combined extracts were washed (dilute $NaHCO_3$, H_2O). After drying, the solvent was removed under reduced pressure to give 5.18 g (55%) of crude product. Recrystallization from ether–petroleum ether furnished 3.6 g (40%) of white crystals, mp 192–195°.

In a pilot experiment, the product was recrystallized from ether–petroleum ether to give white crystals: mp 195–197°; $[\alpha]D$ −11°; no significant absorption in the ultraviolet; λ_{max} 2.94, 5.91, 6.10 μ; nmr, 38.5 (18-H), 53 (doublet, J = 7 cps; 16-CH_3), 56.5 (19-H), 62 (17-CH_3), 114 (OH), 125 (21-H), 215 (3-H), 322 (11-H) cps; ORD,[16] positive Cotton effect, $[M]_{368,315}$ +3120°, +2740°.

Anal. Calcd for $C_{29}H_{36}O_2$: C, 80.18; H, 10.73. Found: C, 79.99; H, 10.76.

B. From 3β-Acetoxy-5α-pregna-9(11),16-dien-20-one (I).—By the methylation procedure described in method A, 9.62 g of I gave 8.84 g of fluffy powder. Hydrolysis of the acetoxy group was ensured by treatment of the material in 400 ml of methanol with 12 ml of 10% K_2CO_3 solution at the reflux temperature for 30 min. The resulting cooled solution was neutralized with AcOH (5 ml), concentrated to a small volume, diluted with water, and extracted several times with CH_2Cl_2. The combined extracts were washed with water, dried, and taken to dryness to give 8.8 g of syrup. Treatment of this material with Girard's "T" reagent as described in method A gave 1.88 g (20%) of product, mp 184–186°. This material was identical, by the usual criteria, with that obtained in A.

Sodium salt of 21-ethoxalyl-3β-hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (IIIc) was prepared from IIc (2.5 g) by the procedure described above for the preparation of the sodium salt of IIIa; there was obtained 3.4 g (100%) of amorphous product which gave a deep red color with 1% alcoholic $FeCl_3$; λ_{max} 2.85, 5.83, 6.02, 6.16, 6.70, 8.15 μ.

21-Bromo-16α,17-dimethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIc). A. From the Ethoxalyl Derivative IIIc.—When prepared by the A procedure for the preparation of VIa (above), 3.5 g of the sodium salt furnished 2.4 g (76%) of amorphous material, which did not give any color with 1% alcoholic $FeCl_3$; λ_{max} 2.88, 5.84, 6.13 μ. This material was used without further purification.

B. By Direct Bromination of 3β-Hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (IIc).—To a stirred solution of 5 g of IIc in 100 ml of absolute alcohol (cooled to 0°) was added 10 ml of a solution of 50 ml of absolute alcohol containing 18 g of HCl[17] followed by dropwise addition (1 hr) of 65 ml of a solution of 100 ml of absolute alcohol containing Br_2 (5.81 g). After an additional 5 min the solution was poured into 800 ml of water and filtered to give 5.88 g (96%) of amorphous material, which was used without further purification.

21-Acetoxy-3β-hydroxy-16α,17-dimethyl-5α-pregn-9(11)-en-20-one (VIIc).—A solution of 5.9 g of VIc (prepared by method B above) and 3.4 g of anhydrous NaOAc in 55 ml of DMF containing 0.2 ml of AcOH was stirred under N_2 at 55–60° for 72 hr. The cooled solution was poured into 300 ml of water and the resulting solution was extracted three times with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated to dryness to furnish an amorphous solid, which was chromatographed on silica gel. Elution with 3 l. of 10% ether in benzene, followed by evaporation of the eluate, furnished 3.2 g (55% from IIc) of product, mp 122–126°. Two recrystallizations from acetone–petroleum ether gave white crystals: mp 131–132°; $[\alpha]D$ −5°; no significant absorption in the ultraviolet; λ_{max} 2.90, 5.72, 5.83, 6.10, 8.13 μ.

Anal. Calcd for $C_{25}H_{38}O_4 \cdot 0.5H_2O$: C, 72.96; H, 9.55; H_2O, 2.18. Found: C, 73.41; H, 9.43; H_2O, 1.72 (Karl Fischer).

In another experiment treatment of 2.4 g of crude 21-bromide VIc, prepared by method A above, in 130 ml of DMF with 7 g of anhydrous NaOAc, furnished 616 mg (21% from IIc), mp 128–130°.

21-Acetoxy-17-ethyl-3β-hydroxy-5α-pregn-9(11)-en-20-one (VIIb) *via* Direct Bromination of IIb.—Direct bromination of 1 g of IIb in the manner described above in method B for the preparation of VIc furnished 1.2 g of VIb, 1 g of which was treated with NaOAc according to the procedure described above for the preparation of VIIc to give 1 g of amorphous material. The product was chromatographed on 40 g of silica gel. Elution with 1 l. of 15% ether in benzene followed by evaporation of the eluate furnished 504 mg (50% from IIb) of VIIb, mp 139–143°.

