cps).

B. Metal–Alcohol Reduction.—Sodium (0.6 g) was added to a solution of 65 mg of **3a** in 20 ml of 2-propanol in a nitrogen atmosphere. The solution was boiled for 30 min, cooled, diluted with water, and concentrated until crystallization occurred. The product (65 mg) contained 5% of the 17β alcohol **3b** by tlc. The remainder, although homogeneous to tlc, was shown to be a 3:1 mixture of the *cis*-α derivative **3a**/*trans*-β **2b** by nmr analysis of the 17-proton region of the acetylated mixture.

17β-Hydroxygon-4-en-3-one (Dinortestosterone) (6a). A. From the *trans* Ketone 2a (Procedure A).—Lithium wire (1.5 g) was added portionwise over 0.5 hr to a solution of 0.24 g of norestradiol methyl ether (**2b**) in 80 ml of ether, 160 ml of ammonia, and 80 ml of *t*-butyl alcohol. After 3 hr more, methanol was added dropwise to decolorize the solution. The ammonia was distilled and the remaining mixture was diluted with water. The product, isolated by benzene extraction, was dissolved in 20 ml of ethanol containing 1 ml of concentrated hydrochloric acid. The solution was boiled for 1 hr and the product was isolated by extraction with benzene, yielding 0.22 g of semicrystalline material. Recrystallization from methylene chloride–hexane (Darco) afforded 0.14 g of dinortestosterone: mp 193–197°; λ_{max} 2.95, 6.02 μ; λ_{max} 241 mμ (4.22); Δν 328 (17α-H; W_h = 18 cps), 352 (4-H) cps; ORD (*c* 1.0, CH_3OH), $[\phi]_{589}$ 63°, $[\phi]_{339}$ −1510° tr, $[\phi]_{251}$ 7600°.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.36. Found: C, 78.16; H, 9.48.

Gon-4-ene-3,17-dione (Dinorandrostenedione) (6b).—Dinortestosterone (37 mg, **6a**) in 1 ml of pyridine was added to the Sarett reagent from 0.2 g of chromium trioxide.[24] The solution was stirred for 2 hr, and the product was isolated by dilution with water and extraction with ether. Recrystallization from acetone–hexane gave 29 mg of the pure compound: mp 150–152°; λ_{max} 5.78, 5.99 μ.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.07; H, 8.44.

Gona-1,3,5(10)-triene-3,17β-diol (18-Norestradiol) (2e).—A

(22) The chromatograms described were uniformly run on a weight of silica gel 60 times the weight of compound adsorbed. Thin layer chromatograms were also run on silica. We wish to thank Dr. E. G. Daskalakis and staff for their competent execution of these chromatograms.

(23) This ORD curve was provided by Professor C. Djerassi, for which we thank him.

(24) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

solution of 0.23 g of 18-norestradiol methyl ether in 20 ml of diethylene glycol containing 2 g of potassium hydroxide was heated at 210° in an atmosphere of nitrogen for 6 hr. The solution was cooled and diluted with aqueous acetic acid. The resulting crystal mass was filtered and recrystallized from aqueous ethanol to give 0.11 g of the desired compound: mp 251–253°; λ_{max}^{KBr} 2.92, 3.16 μ; $[\alpha]_D$ 70°. The analytical sample was obtained by sublimation.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.80; H, 8.64.

Use of pyridine hydrochloride in this demethylation was less satisfactory. Sodium borohydride reduction of 18-norestrone (**2d**) also gave the 17β-hydroxy compound **2e** in good yield.

3-Hydroxygona-1,3,5(10)-trien-17-one (18-Norestrone) (2d).—A solution of 0.25 g of norestradiol **2e** in 100 ml of acetone at 5° was treated with a solution of 0.4 ml of 4 *N* chromic acid.[25] After 5 min the solution was diluted with water, and the product was isolated by extraction with benzene. The crystalline residue was recrystallized from acetone to yield 60 mg of the pure 17 ketone **2d**: mp 245–248°; λ_{max} 3.07, 5.84 μ; λ_{max} 281 mμ (3.34); $[\alpha]_D$ 168°.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 80.02; H, 8.10.

