

Totally Synthetic Steroid Hormones. XVII.¹
Further Studies on the Synthesis of *dl*-18-Methylandrosterone and
***dl*-18-Methylpregnane Derivatives**

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Received May 1, 1967

dl-18-Methyltestosterone (X) and *dl*-18-methylprogesterone (XXII) have been synthesized through the Simmons-Smith methylenation of *dl*-17 β -acetoxy-18-methylestr-5(10)-en-3 β -ol (IV). *dl*-18-Methylandrosterone-4-ene-3,17-dione (XV) has been synthesized through interacting *dl*-17 β -acetoxy-5 α ,10 α -epoxy-18-methylestran-3 α -ol (XII) with CH₂MgBr. The pure *dl*-17 β -acetoxy-18-methylestr-5(10)-en-3 α - and -3 β -ols III and IV have been prepared from *dl*-17 β -acetoxy-18-methylestr-5(10)-en-3-one (II) by a novel sequence involving epoxidation, NaBH₄ reduction, separation into the corresponding pure 5 α ,10 α -epoxy-3 α -ol XII, 5 β ,10 β -epoxy-3 β -ol XIII, and de-epoxidation. *dl*-17 β -Acetoxy-18-methylestr-5(10),9(11)-dien-3 α -ol (XXVI) has been selectively methylenated at the 5,10 position by the Simmons-Smith reagent and the product has been transformed to a steroid formulated as *dl*-17 β -acetoxy-9 α -chloromethylestr-4-ene-3-one (XXX). The progestational and antiestrogenic activities of *dl*-18-methylprogesterone XXII are reported and compared with the corresponding activities of progesterone, 19-norprogesterone, and *dl*-18-methyl-19-norprogesterone.

The biologically important properties which we recently reported³⁻⁹ for a series of totally synthetic *dl*-18-methylestrane (13 β -ethylgonane) derivatives necessitated the preparation of appropriate 10 β -methyl analogs. The preceding paper¹ described the total synthesis of several of such analogs through the introduction of a single carbon substituent at the 10 position of the *dl*-18-methylestrane nucleus. We now report syntheses using the same principle which provide alternate routes to *dl*-18-methyltestosterone, *dl*-18-methylprogesterone, and related substances.

***dl*-18-Methyltestosterone and *dl*-18-Methylandrosterone-4-ene-3,17-dione.**—Because 3-oxygenated 18-methylestrane derivatives were readily available from our earlier work³ we chose to prepare *dl*-18-methylandrosterone-4-ene-3-ones through the Simmons-Smith methylenation¹⁰ of appropriate 18-methylestr-5(10)-en-3-ols. Notably, testosterone has been obtained through a Simmons-Smith reaction with the 17 β -2'-tetrahydropyranyloxyestr-5(10)-en-3 β -ol present as a minor component in admixture with the corresponding 3 α -epimer,¹¹ and *dl*-8 α -androsterone-4-ene-3,17-dione has been formed by related experiments in the *dl*-8 α -estrane series.¹² Since the Simmons-Smith methylenation of homoallylic alcohols is stereochemically controlled by the configuration of the hydroxyl,^{11,13} *dl*-18-methylestr-

5(10)-en-3 β -ols were required. Reduction of the acetate II, of the corresponding alcohol I,^{3,14} with sodium borohydride in methanol gave a difficultly separable mixture of the corresponding 3-ols judged by thin layer chromatography to contain the epimers in a 4:1 ratio. By analogy with previous findings on the reduction of 17 β -acetoxy- and -propionoxyestr-5(10)-en-3-ones under similar conditions,¹⁵ the major component is expected to be the unwanted 3 α -ol III. After chromatography on silica gel, the mixture contained approximately equal amounts of the epimers and was treated with the Simmons-Smith reagent¹⁰ (prepared from an appropriately activated zinc-copper couple¹⁶) to afford a crystalline product apparently containing the cyclosteroid VII and unreacted III. This mixture, after oxidation with chromium trioxide in pyridine,¹⁷ readily yielded pure VIII and the latter, on keeping at room temperature in CHCl₃ saturated with HCl and reacylating the partially hydrolyzed product, gave *dl*-18-methyltestosterone acetate (IX) which was identical with a sample prepared through the addition of hydrogen cyanide to 17 β -hydroxy-18-methylestr-5(10)-en-4-one.¹ A similar process starting from pure IV (below) and involving a final saponification gave *dl*-18-methyltestosterone (X), identical with the previously described substance.¹ Having established the feasibility of the route from IV to IX, we next desired to increase the yield of IV. The use of different reagents for reducing II offered little hope for improvement since the corresponding ketol I with LiAlH₄, lithium tri-*t*-butoxyaluminum hydride, or Adam's catalyst in ethanol gave mixtures of 3-hydroxy epimers correspond-

(1) Part XVI: D. P. Strike, D. Herbst, and H. Smith, *J. Med. Chem.*, **10**, 446 (1967).

(2) Postal address: P.O. Box 8299, Philadelphia, Pa. 19101.

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(7) R. A. Edgren and H. Smith, "Hormonal Steroids, Biochemistry, Pharmacology, and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids," Vol. 2, Academic Press Inc., New York, N. Y., 1965, p 161.

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(14) This and other racemic steroids described in this paper are depicted by the enantiomorphs having the 13-alkyl group in the β configuration. Enantiomorphs with the same absolute configuration as the naturally occurring series are given the prefix *d* in accord with the convention proposed by L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 336.

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(16) E. LeGoff, *ibid.*, **29**, 2048 (1964).

(17) G. E. Arlt, G. I. Poots, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer, and L. H. Saret, *J. Am. Chem. Soc.*, **76**, 1715 (1954).