Acknowledgments.—We wish to thank Mr. J. Nocera and Dr. P. Kohlbrenner for a substantial supply of certain intermediates, Mr. W. Fulmor and staff for the spectroscopic and polarimetric data, Mr. L. Brancone and staff for the microanalytical data, Mr. C. Pidacks and staff for the partition chromatography work, and Dr. G. Tonelli and staff of the Experimental Therapeutics Research Section of these laboratories for the biological evaluation.

Some 17α-Cyclopropyl Steroids

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Cyclopropyllithium was employed to prepare 17α-cyclopropylestradiol 3-methyl ether, the parent member of a series of 17α-cyclopropylestrenes, and for the preparation of 17α-cyclopropyltestosterone. Various chemical transformation products of the former compound are described, and the biological activities that were found are reported.

The description by Seyferth and Cohen[1] of a convenient preparation of cyclopropyllithium led us to the application of this reagent to the synthesis of a number of 17α-cyclopropyl-substituted steroids, which were at that time unknown. More recently, Lehmann, *et al.*,[2] have reported the synthesis of several of these compounds by the use of the Simmons–Smith reagent upon appropriate olefinic precursors; in this way compounds **2**, **5**, and **15** were prepared.

The reaction of cyclopropyllithium with estrone 3-methyl ether afforded a single 17-cyclopropyl-substituted product, which was presumed, on the basis of prior experience[3] with various organometallic reagents, to be the 17α-alkylated isomer **2** (Chart I).

A substantial amount of the ketone always remained unconverted and had to be removed either by chromatography or by condensation with a Girard reagent (see Experimental Section). Reduction of **2** with Li and alcohol in liquid ammonia[4] afforded the 1,4-dihydroenol ether **3** in high yield; oxalic acid hydrolysis[4] of **3** then provided the useful intermediate 17α-cyclopropyl-17-hydroxyestr-5(10)-en-3-one (**4**).

(1) D. Seyferth and H. M. Cohen, *J. Organometal. Chem.* (Amsterdam), **1**, 15 (1963).

(2) H. G. Lehmann, H. Muller, and R. Weichert, *Ber.*, **98**, 1470 (1965).

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

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

Chart I

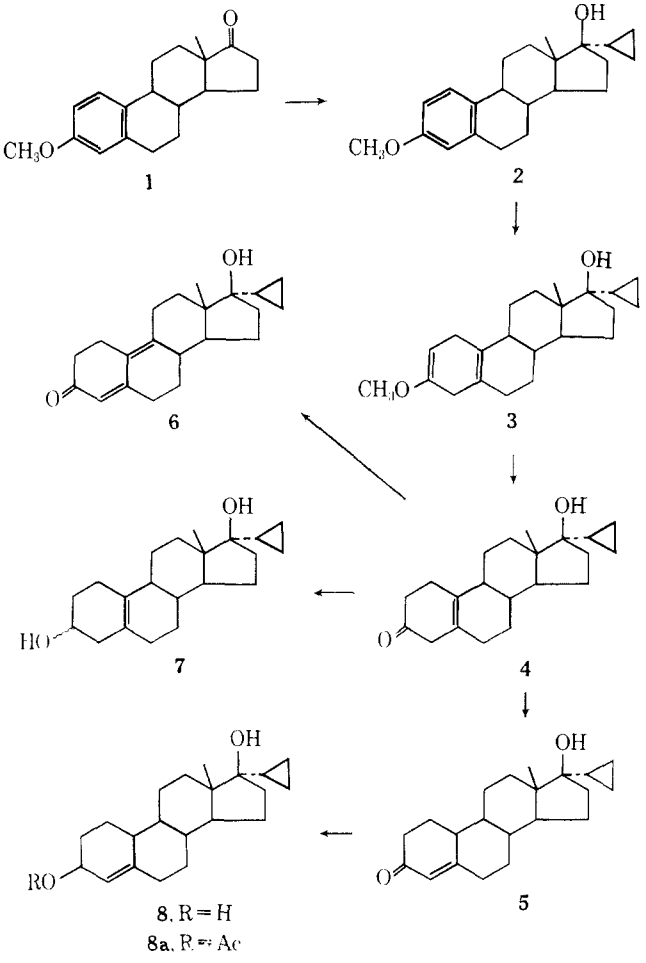
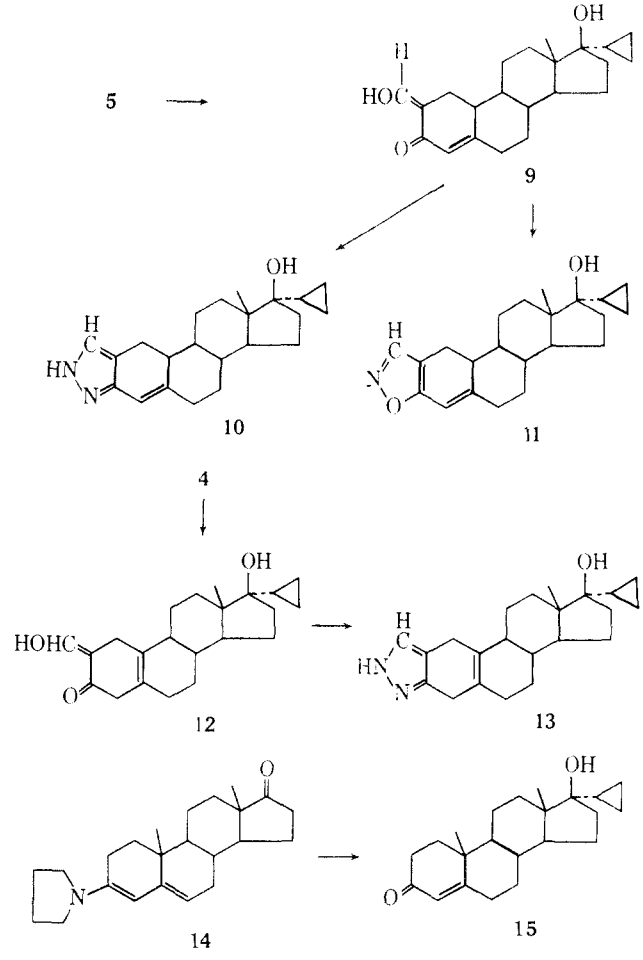