17β-Hydroxy-13α-gon-4-en-3-one (6c).—The estradiol **3b** was reduced according to procedure A. The resulting product, 0.5 g of an oil, was dissolved in 20 ml of methanol, 4 ml of water, and 2 ml of concentrated hydrochloric acid. This solution, after 18 hr at room temperature, was diluted with water and extracted with benzene. The residue (0.50 g) on chromatography yielded fractions (0.18 g), eluted with 15% ethyl acetate–benzene, which were combined and recrystallized from acetone–hexane to provide 60 mg of the pure testosterone derivative **6c**: mp 145–147°; λ_{max} 2.92, 6.05 μ; λ_{max} 241 mμ (4.22); $\Delta\nu$ 246 cps (17-H; W_h = 9 cps); $[\alpha]_D$ +51°.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.16; H, 9.09.

18,19-Dinorpregna-2,5(10)-diene-3,20β-diol 3-Methyl Ether.—The unsaturated ketone **4a** (1.2 g) was reduced with lithium ammonia according to procedure A. The product crystallized from ether and was recrystallized from acetone–hexane to yield 0.20 g of the 20β-hydroxy derivative: mp 142–144°; λ_{max} 2.71, 5.84 (m, enol ether), 5.96 (m, enol ether) μ; $\Delta\nu$ 67 and 73 cps (21-CH_3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.14; H, 9.74.

20-Hydroxy-18,19-dinorpregn-4-en-3-one (7a,b).—A slurry of 0.10 g of 18,19-dinorpregna-2,5(10)-diene-3,20β-diol 3-methyl ether in 10 ml of methanol containing 2 ml of water and 1.5 ml of concentrated hydrochloric acid was stirred at room temperature for 3 hr. The solution was diluted with water and the precipitate separated by filtration. Recrystallization of the product from acetone–hexane gave the 20β isomer **7a**: mp 147–148°; λ_{max} 2.75, 5.99 μ; $\Delta\nu$ 68 and 74 (21-CH_3) cps. The 20-H signal was a broad multiplet centered at 225 cps (W_h = 15 cps).

Anal. Calcd for $C_{19}H_{28}O_2 \cdot {}^1/_2C_3H_6O$: C, 78.30; H, 9.82. Found: C, 78.32; H, 9.71.

The same procedure on the noncrystalline portion of the lithium–ammonia product (from reduction of **4a**) gave the 20α isomer **7b** with mp 175–178°; λ_{max} 2.88, 6.02 μ; $[\alpha]_D$ 64°; $\Delta\nu$ 68 and 74 (21-CH_3) cps. The 20-H was a multiplet centered at 231 (W_h = 10 cps).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.08; H, 9.84.

An additional amount of the lower melting isomer was obtained by chromatography of the mother liquors.

18,19-Dinorprogesterone (7c).—A solution of 1.0 g of the crude dihydro alcohols **7a,b** in 20 ml of pyridine was oxidized with the Sarett reagent from 1.0 g of chromium trioxide.[24] The mixture, after being stirred at room temperature for 1 hr, was diluted with water and extracted with ether. The product was chromatographed, fractions eluted with 10% ethyl acetate in benzene being combined and recrystallized from acetone–hexane to yield 0.30 g of dinorprogesterone (**7c**): mp 137–139°; λ_{max} 5.87, 6.01 μ; λ_{max} 240 mμ (4.15); ORD (*c*, 1.0; CH_3OH), $[\phi]_{589}$ +87°, $[\phi]_{435}$ +400° pk, $[\phi]_{336}$ −1450° tr, $[\phi]_{283}$ +8700°, $[\phi]_{255}$ +17,400°.[26]

(25) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(26) Professor W. Klyne kindly provided this ORD curve.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.12.

Also obtained from this chromatogram were small amounts of starting material and a high melting material (dimer?). Oxidation of the pure epimers, **7a** or **7b**, gave **7c**.

Treatment of dinorprogesterone with base to effect equilibration caused no apparent formation of the 17-iso derivative as determined by the homogeneity of the material to paper chromatography, tlc, and nmr spectroscopy.