ing closely in composition to that formed from I with NaBH_4 in methanol, and reduction of I under Meerwein-Ponndorf conditions gave intractable mixtures. Accordingly, we sought to develop an alternate, more stereoselective synthesis of IV and also to invert the 3-hydroxyl groups in mixtures of III and IV containing ca. 80% of the former epimer. The most efficient synthesis involved an initial conversion of II with *m*-chloroperbenzoic acid in benzene to the gummy mixture of epoxides XI which, on thin layer chromatography, showed two components of closely similar polarity in approximately equal amounts. Reduction of the mixture with NaBH_4 in methanol at -70° , followed by a simple chromatography on alumina, gave two single epoxy alcohols XII and XIII, and deoxygenation of each by a procedure due to Cornforth, *et al.*,¹⁸ yielded III and IV, respectively. Using this route, XII, XIII, III, and IV were obtained from II in over-all yields of 37, 39, 14, and 27%, respectively, and II is convertible to X in an over-all yield of ca. 9.5%. The structures of III and IV follow from their pmr spectra which display signals for the C_3 protons at δ 3.85 and 4.03 ppm of half-height widths 19 and 10 cps, respectively, in good agreement with δ values of 3.77 and 4.0 ppm, and corresponding half-height widths of 19 and 11 cps, previously reported^{13a} for the 3 β - and 3 α -protons in 17 β -propionyloxyestr-5(10)-en-3 α - and -3 β -ols, respectively. We have no rigid proof for the stereochemistry at the 5 and 10 positions in XII, but the 5 α ,10 α -epoxy configuration may be deduced from the following data. Treatment of XII with CH_3MgBr in refluxing benzene-ether, followed by oxidation with the Jones reagent¹⁹ gave a hydroxydione, probably XIV, which was converted by methanolic KOH to the *dl*-18-methylandrostenedione XV, identical with a sample prepared by oxidizing *dl*-18-methyltestosterone. The 10 β -methyl configuration of the latter is well founded so that, assuming a normal *trans*-diaxial opening²⁰ of the epoxide ring by the Grignard reagent, a 5 α ,10 α -epoxy structure follows for XII and a 5 α ,10 β configuration for XIV. Accepting that the mixture XI contains approximately equal amounts of the two isomers, then the over-all yields of III, IV, XII, and XIII from II indicate that XII and XIII are derived from different epoxides, thus enabling the 5 β ,10 β -epoxy configuration to be assigned to XIII. This assignment could not be readily confirmed by oxidizing XII and XIII to different epoxy ketones, since conditions which were vigorous enough to oxidize the C_3 alcoholic group led to intractable products, probably because of concomitant fission of initially formed, labile 5,10-epoxy 3-ketones. However, supporting evidence was derived, as before, by interacting XIII with CH_3MgBr and oxidizing the product to obtain a hydroxydione $\text{C}_{20}\text{H}_{30}\text{O}_3$, which was recovered unchanged under conditions whereby XIV readily gave XV. This behavior is consistent with a 5-methyl-10-hydroxy structure for the hydroxydione and assuming a *trans*-diaxial scission of the epoxide ring, a 5 α ,10 β configuration for the hydroxydione, and a 5 β ,10 β -epoxy configuration for

XIII. The conversion of XII to XV constitutes a further total synthesis of the *dl*-18-methylandrostenone nucleus although the over-all yield from XII is very low (ca. 3%).

Inversion of the 3 α -oxy function in the crude mixture of III and IV obtained by NaBH_4 reduction of II was effected by conversion to the mixture of 3-tosylates XVI followed by refluxing with either potassium acetate in acetic anhydride-dimethylformamide,²¹ tetra-*n*-butylammonium acetate in methyl ethyl ketone,²² or allyl alcohol in benzene.²³ The products from the first two reactions, after saponification, gave the 3 β -ol VI in yields of 15 and 10%, respectively. That from the third reaction, after cleavage of the 17-acetoxy and 3-allyloxy groupings with Li in liquid ammonia, gave VI in an over-all yield of 15%.

A major by-product from the first reaction was a crystalline mixture shown by gas-liquid partition chromatography to contain at least three components in the ratios 47:43:10 (see Experimental Section). The pmr spectrum of this mixture displayed signals for allylic, vinylic, and aromatic protons as broad singlets at δ 2.60 and 5.70 and a complex multiplet in the δ 7.0-7.30 region, respectively, which are ascribable to the allylic, vinylic, and aromatic protons at C_1 - C_4 in structures of the types XVII and XVIII. The ultraviolet absorption spectrum showed λ_{max} 263 $\text{m}\mu$ (ϵ 1300) consistent with the presence of homoannular conjugated diene component(s).²⁴ Apparently, therefore, the by-product contains constituents derived from the elimination of the 3-tosyloxy group and subsequent dehydrogenation or disproportionation of the products. The evidence does not exclude the formation of monoolefinic steroids which could be formed in the disproportionation of XVII. The same by-product was formed, although in lower yield, by acylating the product of the third inversion reaction sequence. In no case did we detect the formation of 10-oxygenated 3,5-cyclosteroids as has been previously observed^{18a,25} during the solvolysis of various 3 α - and 3 β -mesyloxyestr-5(10)-enes. After the completion of our work Levine and his colleagues^{15b} reported the conversion of 17 β -propionyloxyestr-5(10)-en-3 α -ol to its 3 β -epimer in an over-all yield of 50% by conversion to the 3 α -mesylate, displacement of the 3-mesyloxy group by refluxing in acetone with tetramethylammonium formate, and saponification of the resulting formate. They also disclosed the formation of an uncharacterized by-product described as a ring A diene mixture.

dl-18-Methylprogesterone, which was required for comparison of its biological activities with those of progesterone and *dl*-18-methyl-19-norprogesterone,⁹ was synthesized from VIII through initial ketalization, saponification, and oxidation with chromium trioxide

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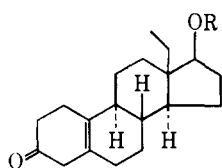
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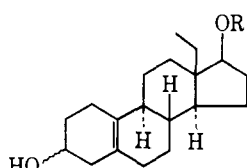
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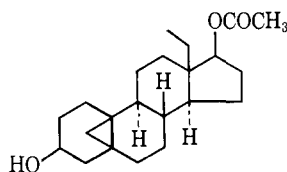
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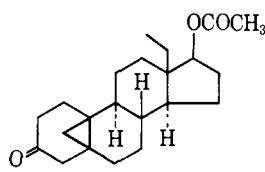
I, R = H
II, R = COCH₃



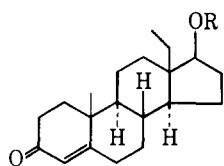
III, 3 α -OH; R = COCH₃
IV, 3 β -OH; R = COCH₃
V, 3 α -OH; R = H
VI, 3 β -OH; R = H



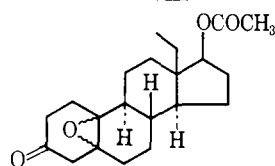
VII



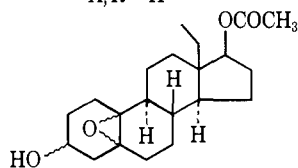
VIII



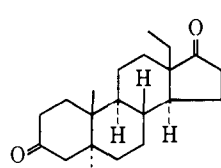
IX, R = COCH₃
X, R = H



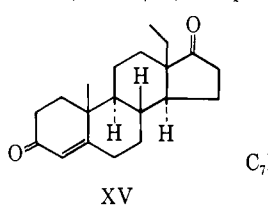
XI



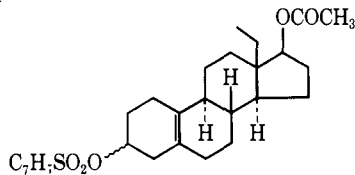
XII, 3 α -OH; 5 α , 10 α -epoxide
XIII, 3 β -OH; 5 β , 10 β -epoxide