Chart II



The isomerization of **4** to its Δ^4-3-keto counterpart **5** was effected with base because of the sensitivity of the 17α-cyclopropyl-17β-hydroxy system to strongly acidic reagents.[5] When the unconjugated ketone **4** was treated with 1 molar equiv of pyridinium bromide perbromide in pyridine,[6] the 4,9(10)-diene **6** was obtained in good yield.

Reduction of **4** with lithium aluminum tri(*t*-butoxy)hydride gave a fairly sharp-melting mixture[7] of the two 3-hydroxy compounds **7** (in which the less polar component predominates) which could not be resolved into its pure components by chromatography on either a column or thick layer plates. However, reduction of the isomeric conjugated ketone **5** with the same reagent gave a crude product from which the greatly predominant isomer, assigned the 3β-hydroxy structure (**8**),[8] was readily isolated.

Formylation[9] of the conjugated ketone **5** was accomplished in high yield with excess sodium methoxide and ethyl formate in benzene solution (see Chart II). The 2-hydroxymethylene compound **9** was then converted, with hydrazine hydrate in acetic acid solution, into the corresponding A-ring-fused pyrazole **10**.[9] In a buffered acetic acid solution of hydroxylamine hydrochloride, **9** was transformed into the conjugated isoxazole **11**.[10]

By utilization of the procedure of Wiedhaup, *et al.*,[11] which employs only 1 equiv of sodium methoxide, the β,γ-unsaturated ketone **4** was converted to its corresponding 2-hydroxymethylene derivative **12** in moderate yield. Compound **12** was crystalline and possessed appropriate spectral properties (see Experimental Section); most indicative of the assigned structure was its ultraviolet absorption maximum at 280 mμ (ϵ 8000), which clearly showed the presence of a nonconjugated hydroxymethylene ketone.[9]

The conversion of **12** into its pyrazole derivative **13** was effected easily with hydrazine hydrate in ethanolic solution. However, the preparation of the corresponding isoxazole did not proceed in a straightforward manner; this compound will be the subject of another publication.

17α-Cyclopropyltestosterone (**15**) was prepared by the reaction of cyclopropyllithium with the 3-pyrrolidyl enamine (**14**) of androst-4-ene-3,17-dione, followed by hydrolysis of the protective group.

(5) Some rearrangements and other reactions of the 17α-cyclopropyl-17β-hydroxy system will be the subject of another paper.

(6) (a) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960); (b) M. Perelman and E. Farkas, U. S. Patent 3,086,027 (April 16, 1963).

(7) S. G. Levine, N. H. Eudy, and E. C. Farling [*Tetrahedron Letters*, 1517 (1963)] found that the reduction of 17β-propionoxyestr-5(10)-en-3-one with lithium aluminum tri(*t*-butoxy)hydride gave a product composed of 81–83% 3α-hydroxy compound and 13–15% of the 3β-epimer; the components were separable by means of column chromatography.

(8) Reference 3, p 270.

(9) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Cavagnas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(10) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(11) K. Wiedhaup, A. J. H. Nollet, J. G. Korsloot, and H. O. Huisman, *Tetrahedron Letters*, 1599 (1965).