18,19-Dinorpregna-1,3,5(10),16,20-pentaene-3,20-diol 3-Methyl Ether 20-Acetate (5).—A solution of 6.00 g of the unsaturated ketone **4a** and 4.5 g of *p*-toluenesulfonic acid in 450 ml of *i*-propenyl acetate was distilled slowly for 8 hr. The cooled solution was diluted with ether and aqueous potassium bicarbonate. Ether extraction yielded a crystalline residue which was purified by trituration with benzene–hexane and recrystallized from methanol yielding 1.6 g of the enol acetate **5** as fine platelets: mp 137–139°; λ_{max} 5.72 μ; λ_{max} 230 mμ (4.27).

Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.12; H, 7.72.

3,21-Dihydroxy-18,19-dinorpregna-1,3,5(10),16-tetraen-20-one 3-Methyl Ether 21-Acetate (8a).—The crude enol acetate **5** (from 1.2 g of **4a**) and 2.5 g of N-iodosuccinimide were heated in 5 ml of dioxane at 90° under nitrogen for 1 hr. Methanol (20 ml) was added to the solution followed by excess aqueous potassium iodide. The color was discharged with aqueous sodium thiosulfate and the resulting crystal mass (1.8 g) was collected on a filter. The crude iodo compound in 50 ml of acetone was treated with a slurry of 4 g of potassium bicarbonate ground in 3 ml of acetic acid. After 18 hr at the reflux temperature, the solution was diluted with water and filtered. The crystalline material was recrystallized twice from methanol (Darco) to yield 0.45 g of the pure acetate **8a**: mp 156–158°; λ_{max} 5.73, 5.93 μ; λ_{max} 231 mμ (4.17); $[\alpha]_D$ 66°.

Anal. Calcd for $C_{22}H_{26}O_4 \cdot {}^1/_2CH_4O$: C, 72.94; H, 7.62. Found: C, 73.05; H, 7.23.

Chromatography of the mother liquors provided an additional 0.15 g of the same material from fractions eluted with 2% ethyl acetate in benzene.

3,21-Dihydroxy-18,19-dinorpregna-1,3,5(10)-trien-20-one 3-Methyl Ether 21-Acetate (8b).—The acetate **8a** (0.43 g) and 0.3 g of 5% palladium-on-charcoal catalyst in 30 ml of ethyl acetate were stirred in an atmosphere of hydrogen for 6 hr. The mixture was filtered and the filtrate was evaporated. The crystalline residue was recrystallized from acetone–hexane and then from hexane to yield 0.24 g of the acetate **8b**, mp 114–115°, as cottony rods: λ_{max} 5.70, 5.82 μ.

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.03; H, 7.62.

18,19-Dinorcorticosterone (9).—A solution of 0.25 g of the acetate **8b** and 0.10 g of *p*-toluenesulfonic acid in 150 ml of benzene and 30 ml of ethylene glycol was distilled slowly for 6 hr. The solution was cooled and diluted with aqueous potassium bicarbonate. The product, isolated by benzene extraction, was reduced with lithium–ammonia according to procedure A. The resulting material, isolated by benzene extraction, was dissolved in 25 ml of methanol, 4 ml of water, and 3 ml of concentrated hydrochloric acid. This solution was boiled for 30 min, cooled, and diluted with water. The product was isolated by extraction with benzene and was recrystallized from acetone–hexane to yield 40 mg of the pure dinorcorticosterone **9**: mp 168–171°; λ_{max} 2.90, 5.85, 6.01 μ.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.39; H, 8.41.

Registry No.—**1**, 15093-11-5; **2a**, 4147-10-8; **2b**, 15206-28-7; **2d**, 4732-79-0; **2e**, 15093-14-8; **3a**, 4248-04-8; **3b**, 15093-16-0; **3c**, 15093-17-1; **4b**, 15094-83-4; **5**, 15094-84-5; **6a**, 4732-80-3; **6b**, 15094-86-7; **6c**, 15094-87-8; **7a**, 15094-88-9; **7b**, 15094-89-0; **7c**, 2299-98-1; **8a**, 15094-91-4; **8b**, 15094-92-5; **9**, 15094-93-6; 13α-gona-1,3,5(10)-triene-3,17β-diol 3-methyl ether 17-acetate, 15094-94-7; 13α-gona-1,3,5(10)-triene-3,17α-diol 3-methyl ether 17-acetate, 15206-30-1; 18,19-dinorpregna-2,5(10)-diene-3,20β-diol 3-methyl ether, 15094-95-8.