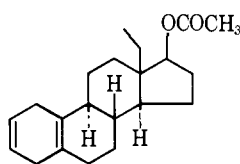
XIV



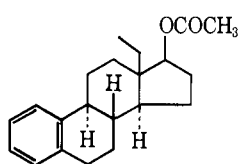
XV



XVI



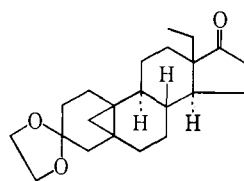
XVII



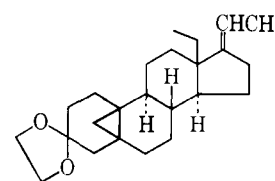
XVIII

pyridine,¹⁷ to the oxoketal XIX, which was converted by ethylenetriphenylphosphorane to the pregnene XX. The latter is assigned a configuration in which the C₂₀-hydrogen is *anti* to the main bulk of the steroid nucleus, on the basis of its pmr spectrum which displays the C₂₀-proton as a quartet centered at δ 5.18, and the C₂₁-protons as a doublet at δ 1.67. In a related series of 17-ethylidene-18-methylestrane derivatives having the same geometrical configuration, these protons have been observed in the ranges δ 5.22–5.25 and 1.73–1.78, respectively, whereas in the corresponding geometrical isomers in which the C₂₀-proton is *syn* to the main bulk of the steroid nucleus, they lie within the ranges δ 4.99–5.09 and 1.58–1.61, respectively.^{9,26}

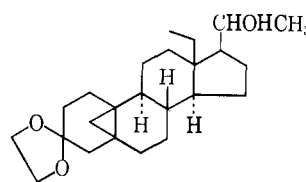
Hydroboration of XX followed by H₂O₂ oxidation gave the crude alcohol XXI to which the 20 α -hydroxy configuration can be assigned, assuming the usual α -face attack of diborane and oxidation of the resulting borane without inversion of configuration. Jones' oxidation followed by treatment at room temperature with CHCl₃-HCl transformed XXI to the required *dl*-18-methylprogesterone XXII in 13% over-all yield from VIII. The 17 β -acetyl configuration in XXII is confirmed by the pmr spectrum which displays the 18 α -methyl protons as a triplet centered at δ 0.70 in agreement with the value δ 0.67 found for 18-methylprogesterone²⁷ and *dl*-18-methyl-19-norprogesterone.⁹ As with *dl*-18-methyl-19-norprogesterone,⁹ treatment with methanolic KOH equilibrates the 17 β -acetyl group in XXII with formation of a mixture shown by pmr spectroscopy (*cf.* ref 9) to contain the 17 β and 17 α epimers in a ratio of *ca.* 1:3.



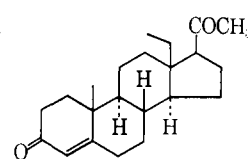
XIX



XX



XXI



XXII

Simmons-Smith Methylenation of *dl*-17 β -Acetoxy-18-methylestra-5(10),9(11)-dien-3 α - and -3 β -ols.—We wished to determine whether the Simmons-Smith methylenation of a gona-5(10),9(11)-dien-3-ol would be selectively directed to the 5(10) double bond by the 3-hydroxyl group. The alcohols XXVI and XXVII required for this study were prepared as a crystalline mixture by reducing the dienone XXV with NaBH₄, XXV being obtained from II by a standard route²⁸ involving bromination-dehydrobromination, conversion of the resulting dienone XXIII to the enamine XXIV, and formic acid hydrolysis. Simmons-Smith methylenation of the mixture of XXVI and XXVII at 90° under pressure¹¹ afforded, after chromatography, two products in yields of 24 and 8%, respectively. The pmr spectra of both substances displayed geminal cyclopropyl and vinylic proton signals in the δ 0.5–0.70 and 5.40–5.75 regions, respectively, thereby confirming methylenation at the 5(10) rather than the 9(11) positions. Catalytic hydrogenation of the mixture of XXVI and XXVII gave an almost quantitative yield of a product resulting from saturation of the 9(11) double bonds and containing, from thin layer chromatography, *ca.* 80% of III and 20% of IV. It therefore follows that the major methylenation product is derived from the major component XXVI, and, assuming stereochemical control of the introduction of the C₁₉-methylene by the 3-hydroxyl group, is formulated

(26) B. Gadsby and A. P. A. Jansen (John Wyeth and Brother Ltd., Taplow, England) and D. P. Strike, R. P. Stein, and H. Smith, unpublished work.

(27) G. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, **31**, 1026 (1966).

(28) G. Nominé and R. Bucourt, U. S. Patent 3,033,856 (1962).

as XXVIII. Oxidation of XXVIII with the Jones' reagent¹⁹ gave an oily ketone which, on treatment with $\text{CHCl}_3\text{-HCl}$, afforded a chloro ketone $\text{C}_{22}\text{H}_{31}\text{ClO}_3$, λ_{max} 242 μ (ϵ 13,100), to which structure XXX is assigned as follows. The pmr spectrum shows no high-field signal characteristic of a newly introduced methyl group, but an AB four-line resonance pattern at δ 3.32, 3.51, 3.58, and 3.77 (outer lines rather diffuse), $J = 11$ cps, which is consistent with a quaternary chloromethyl group (*cf.* ref 29). The spectrum also displays a vinylic proton signal as a broad, ill-resolved singlet of half-height width $\bar{\nu}$ cps which is closely similar in shape to that shown by the C_4 -proton in various Δ^4 -3-ketonic 19-norsteroids,³⁰ and attributable to the C_4 -proton strongly coupled with the axial 6β - and 10β -protons in the structure XXX. The mass spectrum confirms the estrane structure showing, besides a principal ion at m/e 378 (corresponding to XXX with the loss of hydrogen chloride), an ion at m/e 110, corresponding to the radical ion XXXI.³¹ We therefore formulate the chloro ketone as XXX and suggest that its production