Biological Results.—The myotrophic and androgenic activities of these compounds were determined by the method described by Hershberger, *et al.*[12] The estrogenicity was estimated by the method of Lawson, *et al.*[13] Progestational activity was evaluated by the Clauberg test in rabbits.[14] Cyclopropylestradiol methyl ether (**2**) was found to be a potent estrogen. The dihydroenol ether **3** was estrogenic but not progestational, whereas **4** was both estrogenic and progestational. Conjugated ketone **5** (17α-cyclopropyl-19-nortestosterone) was observed to be weakly androgenic as well as progestational. Diol **8** and its monoacetate **8a** were each about one-half as myotrophic as methyltestosterone by oral assay, but only 0.06 to 0.03 times as androgenic. Both compounds were also moderately progestational and were estrogenic. The mixture of epimeric diols **7** was progestational and estrogenic, and the dienone **6** was found to be a strong progestin. Oral progestational response in the rabbit was seen with the hydroxymethylene derivative **12** but was absent from its derived pyrazole **13**. The same activity was present to a moderate degree in the conjugated isoxazole **11**, but was absent in the conjugated pyrazole **10**, which was found to be estrogenic. Cyclopropyltestosterone (**15**) was found to be weakly androgenic.

Experimental Section[15]

17-Cyclopropyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (2).—To a stirred solution in ether of cyclopropyllithium[1] prepared from 2.0 g (288 g-atoms) of Li, 15.75 g (130 mmoles) of bromocyclopropane, and 130 ml anhydrous ether was added a warm solution of 11.37 g (40 mmoles) of estrone methyl ether (**1**) in 125 ml of dry tetrahydrofuran (THF), and the mixture was stirred and refluxed overnight. The cooled solution was then hydrolyzed by the addition of 100 ml of saturated sodium potassium tartrate solution, and the separated organic layer was washed successively with 50 ml of 2 *N* HCl, 25 ml of saturated $NaHCO_3$, two 50-ml portions of H_2O, and 50 ml of saturated NaCl. The combined aqueous washes were back-extracted with ether, which was similarly washed and added to the organic phase. Drying and evaporation of the organic phase gave an oil which, on chromatography over Merck alkaline alumina with ether–pentane mixtures, afforded 2.00 g of unreacted estrone methyl ether (eluted with 30% ether). Further elution, with 40–60% ether, gave 7.85 g of crude **2**. Two recrystallizations from acetonitrile provided 4.90 g of pure **2**: mp 120.5–122.0°; $[\alpha]^{25}D$ +44.3°; infrared, ν_{max} 2.87, 3.25, 3.42, 3.50, 6.23, 6.32, 6.66, 6.84, 8.09 μ; nmr (external TMS standard) signals, 455–415 (aromatic ring), 249 (OCH_3), 83 (angular CH_3), and 50–59 cps (cyclopropyl) [lit.[2] mp 116–116.5°, $[\alpha]^{22}D$ +42.0° (*c* 0.79)].

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.92; H, 9.26. Found: C, 80.72; H, 9.22.

In an alternative purification procedure, the crude product from the reaction of 920 mmoles of cyclopropyllithium with 460 mmoles of estrone methyl ether (**1**) was added to 250 ml of ethanol, 50 ml of AcOH, and 28 g (150 mmoles) of Girard "P" reagent. The solution was refluxed for 1 hr, cooled, diluted with 2 l. of cold water, and extracted with 3 l. of ether. The separated ether layer was washed with 500 ml of cold water, and the combined aqueous phase and wash was back-extracted with 500 ml of ether. The ether phases were combined, washed successively (2 *N* NaOH, four times with H_2O, and once with saturated NaCl), and then was dried (Na_2SO_4) and evaporated. Crystallization of the residue from acetonitrile gave **2** (69.85 g), mp 118–122°. Acidification of the combined aqueous solution with 50 ml of concentrated HCl gave, after filtration, washing, and drying of the precipitate, 32 g of **1**, mp 172–174°.

17-Cyclopropyl-3-methoxyestra-2,5(10)-dien-17β-ol (3).—A solution of 1.00 g (3.18 mmoles) of **2** in 75 ml of absolute ether and 95 ml of anhydrous NH_3 was stirred under N_2 while 0.93 g (42 equiv) of Li wire was added in small pieces. Ten minutes later, addition of absolute ethanol was begun at a moderate rate; the 15.0 ml required to decolorize the solution was added during 20 min. The NH_3 was allowed to evaporate and when the residual solution reached room temperature, 400 ml of ice and water were added, followed by an additional 300 ml of ether. The separated water layer was extracted with 100 ml of ether, and the combined ether solution was washed with two 50-ml portions of water and saturated NaCl solution (100 ml). After having been dried (Na_2SO_4), the solution was evaporated and the residue was crystallized from hexane to give 0.70 g of **3**, mp 125–128°. The infrared spectrum showed characteristic dihydroanisole absorption at 5.92 and 6.02 μ, and a sharp hydroxyl band at 2.9 μ. Only end absorption was seen in the ultraviolet region. A second crop of crystals was also obtained: 0.07 g, mp 122–126°. The analytical sample (from ether–hexane) had mp 125–129° (129–131° in an evacuated capillary), $[\alpha]^{25}D$ +94.0°.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.67; H, 10.05.

17α-Cyclopropyl-17-hydroxyestr-5(10)-en-3-one (4).—A solution of 0.197 g (0.61 mmole) of **3** in 20 ml of methanol was mixed with a solution of 0.23 g of oxalic acid dihydrate in 3 ml of water. After being kept for 40 min at room temperature, the solution was transferred to a separatory funnel with 125 ml of ether. The ether phase was washed ($NaHCO_3$, H_2O, saturated NaCl). Drying and evaporation of the ether solution left a residue which was crystallized from ether–hexane to give 0.125 g of **4**, mp 145–150°. The infrared spectrum showed C=O (5.86 μ) and OH (2.85 μ) absorption. The ultraviolet spectrum indicated the presence of a small amount of conjugated ketone as an impurity: λ_{max} 240 mμ (ε 350). No vinyl protons could be seen in the nmr spectrum, and the cyclopropyl and angular methyl group protons were apparent.

In a scaled-up preparation (7.0 g of steroid, 21.3 mmoles), a 93% yield of comparable material was obtained. Recrystallization from ethyl acetate–hexane afforded the analytical sample, mp 150.5–153° (in an evacuated capillary 152.5–154°), $[\alpha]^{25}D$ +156.4°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.34; H, 9.66.

17α-Cyclopropyl-17-hydroxyestr-4-en-3-one (5).—One milliliter of 2 *N* NaOH solution was added to a solution of 2.0 g (6.36 mmoles) of **4** in 75 ml of methanol. After 30 min at room temperature, the isomerization was complete, as indicated by thin layer chromatography (tlc). The base was neutralized by the addition of a few drops of AcOH, and the solution was then evaporated to dryness at room temperature under reduced pressure. The residue was taken up in ether and the solution was washed, dried, and evaporated. Crystallization of this residue from ether–hexane gave 1.7 g of **5**, mp 132–133°, $[\alpha]^{25}D$ +13.7°, λ_{max} 241 mμ (ε 17,600).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.99; H, 9.39.

A second crop of crystals, 0.21 g, mp 129–132.5°, was also isolated. In later preparations of this compound, a higher melting polymorphic form of **5** was always isolated, mp 144.5–146° [lit.[2] mp 139.5–140.5°, $[\alpha]^{22}D$ +11.1°, λ_{max} 240 mμ (ε 16,900)].

17α-Cyclopropyl-17-hydroxyestra-4,9(10)-dien-3-one (6).—A solution of 12.6 g (40 mmoles) of **4** in 250 ml of dry pyridine was stirred and held at 3 ± 2° with an ice bath, while 14 g (44 mmoles) of pyridinium bromide perbromide was added in small portions during 30 min. The pale yellow mixture, now containing some precipitate, was stirred at room temperature for 5 hr and then was diluted with 3 l. of cold water. The precipitation product was collected by filtration, washed with water, dried, and recrystallized from ether. Three crops of crystals, totalling 9.70 g and melting in the range 147–151.5° were obtained. The analytical sample of **6** (from ether) had mp 151–152°; $[\alpha]^{25}D$ −295.8°;

(12) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Expil. Biol. Med.*, **83**, 175 (1953).

(13) H. D. Lawson, C. G. Heller, J. B. Golden, and E. I. Severinghuas, *Endocrinology*, **24**, 35 (1939).

(14) C. Clauberg, *Zentr. Gynaekol.*, **54**, 2757 (1930).

(15) Melting points were determined in open capillaries in an oil bath with a calibrated thermometer, and are accurate to ±1°. Optical rotations were measured using 1% solutions of the compounds in $CHCl_3$; ultraviolet spectra were measured using solutions in 95% EtOH. The infrared spectra were determined with KBr pellets, and the nmr spectra were recorded for $CDCl_3$ solutions. Thanks are expressed to Mr. K. D. Fleischer, Mr. C. Josephs, and Mr. J. Hodecker for microanalyses and to Mrs. G. Barnett for optical rotations. We also wish to thank Dr. R. K. Kullnig, Miss C. M. Martini, Mrs. M. Becker, Mrs. E. Boll, and Mr. M. Priznar for the infrared, ultraviolet, and nmr spectra.

λ_{max} 218 mμ (ε 5800) and 306 mμ (ε 20,700); in the infrared, λ_{max} 2.80, 2.91, 3.26, 3.42, 3.51, 6.05, 6.27, 6.34, and 6.89 μ. The nmr spectrum showed a single vinyl proton and was otherwise appropriate.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03; Found: C, 80.83; H, 9.06.