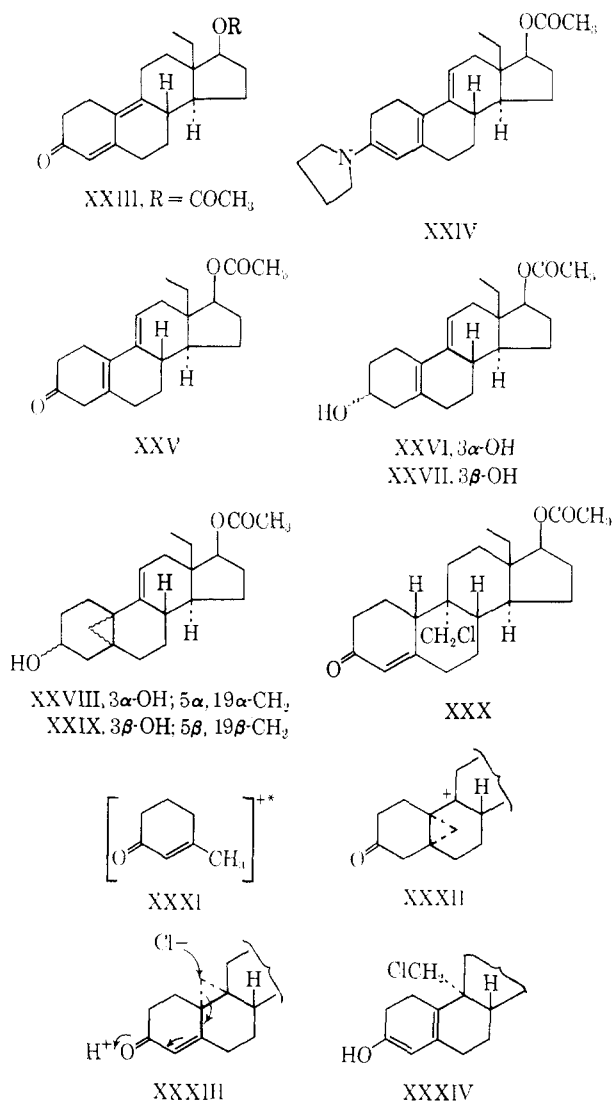


TABLE I

RELATIVE PROGESTATIONAL AND ANTIESTROGENIC ACTIVITIES OF PROGESTERONE AND ITS HOMOLOGS

Compound	Prog. ^a	Antiest. ^b
Pregesterone	100	100
19-Norprogesterone	800	1000
<i>dl</i> -18-Methyl-19-norprogesterone	1000	2500
<i>dl</i> -18-Methylprogesterone	25	300

^a Progestational activity. ^b Antiestrogenic activity.

from XXVIII may involve initial protonation of the 9(11) bond to give a cation XXXII, which, by deprotonation at C_4 and the appropriate electron pair shift or shifts, can form the ketone XXXIII. Protonation of the C_3 -carbonyl and attack by Cl^- or its equivalent at C_{13} as shown would then give XXXIV which, under the reaction conditions, would be expected to ketonize to the more stable of the two possible 10 epimers.

Biological Activities.—The progestational and antiestrogenic properties of *dl*-18-methylprogesterone were determined in the Clauberg test,³² and a vaginal cornification inhibitory test,³³ respectively. The results are given in Table I together with those obtained in these laboratories for the homologs, 19-norprogesterone and *dl*-18-methyl-19-norprogesterone. Baddeley, *et al.*,³⁴ have described the synthesis of *d*-XXII by an alternate process without disclosing its biological properties. The data show that, of the four compounds in Table I, the 19-nor and 18-methyl-19-nor homologs of progesterone possess the greatest potential clinical utility as progestational and antifertility agents. Similarly, in the testosterone series various 19-nor and 18-methyl-19-nor compounds have proved superior in experimental animals as anabolic, progestational, and antiestrogenic agents to their corresponding androstane and 18-methyl-androstane analogs.¹ Since it has been shown that the progestational, antiestrogenic, and androgenic properties of various *dl*-18-methylestrane derivatives are confined to the enantiomorphs corresponding in absolute configuration to the natural steroids,^{35,36} the *d* enantiomorph corresponding to the racemate XXII probably has twice the biological potencies shown.

Experimental Section

All evaporations were under reduced pressure. Melting points were taken on a Kofler block under microscopic magnification or in capillary tubes using the Thomas-Hoover apparatus. Ultraviolet absorption spectra (uv) were recorded in 95% ethanol solution on a Perkin-Elmer 450 spectrophotometer. Infrared absorption spectra (ir) were obtained in KBr or Nujol dispersions using a Perkin-Elmer Model 21 spectrophotometer and were compatible with the assigned structures. Except where stated otherwise pmr spectra were measured with a Varian Associates A-60 spectrometer on 10–15% solutions in CDCl_3 containing $(\text{CH}_3)_4\text{Si}$ as internal reference standard. Chemical shifts are expressed in δ units measured downfield from the reference, and coupling constants, J , in cps. The former should be accurate to ± 0.01 ppm, the latter to ± 0.5 cps. Thin layer chromatography (tlc) was conducted on silica gel chromatoplates prepared with rice starch as binder³⁴ under irrigation with benzene-ethyl acetate mixtures. Thin layer chromatograms were visualized with acidified phosphomolybdic acid reagent. Gas-liquid partition chromatography (glpc) was performed with a Perkin-Elmer vapor fractometer Model 154-C with the sample in CH_2Cl_2 at a flow rate of 80 cc/min of He on a 2-m column packed with Celite

(29) R. Giugig and A. D. Cross, *J. Org. Chem.*, **31**, 1761 (1966).

(30) T. W. Widdarack, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).

(31) V. I. Zaretskii, N. S. Wulfson, and V. L. Sadovskaya, *Tetrahedron Letters*, 3879 (1966).

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containing 3% w/w fluorosilicone QF-1 as the stationary phase. Mass spectra were determined on an Atlas CH 4 mass spectrometer.

***dl*-17 β -Acetoxy-18-methylestr-5(10)-en-3-one (II).**—*dl*-17 β -Hydroxy-18-methylestr-5(10)-en-3-one³ (70 g) was kept overnight at room temperature in Ac₂O-pyridine (350:400 ml). The product was recrystallized from hexane-ether to give the acetate (50.0 g), mp 109–114°. The analytical sample had mp 110–114° (from hexane-ether).

Anal. Calcd for C₂₁H₃₀O₃: C, 76.32; H, 9.15. Found: C, 76.26; H, 9.38.

***dl*-17 β -Acetoxy-5 α ,10 α -epoxy-18-methylestran-3 α -ol (XII) and *dl*-17 β -Acetoxy-5 β ,10 β -epoxy-18-methylestran-3 β -ol (XIII).**—II (40.2 g) was stirred for 10 min at room temperature with 80% *m*-chloroperbenzoic acid (36 g) in benzene (1.75 l.). The mixture was washed with 5% aqueous NaOH and water, then dried and evaporated to an oily mixture of the epoxides XI (42.9 g) which was stirred for 2 hr at –70° (bath) with NaBH₄ (21.5 g) in methanol (2 l.). Acetic acid (7.5 ml) was then added over 2 hr (bath –70°); the mixture was allowed to warm to room temperature, concentrated to 500 ml, diluted with water, and extracted (CHCl₃). The extracts were washed with 5% aqueous KHCO₃ and water, dried, and evaporated to an oily solid (44.6 g) which was chromatographed on neutral alumina. Elution with benzene gave the β -oxide XIII (16.5 g). An aliquot after two recrystallizations from acetone-hexane gave the analytical sample: mp 126–128°; nmr, triplet δ 0.93, J = 7 cps (18a-H), 3-proton singlet δ 2.04 (acetate CH₃), 1-proton multiplet δ 3.80, half-height width 16 cps (3 α -H), 1-proton triplet δ 4.68, J = 8 cps (17 α -H).