17-Cyclopropylestr-5(10)-ene-3,17β-diol (7).—A solution of 3.15 g (10 mmoles) of 17α-cyclopropyl-17-hydroxyestr-5(10)-en-3-one (**4**) in 100 ml of dry THF was stirred at room temperature while 4.32 g of lithium aluminum tri(*t*-butoxy)hydride was added. After 4 hr at room temperature most of the solvent was removed at reduced pressure and the residue was added to 2 l. of cold water. The mixture was neutralized with AcOH, then filtered to give 4.8 g of a solid. Trituration of this with warm methanol, filtration, and evaporation of the filtrate gave 3.25 g of a residue. Two crystallizations from acetone afforded 2.4 g of crystals, mp 124–127°. Although tlc clearly showed the material to be a mixture of two compounds of very similar polarity, the mixture could not be resolved into its components by any of a number of means employed, including thick layer chromatography. Small samples were converted to the 3-acetates and 3-benzoates, respectively, but the esters resisted separation similarly. A final crystallization from acetone furnished the analytical sample, mp 127–130°, $[\alpha]^{25}D$ +128.9°.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.42; H, 9.97.

17-Cyclopropylestr-4-ene-3β,17β-diol (8).—Lithium aluminum tri(*t*-butoxy)hydride (12.4 g, 60 mmoles) was added to a solution of 6.29 g (20 mmoles) of **5** in 150 ml of THF. The solution was stirred at room temperature for 1.5 hr, after which time the excess reagent was destroyed by the cautious addition of a solution of acetic acid (4 ml) in THF (20 ml). The reaction mixture was diluted with 2.5 l. of water and this mixture was made weakly acidic (AcOH). The precipitated product was collected by filtration, washed, and dried; crystallization from ethyl acetate gave 5.30 g, mp 137–140°, and 0.20 g of a broad-melting second crop. Several recrystallizations from acetone–hexane provided the analytical sample (homogeneous to tlc), mp 142–144°, then 149–152.5°, $[\alpha]^{25}D$ +1.4°.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.57; H, 10.43.

17-Cyclopropylestr-4-ene-3β,17β-diol 3-Acetate Monohydrate (8a).—A mixture of 1.0 g (3.1 mmoles) of **8**, 2.0 ml of dry pyridine, and 1.0 ml of Ac_2O was warmed until the solid dissolved. The solution was kept 17 hr at room temperature, then poured into 300 ml of water. The crystalline ester was filtered off, washed, and dried in air to give 1.15 g, mp 85–105°. The compound could only be crystallized from aqueous alcohols as a somewhat unstable monohydrate; the analytical sample, from aqueous methanol, had mp 93–105°, $[\alpha]^{25}D$ −43.5°. The spectra were appropriate, with the exception that in the infrared (KBr pellet) a double C=O peak appeared. In solution ($CHCl_3$ and also CS_2) only normal acetate C=O absorption was seen, at 5.83 and 5.78 μ, respectively.

Anal. Calcd for $C_{23}H_{34}O_3 \cdot H_2O$: C, 73.37; H, 9.64; H_2O, 4.81. Found: C, 73.20; H, 9.28; H_2O (Karl Fischer), 4.60.

17α-Cyclopropyl-17-hydroxy-2-(hydroxymethylene)estr-4-en-3-one (9).—To a solution of **5** (12.6 g, 40 mmoles) in 150 ml of dry benzene and 40 ml of ethyl formate was added 6.5 g (120 mmoles) of sodium methoxide (Matheson Coleman and Bell) and the mixture was stirred under N_2 at room temperature. The reaction was mildly exothermic; after 3.5 hr another 15 ml of ethyl formate was added. After 21 hr, 100 ml of water was added and stirring was continued for 0.5 hr. The layers were separated and the benzene phase was washed with 50 ml of 2 *N* NaOH. The combined aqueous phase was extracted once with 100 ml of ether; a stream of CO_2 was then passed through it for several hours to precipitate the product. The aqueous layer was decanted from the gummy precipitate, which was then redissolved in 350 ml of 0.3 *N* NaOH and reprecipitated with CO_2 as before, this time appearing as a finely divided amorphous yellow powder. The product was collected on a filter, washed with water, and dried, giving 13.20 g of solid, with λ_{max} 248 (ε 10,400) and 307 mμ (ε 4500).

17-Cyclopropylestr-4-eno[3,2-*c*]pyrazol-17β-ol (10).—A cool (10°) solution of 5 ml of hydrazine hydrate in 15 ml of AcOH was added to a cool solution of 6.5 g of **9** in 35 ml of AcOH. The mixture was kept at room temperature for 1.5 hr and then quenched in water; the product was collected by filtration, washed with water, and dried. The tan amorphous pyrazole was purified by column chromatography on Florisil (elution with 10 and 20% ether in benzene) and by thick layer chromatography on silica gel (development with ethyl acetate). Crystallization was effected from aqueous ethanol, affording 2.6 g of a metastable hemihydrate, mp 140–150°, λ_{max} 261 mμ (ε 10,100). A final recrystallization from aqueous ethanol provided the analytical sample of **10**, mp 143–148°, $[\alpha]^{25}D$ −10.2°.

Anal. Calcd for $C_{22}H_{30}N_2O \cdot 0.5H_2O$: C, 76.04; H, 8.99; N, 8.06. Found: C, 76.13; H, 9.06; N, 8.13.

17-Cyclopropylestr-4-eno[2,3-*d*]isoxazol-17β-ol (11).—A solution of 3.27 g (24 mmoles) of $NaOAc \cdot 3H_2O$ and 0.85 g (12.2 mmoles) of hydroxylamine hydrochloride in 5 ml of water was added to a solution of 4.1 g (12 mmoles) **9** in 25 ml of warm (*ca.* 40°) AcOH. The clear solution was kept at room temperature for 1.5 hr and then was poured into 1.5 l. of cold water. After neutralization of the mixture with dilute NaOH solution it was filtered and the crude product was washed with water and dried. The 3.7 g of crude solid thus obtained was purified by thick layer chromatography on silica gel (developed with 50% ether in pentane) followed by crystallization from a mixture of ether and hexane to give 2.09 g of **11**: mp 137–139°; $[\alpha]^{25}D$ +77.4°; ultraviolet, λ_{max} 287 mμ (ε 11,800); infrared, λ_{max} 2.91, 3.24, 3.33, 3.42, 3.46, 3.50, 6.13, 6.21, 6.79, and 6.99 μ.

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 78.91; H, 8.95; N, 4.37.

17α-Cyclopropyl-17-hydroxy-2-(hydroxymethylene)estr-5(10)-en-3-one (12).—A solution of 6.30 g (20 mmoles) of **4** in 75 ml of dry benzene and 10 ml of ethyl formate was stirred at room temperature under N_2 while 1.08 g (20 mmoles) of sodium methoxide (Matheson Coleman and Bell) was introduced. After 45 min the deep orange reaction mixture was poured into a separatory funnel containing 200 ml of ether and 100 ml of water. After thorough agitation and separation of the layers, the organic phase was washed with 100 ml of water. Acidification of the combined aqueous solution by bubbling CO_2 through it caused the precipitation of a yellow solid; after being filtered off, washed, and dried, it weighed 1.15 g and had mp 183–195°. Evaporation of the organic phase under reduced pressure gave a yellow gum which on trituration with ether became crystalline. Filtration and drying gave 2.50 g of crystals, mp 187–200°. Ultraviolet spectra and tlc examination showed the two solid fractions to be both composed largely of the hydroxymethylene derivative **12**. They were combined and crystallized from ethyl acetate, affording 2.00 g of pure **12**, mp 202–208° dec. One more recrystallization from ethyl acetate provided the analytical sample, mp 202–208° dec. In an evacuated capillary, the melting point was 208–210° dec; $[\alpha]^{25}D$ +111.3°; ultraviolet, λ_{max} 280 mμ (ε 8000); infrared, λ_{max} 2.85, 3.29, 3.35, 3.46, 3.49, 3.53, 5.96, 6.13, 6.34, 6.59, 6.82, and 6.89 μ.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.24; H, 9.01.

17-Cyclopropylestr-5(10)-eno[3,2-*c*]pyrazol-17β-ol (13).—To a suspension of 3.4 g (10 mmoles) of **12** in 50 ml of absolute ethanol was added 2.5 ml (50 mmoles) of hydrazine hydrate. Within 1 min the suspended solid dissolved, and the resulting clear light yellow solution was kept at room temperature for several hours. Evaporation of the solvent under reduced pressure afforded a solid residue which was crystallized from ethyl acetate giving 2.70 g of crystals, mp 190–200° dec. In an evacuated capillary, the melting point was 217–220° dec. Because of tenacious solvation with ethyl acetate, revealed by spectral and elemental analyses, the analytically pure sample of **13** was obtained by recrystallization from a mixture of CH_2Cl_2 and CH_3CN: 2.0 g; mp 220–221° dec (evacuated capillary); $[\alpha]^{25}D$ +94.2°; λ_{max} 223 sh (ε 17,500); infrared, λ_{max} 2.87, 3.07, 3.44, 6.24, 6.58, 6.81, and 6.89 μ.

Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.10; H, 8.77; N, 8.46.

17α-Cyclopropyl-17-hydroxyandrost-4-en-3-one (15). To a stirred solution of cyclopropyllithium[16] in ether, prepared from 1.95 g (280 g-atoms) of Li and 15.7 g (130 mmoles) of bromocyclopropane in 125 ml of anhydrous ether, was added a solution of 11.4 g (32.5 mmoles) of 3-pyrrolidinoandrosta-3,5-dien-17-one (**14**) (mp 221–224°)[16] in 200 ml of dry THF. The solution was refluxed overnight under N_2 and was then treated with 20 ml of

(16) Prepared from 10 g of androstenedione and 4 ml of pyrrolidine in 35 ml of methanol, according to the method of J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Hoyt, *J. Am. Chem. Soc.*, **78**, 130 (1956).