Anal. Calcd for C₂₁H₃₂O₄: C, 72.38; H, 9.26. Found: C, 72.43; H, 9.14.

Elution of the chromatogram with ether-benzene (1:4) gave the α -oxide (15.9 g). An aliquot, after two recrystallizations from acetone-hexane, had mp 155–158°; nmr, triplet δ 0.95, J = 6 cps (18a-H), 3-proton singlet δ 2.02 (acetate CH₃), 1-proton multiplet δ 3.59, half-height width 20 cps (3 β -H).

Anal. Found: C, 72.34; H, 8.87.

***dl*-17 β -Acetoxy-18-methylestr-5(10)-en-3 α -ol (III).**—XII (1.0 g) was added to a stirred suspension of zinc dust (1.6 g) in AcOH-H₂O (25:3 ml) containing NaI (1.5 g) and NaOAc (0.52 g). The mixture was stirred at room temperature for 1 hr, filtered, diluted with ether, and washed successively with water, 5% KHCO₃, and water, dried, and evaporated. The residue was chromatographed on neutral alumina and the product was eluted with 1:1 benzene-hexane and recrystallized from hexane-acetone to give the alcohol (0.32 g): mp 122–123°; nmr, 3-proton triplet δ 0.93, J = 7 cps (18a-H), 3-proton singlet δ 2.03 (acetate CH₃), 1-proton multiplet δ 3.85, half-height width 19 cps (3 β -H), 1-proton triplet δ 4.75, J = 7 cps (17 α -H).

Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 75.98; H, 9.59.

***dl*-18-Methylestr-5(10)-ene-3 α ,17 β -diol (V).**—III (1.0 g) was refluxed in methanol-10% aqueous NaOH (100:10 ml) for 1 hr. Recrystallization of the product from acetone-ether gave the diol V (0.7 g), mp 152–154°.

Anal. Calcd for C₁₉H₃₀O₂: C, 78.57; H, 10.41. Found: C, 78.26; H, 10.37.

***dl*-17 β -Acetoxy-18-methylestr-5(10)-en-3 β -ol (IV).**—XIII (15.1 g) in AcOH-H₂O (150:10 ml) was added over 15 min at 0° (bath) to a stirred suspension of zinc dust (24 g) in AcOH-H₂O (185:15 ml) containing NaI (24 g) and NaOAc (7.8 g). The mixture was stirred for 1 hr at room temperature, filtered, and concentrated to 100 ml, and the resulting slurry was dissolved in ether. The solution was washed successively with water, 10% aqueous NaHSO₃, 5% aqueous KHCO₃, and water, dried, and evaporated. The residue in benzene was filtered through neutral alumina, and the product was recrystallized from ether-hexane to give the alcohol (9.9 g), mp 117–118°. An aliquot, after two recrystallizations from ether-hexane, gave the analytical sample: mp 118–120°; nmr, 3-proton triplet δ 0.93, J = 7 cps (18a-H), 3-proton singlet δ 2.03 (acetate CH₃), 1-proton multiplet δ 4.03, half-height width 10 cps (3 α -H), 1-proton triplet δ 4.71, J = 8 cps (17 α -H).

Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 75.59; H, 9.47.

***dl*-18-Methylestr-5(10)-ene-3 β ,17 β -diol (VI).**—IV (0.4 g) was refluxed in methanol-10% aqueous KOH (100:10 ml) for 1 hr. Recrystallization of the product from ether gave the diol (0.3 g): mp 191–195°; nmr [in CDCl₃-(CD₃)₂SO, 9:1], 3-proton triplet δ 0.92, J = 7 cps (18a-H), 1-proton triplet δ 3.67, J = 8 cps

(17 α -H), 1-proton multiplet δ 3.93 (3 α -H), half-height width ca. 14 cps.

Anal. Calcd for C₁₉H₃₀O₂: C, 78.57; H, 10.41. Found: C, 78.47; H, 10.57.

***dl*-17 β -Acetoxy-18-methyl-5 β -cycloandrostan-3 β -ol (VII).**—IV (13 g) in ether (200 ml) was added during 20 min to a refluxing suspension of zinc-copper couple¹⁶ (35 g) in CH₂I₂-ether (70 g:300 ml), with slow distillation of the ether to maintain a constant volume. The cooled mixture was added to ice-water and extracted (CHCl₃), and the extracts were washed with aqueous NaHCO₃ and dried. The crude crystalline product (9.75 g) after recrystallization from ether gave the alcohol (8.6 g): mp 156–157°; nmr, 2-proton singlet δ 0.39 (19-H), 3-proton triplet δ 0.93, J = 6.5 cps (18a-H), 3-proton singlet δ 2.01 (acetate CH₃), 1-proton multiplet δ 3.58 (3 α -H), 1-proton triplet δ 4.65, J = 7.5 cps (17 α -H). A second crop (0.44 g) was obtained by concentration of the mother liquors.

Anal. Calcd for C₂₂H₃₄O₃: C, 76.26; H, 9.89. Found: C, 76.40; H, 9.40.

***dl*-17 β -Acetoxy-18-methyl-5 β ,19-cycloandrostan-3-one (VIII).**—Chromic acid¹⁰ (8 N) was added during 1 min to VII (2.85 g) in acetone at 0° (bath). The cooling bath was removed, and, after 15 min, the solution was added to ice-water and the resulting mixture was extracted with ethyl acetate. Recrystallization of the product from hexane gave the ketone (2.15 g), mp 130–136°. The analytical sample had mp 134–136° (from ether); nmr, 2-proton singlet δ 0.49 (19-H), 3-proton triplet δ 0.93, J = 6.5 cps (18a-H), 3-proton singlet δ 2.02 (acetate CH₃), 2-proton singlet δ 2.52 (4-H), 1-proton triplet δ 4.68, J = 8.0 cps (17 α -H).

Anal. Calcd for C₂₂H₃₂O₃: C, 76.70; H, 9.36. Found: C, 76.90; H, 9.11.

***dl*-17 β -Acetoxy-18-methylandrostan-4-en-3-one (*dl*-18-Methyltestosterone Acetate) (IX).**—VIII (60 mg) was kept at room temperature for 60 hr in CHCl₃ (15 ml) previously saturated at room temperature with HCl. Evaporation of the washed and dried solution gave crystals (40 mg) which were kept overnight at room temperature in pyridine-acetic anhydride (0.3:0.25 ml). Recrystallization of the product from hexane-ether gave the acetate (25 mg), mp 158–161°, identical in uv, ir, and pmr spectra with material prepared as previously described.¹

Anal. Calcd for C₂₂H₃₂O₃: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.07.

***dl*-17 β -Hydroxy-18-methylandrostan-4-en-3-one (*dl*-18-Methyltestosterone) (X).**—VII (2.25 g) was kept for 60 hr at room temperature in CHCl₃ (120 ml) previously saturated with HCl at room temperature. The product, which was shown by tlc to contain IX and X in a 7:3 ratio, was refluxed for 40 min in methanol-10% aqueous KOH (100:10 ml). The product was percolated in CHCl₃-CH₃OH-methanol (98:2) through silica gel and recrystallized from acetone to give the alcohol (1.5 g), mp 182–187°, having an infrared absorption spectrum identical with a sample prepared as described previously.¹

Inversion Experiments with Mixtures of *dl*-17 β -Acetoxy-18-methylandrostan-5(10)-en-3 α - and -3 β -ols. A.—The mixture of III and IV (3 g, total crude product obtained by reducing II with NaBH₄ in CH₃OH) was kept at room temperature for 16 hr with *p*-toluenesulfonyl chloride (3 g) in pyridine (80 ml) to give the oily product XVI (3.4 g) which was uniform by tlc. XVI (2 g) was kept at 115–120° (internal temperature), for 4 hr with KOAc (5.25 g) in DMF-Ac₂O-H₂O (45:3:1.5 ml). The cooled mixture was added to water and extracted with ether and the product was chromatographed on silica gel (80 g). Elution with hexane-benzene (2:3) gave crystals (0.65 g) which were recrystallized from methanol to give the mixture containing XVII, XVIII, and homoannular diene component(s) (0.46 g): mp 114–115°; uv, λ_{max} 263, 272.5, and 288 (sh) m μ (ϵ 1300, 1000, and 350); ir, λ_{max} 3.50, 5.75, 6.25, 6.75, 8.05, and 13.50 μ ; nmr, triplet δ 0.92, J = 6.5 cps (18a-H), singlets δ 2.01 and 2.02 (acetate CH₃), broad singlet δ 2.60 (1- and 4-H in XVII), triplet δ 4.72, J = 8 cps (17 α -H), broad singlet δ 5.70 (2- and 3-H in XVII), multiplet δ 7.0–7.30 (aromatic H in XVIII); glpc, three components retention times 9 min, 10 min 12 sec, and 12 min 36 sec in the ratios 10:47:43.

Anal. Calcd for C₂₁H₂₈O₂, C₂₁H₃₀O₂: C, 80.7, 80.2; H, 9.0, 9.6. Found: C, 80.9; H, 9.3.

Elution with benzene-ethyl acetate (9:1) gave a product (0.57 g) which was rechromatographed on silica gel to give an oil (0.325 g). The latter was kept at room temperature for 72 hr in methanol-10% aqueous KOH (40:4 ml). The product was recrystallized

lized from ether to give $\beta\beta,17\beta$ -diol VI (0.15 g), mp 181–191°, identical with that prepared by saponification of IV.

Anal. Calcd for $C_{26}H_{42}O_2$: C, 78.57; H, 10.41. Found: C, 78.47; H, 10.37.

B. XVI (1 g, prepared as in A) was refluxed for 60 hr with tetra-*n*-butylammonium acetate²² (3 g). The cooled mixture was poured into water and extracted with ether, and the extracts were washed successively with 2 *N* HCl, saturated aqueous $NaHCO_3$, and water. The product was kept at room temperature for 36 hr in methanol-10% aqueous KOH (40:4 ml). The product was recrystallized from ether to give crude VI (0.1 g), mp 158–168°, having an infrared absorption spectrum identical with the sample prepared as in A.

C. XVI (0.5 g) was refluxed for 60 hr with allyl alcohol-benzene (20:20 ml). The oily product (0.5 g) was kept for 48 hr in methanol-10% aqueous KOH (40:4 ml). Li (0.17 g) was added piecemeal with stirring to the resulting oil in THF-liquid NH_3 (35:100 ml), and after 1 hr ethanol (5 ml) was added followed by water (200 ml). The precipitate was filtered off, dried, and recrystallized from ether to give VI (40 mg), mp 172–176°, identical in its spectrum with the material prepared as in A. The residue in the mother liquors was chromatographed on silica gel (40 g), elution with benzene-ethyl acetate giving an oil which, after acylation with acetic anhydride in pyridine, gave a mixture containing XVII, XVIII, etc., mp 114–115°, which was closely similar in spectral properties to that obtained as in A.

***dl*-18-Methylandrosta-4-ene-3,17-dione (XV).** **A.**—Chromic acid¹⁹ (0.3 ml) (8 *N*) was added dropwise with stirring to X (25 mg) in acetone (10 ml) until a red color persisted. Stirring was continued for 30 min and 2-propanol was added dropwise until a green color persisted. The product was recrystallized from acetone-hexane to give the dione XV (18 mg); mp 164–166°; uv, λ_{max} 240 $m\mu$ (ϵ 15,600); nmr, triplet δ 0.80, $J = 7$ cps (18 α -H), 3-proton singlet δ 1.20 (19-H), 1-proton singlet δ 5.73 (4-H).

Anal. Calcd for $C_{26}H_{42}O_2$: C, 79.95; H, 9.39; M, 300. Found: C, 79.65; H, 9.27; M (by mass spectrometry), 300.

B.—XII (2 g) was refluxed for 18 hr under N_2 with 3 *M* ethereal CH_3MgBr (100 ml) in benzene (300 ml). The mixture was added to ice-water, acidified (HCl), and extracted with $CHCl_3$, and the product was chromatographed on neutral alumina. Elution with benzene-ether (3:2) gave a product which was recrystallized twice from $CHCl_3$ to give crude *dl*-18-methylandrosta-3 α ,5 α ,17 β -triol (0.14 g), mp 178–183°, which was dissolved in acetone (200 ml) and treated dropwise with 8 *N* H_2CrO_4 ¹⁹ until a red color persisted. The resulting solid product (0.115 g); ir, λ_{max} 5.85 μ ; uv, no selective light absorption in the 220–250- $m\mu$ region) was kept at room temperature for 1.5 hr in 5% methanolic KOH (30 ml) and the resulting oil was chromatographed on neutral alumina. Elution with benzene gave crystals (50 mg) which were recrystallized from acetone-hexane to give XV, mp 152–157°, undepressed by the sample prepared as in A and showing identical tlc behavior, identical ir and nmr spectra, and an identical mass spectrum, apart from a minor extraneous peak at m/e 310, with the sample prepared as in A.

***dl*-5 α ,18-Dimethyl-10 β -hydroxyestrane-3,17-dione.**—XIII (0.9 g) was treated with CH_3MgBr as in the previous experiment and the product was oxidized with 8 *N* H_2CrO_4 in acetone in the usual way. The resulting solid (0.5 g) was chromatographed on neutral alumina, elution with benzene-ether (9:1) giving crystals (130 mg) which were recrystallized twice from acetone-hexane to give the dione (90 mg); mp 195–200°; nmr, 3-proton triplet δ 0.77, $J = 7$ cps (18 α -H), 3-proton singlet δ 1.25 (5 α -H). The dione was recovered unchanged on treatment with 5% methanolic KOH under conditions whereby XIV gave XV.