water and evaporated to dryness under reduced pressure. To the yellow solid residue there was added 200 ml of methanol, 16 g of $NaOAc \cdot 3H_2O$, 40 ml of water, and 16 ml of AcOH; the resulting solution was refluxed for 4 hr. The methanol was evaporated and 200 ml of 4 *N* HCl was added to the residual mixture of oil and water, which was then extracted (CH_2Cl_2). The extract was washed with dilute base and water and was then dried and evaporated. Chromatography of the residual oil over silica gel (elution with 1:1 ether–pentane) followed by two crystallizations from acetonitrile gave 4.25 g of pure **15**, mp 162.5–163.5°, λ_{max} 242 mμ (ε 16,700), $[\alpha]^{25}D$ +70.2° [lit.[2] mp 158–159°, $[\alpha]^{22}D$ +62.2° (*c* 0.98), λ_{max} 241 mμ (ε 16,500)].

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.27; H, 9.93.

Steroids Possessing Nitrogen Atoms. III. Synthesis of New Highly Active Corticoids. [17α,16α-*d*]Oxazolino Steroids[1]

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The preparation of [17α,16α-*d*]-2′-methyloxazolino analogs of prednisone, prednisolone, and 9α-fluoroprednisolone, from 17α-azido-5α-pregnane-3β,16α-diol-11,20-dione 3,16-diacetate, is described. Preliminary pharmacological data show that the oxazolino analogs of prednisolone and 9α-fluoroprednisolone are significantly active when tested for neoglycogenetic and antiinflammatory activity in the rat.

In our previous paper[2] we described the preparation and demonstrated the structure of 5α-pregnan-3β-ol-11,20-dione[17α,16α-*d*]-2′-methyloxazoline (IIa). Due to the chemical stability of the oxazoline ring, this compound represented an excellent material for continuing our studies aimed at obtaining 17-nitrogen derivatives of steroid hormones. The present paper describes in detail the synthesis of the oxazoline analogs of prednisone, prednisolone, and 9α-fluoroprednisolone.

Starting from IIa which was prepared from the azide I by an improved method compared to that previously described,[2] we obtained excellent yields of pregnanetrione IIIa by oxidation with chromic acid in acetone. The introduction of a bromine atom followed by dehydrobromination led to the 1,2-dehydro derivative IV. Subsequent treatment with SeO_2 in *t*-butyl alcohol gave the diene V. This compound was more easily obtained from the 2,4-dibromo derivative IIIc by heating in dimethylformamide (DMF) with Li salts.

Attempts to introduce a bromine atom at C_{21} in the oxazoline II, under various experimental conditions, have failed. This absence of reactivity is not unusual in 16,17-disubstituted pregnane derivatives and is reported, for instance, for 17α-bromo-3β,16β-diacetoxy-5α-pregnan-20-one[3] and 16α,17α-dihydroxypregn-4-ene-3,20-dione 16,17-acetonide.[4] Allen and Weiss[4a] reported further that 16α,17α-isopropylidenedioxypregnan-20-one derivatives failed to give both 20-semicarbazones and 21-iodo compounds.

By contrast, good results were obtained in our 21-iodination of V according to the Ringold–Stork method modified by Rothman, *et al.*[5] The 21-iodo derivative reacted regularly with triethylammonium acetate to give the oxazoline analog of prednisone acetate (VI).

Conversion of VI into the 11β-hydroxy derivative *via* the 3,20-bis(semicarbazone), reduction with complex metal hydrides, and hydrolysis of the bissemicarbazone did not give appreciable yields of the required compound XII. It was found to be much more convenient to reduce the 20-semicarbazone VII, obtained from IIa, with $NaBH_4$. The facile conversion of IIa to the semicarbazone VII, when compared with the lack of reactivity of 20-ketopregnane-16α,17α-dihydroxyacetonides, suggests that other factors, and not merely steric hindrance, must intervene in order to explain the noteworthy different chemical behavior between the D-ring-fused oxazoline- and dioxolidine-pregnanes. The 11β-hydroxy derivative VIII was hydrolyzed to IX by merely boiling with HCl in aqueous methanol. This process has given better yields than other methods[6] which necessitate the use of pyruvic or nitrous acid. Selective oxidation of the 3-hydroxyl of IX, according to Oppenauer, led to the 3-keto derivative X, and the diene XI was obtained from this, by dibromination in dioxane and dehydrobromination with Li salts and DMF. 21-Acetoxylation performed as described for VI furnished the oxazoline analog of prednisolone (XII).

The synthesis of the 9α-fluoro derivative XV was performed in a routine manner, dehydrating[7] the 11β-hydroxy steroid XII to $\Delta^{1,4,9(11)}$-triene XIII; on adding HOBr to the 9,11 double bond and treating the bromohydrin with alkali the 9β,11β-epoxide XIV was obtained. Reaction of XIV with anhydrous HF supplied the required [17α,16α-*d*]-2′-methyloxazoline of 9α-fluoroprednisolone (XV).[8,9]

Biological Results.[10]—The compounds have been examined for neoglycogenetic[11] and antigranulomatous

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