Anal. Calcd for $C_{28}H_{46}O_2$: C, 75.43; H, 9.50. Found: C, 75.48; H, 9.21.

***dl*-3,3-Ethylenedioxy-5 β ,19-cycloandrostan-17-one (XIX).**—VIII (8.5 g) was refluxed for 16 hr with stirring in benzene (1 l.) containing ethylene glycol (50 ml) and *p*-toluenesulfonic acid (0.5 g) (Dean-Stark water separator). The crude product, on recrystallization from acetone-hexane, gave *dl*-17 β -acetoxy-3,3-ethylenedioxy-5 β ,19-cycloandrostanone (6 g), mp 120–123°. This substance was combined with a second crop (4 g) from the mother liquors and refluxed with KOH in methanol-water (200:20 ml) for 45 min. The resulting solid (7.9 g) was added with stirring at 0° to CrO_3 (15 g) in pyridine (500 ml). Stirring was continued for 15 min at 0° and 2 hr at room temperature, and the mixture was added to water (2 l.) and extracted with ether. The product, after recrystallization from acetone-hexane, gave the ketone (5.2 g), mp 167–169°. The analytical sample, obtained after

two further recrystallizations from acetone-hexane had mp 170–172°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.78; H, 9.21.

***dl*-3,3-Ethylenedioxy-5 β ,19-cyclopregnan-20-one (XXI).** Sodium hydride (4.4 g of 50% mineral oil dispersion) was stirred at 80° under N_2 with DMSO (75 ml) until H_2 evolution ceased. Ethyltriphenylphosphonium bromide (49 g) in DMSO (150 ml) was added with stirring to the cooled solution followed by XIX (4.4 g) in benzene, and the mixture was stirred for 2.5 hr at room temperature and 17 hr at 80°. The cooled mixture was added to water and extracted with ether. The product in benzene was percolated through neutral alumina to give crystals (0 g) which were recrystallized from ether-hexane to give triphenylphosphine oxide (2.9 g), mp 155–156°. Evaporation of the mother liquors gave a residue which was chromatographed on neutral alumina. Elution with hexane gave crude XX (4.4 g). Recrystallization from hexane gave a sample; mp 89–92°; nmr, 2-proton AB system pair of doublets δ 0.38 and 0.49, $J = 4.5$ cps (19-H), doublet δ 1.67, $J = 7.5$ cps (21-H), 1-proton singlet δ 3.87 (ketal bridge), 1-proton quartet δ 5.18, $J = 7.5$ cps (20-H). Diborane (1 *M*) in THF (25 ml) was added under N_2 during 10 min to crude XX (3.5 g) in THF. The mixture was stirred for 1 hr at room temperature and 10% aqueous NaOH (70 ml) was added over 15 min. H_2O_2 (30%) (55 ml) was added during 20 min at 0° (bath) and stirring was continued for 1 further hr. The mixture was diluted with ether and the ether solution was washed successively with water, 10% aqueous $NaHSO_4$, and water and dried. The solid product (3.7 g) was chromatographed on neutral alumina, elution with benzene giving the alcohol (2.1 g), mp 149–151°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.96; H, 10.23. Found: C, 77.08; H, 10.04.

***dl*-18 α -Methylprogesterone (XXII).**—XXI (2.6 g) was kept at room temperature for 17 hr in $CHCl_3$ (270 ml) previously saturated with HCl at room temperature. Chromic acid (8 *N*)¹⁹ was added to the oily product in acetone (100 ml) until a red color persisted. The product, after three recrystallizations from acetone, gave the ketone (0.82 g); mp 178–180°; λ_{max} 241 $m\mu$ (ϵ 15,800); nmr, 3-proton triplet δ 0.69, $J = 7$ cps (18 α -H), 3-proton singlet δ 1.20 (19-H), 3-proton singlet δ 2.20 (21-H), 1-proton singlet δ 5.71 (4-H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.57; H, 9.70.

***dl*-17 β -Acetoxy-18-methylestra-4,9-dien-3-one (XXIII).**—II (35 g) was heated on the steam bath for 1 hr with perchloropyridine hydrobromide (36 g) in pyridine (350 ml). The cooled mixture was filtered, the filtrate was evaporated, and the residue was dissolved in benzene. The solution was washed with 2 *N* HCl and water, dried, and evaporated to an oil which was crystallized from ether to give the ketone, mp 124–127° (23 g). The analytical sample had mp 124–126° (from ether), λ_{max} 303 $m\mu$ (ϵ 21,300).

Anal. Calcd for $C_{25}H_{42}O_2$: C, 76.79; H, 8.59. Found: C, 76.48; H, 8.08.

***dl*-17 β -Acetoxy-18-methyl-3-(1-pyrrolidino)estra-3,5(10,9(11)-triene (XXIV).**—XXIII (23 g) and pyrrolidine (20 ml) were heated for 5 min on the steam bath. The solution was diluted with methanol (200 ml) and heated for 20 min. Filtration of the cooled solution gave the enamine (23 g), mp 154–174°. The analytical sample had mp 164–174° (from methanol); uv, λ_{max} 296 $m\mu$ (ϵ 11,200); nmr, 3-proton triplet δ 0.93, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.01 (acetate CH_3), 4-proton multiplet δ 3.18 (H next to N in pyrrolidine ring), 1-proton singlet δ 4.38 (4-H), 1-proton triplet δ 4.80, $J = 7.5$ cps (17 α -H), 1-proton doublet δ 5.28, $J = 5$ cps (11-H).

Anal. Calcd for $C_{25}H_{42}NO_2$: C, 78.67; H, 9.25; N, 3.67. Found: C, 78.68; H, 8.56; N, 3.74.

***dl*-17 β -Acetoxy-9 α -chloromethyl-18-methylestra-4-en-3-one (XXX).**—XXIV (22 g) was kept at room temperature for 3 min in 98% HCO_2H (30 ml). After 10 min water (100 ml) was added, and after a further 20 min the mixture was extracted with ether. Recrystallization of the product from hexane gave the crude XXV (14.4 g); mp 80–86°; uv, λ_{max} 240 $m\mu$ (ϵ 17,000); nmr, 3-proton triplet δ 0.96, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.06 (acetate CH_3), 2-proton singlet δ 2.87 (4-H), 1-proton triplet δ 4.82, $J = 8$ cps (17 α -H), 1-proton doublet δ 5.60, $J = 5$ cps (11-H). XXV (6 g) was kept in methanol (100 ml) containing $NaBH_4$ for 1 hr at 0° (bath) and 1 hr at room temperature. Recrystallization of the product from hexane

ether gave the mixture of XXVI and XXVII (4.2 g): mp 110–120°; *uv*, λ_{\max} 237 (sh), 242.5, 251 (sh) $m\mu$ (ϵ 18,852, 19,820, 13,070); nmr, 3-proton triplet δ 0.92, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.08 (acetate CH₃), 1-proton multiplet (broad) δ 3.92 (3 ξ -H), 1-proton triplet δ 4.80, $J = 8$ cps (17 α -H), 1-proton doublet, $J = 5.5$ cps (11-H). An aliquot (166 mg) of the foregoing mixture was shaken at atmospheric pressure with H₂ in methanol (10 ml) containing 5% Pd-C (100 mg) until 12 ml of gas had been absorbed (30 min). Recrystallization of the product from ether-pentane gave a mixture containing III and IV, mp 109–112°, having a closely similar infrared absorption spectrum to a mixture of III and IV obtained from the NaBH₄ reduction of II, and shown by tlc to contain ca. 80% of III and 20% of IV. The mother liquors of this material were shown by tlc to contain the same mixture. The mixture of XXVI and XXVII (2 g) was treated with Zn-Cu couple (10 g) and CH₂I₂ (20 g) in ether (150 ml) for 1 hr as previously described, and the mixture was heated in an autoclave for 3 hr at 90°. Trituration of the crude product with ether gave crystals formulated as XXIX (0.12 g): mp 170–180° (after preliminary softening at 150°); nmr, 2-proton singlet δ 0.70 (19-H), 3-proton triplet δ 0.93, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.04 (acetate CH₃), 1-proton multiplet δ 3.63 (broad), half-height width 30 cps (3-H), 1-proton triplet δ 4.82, $J = 8$ cps (17 α -H), 1-proton doublet δ 5.43, $J = 5.5$ cps (11-H). The residue in the mother liquors was chromatographed on neutral alumina (60 g), benzene-hexane (1:1) eluting unidentified material (0.72 g), possibly 3-alkoxy steroids,¹¹ and benzene-ethyl acetate (9:1) eluting a gum (0.51 g) formulated as XXVIII: nmr, 2-proton singlet δ 0.55 (19-H),

3-proton triplet δ 0.97, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.10 (acetate CH₃), 1-proton multiplet δ 3.63 (broad), half-height width 30 cps (3-H), 1-proton triplet δ 4.91, $J = 8$ cps (17 α -H), 1-proton doublet δ 5.72, $J = 5.5$ cps (11-H). Benzene-ethyl acetate (8:2) eluted further XXIX (0.04 g). XXVIII (0.04 g) was oxidized with 8 *N* H₂CrO₄ (0.04 ml) in acetone (10 ml) and the product was worked up as usual to give an oily ketone (0.032 g) uniform by tlc; nmr, 2-proton AB system pair of doublets δ 0.55 and 0.80, $J = 5.5$ cps (19-H), 3-proton triplet δ 0.97, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.08 (acetate CH₃), 2-proton singlet δ 2.52 (4-H), 1-proton triplet δ 4.80, $J = 8$ cps (17 α -H), 1-proton doublet δ 5.70, $J = 6$ cps (11-H). The ketone (20 mg) was kept for 1.5 hr at room temperature in CHCl₃-HCl. The product was recrystallized successively from ether and acetone to give XXX (16 mg): mp 161–164°; λ_{\max} 242 $m\mu$ (ϵ 13,100); nmr, 3-proton triplet δ 0.98, $J = 6.5$ cps (18 α -H), 3-proton singlet δ 2.04 (acetate CH₃), 2-proton AB system, pair of doublets δ 3.42 and 3.68, $J = 11$ cps (9 α -H), 1-proton broad singlet δ 5.95, half-height width 5 cps (4-H).

Anal. Calcd for C₂₂H₃₁ClO₃: Cl, 9.35; M, 378.0. Found: Cl, 9.9; M – 36 (by mass spectroscopy), 342.

Acknowledgments.—We thank Mr. R. E. Bright for the preparation of key intermediates, Dr. R. A. Edgren and his associates, Endocrinological Department, Wyeth Laboratories Inc., for the biological data, and Dr. D. DeJongh, Chemistry Department, Wayne State University, for the mass spectra.

The Synthesis of Certain 17 α -Alkyl Corticoids

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Received February 6, 1967

Revised Manuscript Received May 18, 1967

The preparation of several 17-alkyl-17-deoxy steroids of the corticoid series is described. The 17-alkyl group was introduced *via* Li-liquid ammonia treatment of 3 β -acetoxy-5 α -pregna-9(11),16-dien-20-one (I) followed by appropriate alkylation. Methyl groups at the 16 α and 17 α positions were introduced by a procedure involving 1,4 addition of methylmagnesium iodide to the Δ^{16} -20-keto system of I, or its corresponding 3-tetrahydropyranyl derivative, followed by methylation of the 16 α -methyl-17-enolate anion thus generated. Further elaboration of the resulting 17-alkyl derivatives was carried out by standard procedures. Of particular interest is the synthesis of the 17-methyl and 17-ethyl derivatives of 17-deoxy-9 α -fluoroprednisolone 21-acetate and of 17-deoxy-17-methylhexamethasone 21-acetate.

In this paper we report the synthesis of a variety of 17 α -methyl and ethyl derivatives of the corticoid type. Previous reports^{1a} from this laboratory have described a useful procedure for the preparation of 17-alkyl-pregnan-20-ones, which involves the alkylation of an intermediate 17-enolate anion developed by treatment of a 16-pregnen-20-one with a solution of Li, Ca, or Ba in liquid ammonia. The application of this method to the synthesis of a series of orally effective 17-alkyl-progesterone derivatives has also been described.^{1,2} For the present study we have utilized this method and also have developed a convenient process for the simultaneous introduction of methyl groups at the 16 α and 17 α positions involving Grignard 1,4 addition to a Δ^{16} -20-ketone followed by methylation of the intermediate enolate anion.

Some years prior to this investigation Engel described the synthesis of 17-methylcorticosterone³ and its 11-

dehydro derivative.⁴ From the results reported at that time it appeared that replacement of the hydroxy group at C₁₇ with a methyl group results in a decrease in glucocorticoid and antiinflammatory activity as measured by liver glycogen and local granuloma assays, respectively. On the other hand, the possible effect of this modification on mineralocorticoid activity aroused our interest since it appeared that, with regard to this important parameter of biological activity, there was a qualitative difference between 17-methyl-11-dehydrocorticosterone acetate and cortisone acetate.⁴ We have been unable to find any further reports concerning this preliminary observation nor, to our knowledge, has there been an application of the possibilities thus raised to a 9 α -fluoro-substituted corticoid.

With the hope that 17-alkylation in the corticoid series might in fact result in a favorable separation of certain of the parameters of corticoid activity and encouraged by our own observations² in the progesterone series that at least in some instances 17-ethyl and

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