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4-Substituted Steroids[1]

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A number of steroid analogs containing a hydrocarbon substituent at C-4 have been prepared by either or both of two methods. For one of these methods, direct alkylation of Δ^4-3-keto-steroids, conditions are described which make it a useful preparative procedure. In the case of the second method, which involves treatment of an enol-lactone of a 5-oxo-3,5-seco-A-nor acid with a Grignard reagent followed by base cyclization, the intermediate products of the Grignard reaction have been isolated and evidence is presented bearing on their structure. Rearrangement reactions of some 4,4-dimethyl steroid analogs are described.

Since, at the outset of this work, it had become apparent that profound changes in physiological activity resulted from the removal of C-19 from the steroid molecule,[2] it seemed worthwhile to attempt introduction of hydrocarbon radicals on the steroid nucleus with the hope of effecting similar changes. The results of this work as well as the large amount of data which have been reported subsequently on the effects of methyl substitution at C-4[3] and other positions[4] demonstrate the validity of this general approach. This paper is concerned primarily with the synthesis of a number of 4-substituted androstane and 19-norandrostane derivatives which were prepared in the hope that they would possess high anabolic potency and favorable ratios of anabolic to androgenic activity.

The well-explored scheme (I→III→V→VII→IX) which has as its key step the reaction of a Grignard reagent with the enol-lactone of a 5-oxo-3,5-seco-A-nor acid[5] was chosen for the early experiments, but because of the number of steps involved and the low over-all yields a more direct method was sought. A modification of the dialkylation procedure of Woodward and co-workers[6] was developed which gave fair yields of monoalkylated products which could be separated cleanly from the over-reacted and unreacted materials by chromatography. Identical samples of IXb and XIVb were produced by the two methods and the newly introduced substituent was definitely shown to be at C-4 by the ozonization of 4-methyltestosterone benzoate (IXg) to the same keto-acid IIIg (obtained in the tautomeric lactonol form[7]) that was obtained from testosterone benzoate (Ig).

4-Methylcholestenone (IXa),[3b,8] 4-methyltestosterone (IXb),[3,9] 4-ethyltestosterone (Xb),[9] 4-phenyltestosterone (XIb)[9] and 4-methyl-19-nortestosterone (XIVb) were prepared by the longer procedure.[10] In three of these cases the intermediate products (VIIa, VIIg and VIIIg) of reaction of the Grignard reagent with the enol-lactone were isolated. These materials had spectral characteristics (infrared bands at 2.82–2.92 and 5.87–5.88 μ) which were in better accord with a structure of the cyclized aldol type VII, VIII[11] than with the alternate enol-hemiketal type XIX[12] which has also been suggested.[5b]

An attempt was also made to use this same general scheme of reactions to prepare A-nortestosterone. The appropriate enol-lactone XXV was prepared by acetyl chloride–acetic anhydride dehydration of the corresponding lactonol XXIV which was obtained in turn by ozonization of 2-hydroxymethylenetestosterone (XXIII).[13] However, when this enol-lactone was allowed to react with methylmagnesium bromide and the crude product refluxed in methanolic alkali a gum was obtained which showed none of the expected ultraviolet absorption. No attempt was made to identify the products.[14]

The direct procedure used to introduce a single alkyl group at C-4 was essentially that employed in the synthesis of lanostenol from cholestenone[6] with the exception that limited quantities of alkyl halide (1.00 to 1.25 moles) and base (1.5 moles) were used and the alkylating agent was added slowly to a refluxing solution of the steroid and base in *t*-butyl alcohol. It was found advantageous to conduct the reaction at the boiling point of the solvent since a greater proportion of monoalkylated material was formed as compared with the reaction at room temperature. Thus 17α-methyltestosterone (Ic) gave 15% of the dialkylated material and 49% of the monoalkylation product in refluxing *t*-butyl alcohol while at room temperature yields

(1) N. W. Atwater, THIS JOURNAL, **79**, 5315 (1957).

(2) (a) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); (b) L. G. Hershberger, E. G. Shipley and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, **83**, 175 (1953); (c) W. W. Tulner and R. Hertz, *J. Clin. Endocrinol. and Meta.*, **12**, 916 (1952); (d) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954).

(3) (a) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957); (b) F. Sondheimer and Y. Mazur, THIS JOURNAL, **79**, 2906 (1957).

(4) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955); H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956); G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956); J. A. Campbell, J. C. Babcock and J. A. Hogg, *ibid.*, **80**, 4717 (1958); G. E. Arth, D. B. R. Johnston, John Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160 (1958).

(5) (a) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951); (b) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951); (c) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(6) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *ibid.*, **76**, 2852 (1954); *J. Chem. Soc.*, 1131 (1957).

(7) (a) N. W. Atwater and J. W. Ralls, THIS JOURNAL, **82**, 2011 (1960); (b) R. B. Turner, *ibid.*, **72**, 579 (1950).

(8) G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956).

(9) B. Camerino, D. Cattapan, U. Valcavi and B. Patelli, *Gazz. chim. ital.*, **89**, 674 (1959).

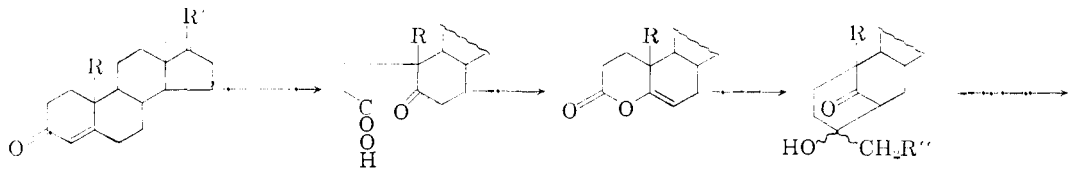
(10) The author wishes to acknowledge the work of Mr. Ivar Laos in preparing two of these substances.

(11) S. A. Julia, A. Eschenmoser, H. Heusser and N. Tarköy, *Helv. Chim. Acta*, **36**, 1885 (1953); K. D. Zwahlen, W. J. Horton and G. I. Fujimoto, THIS JOURNAL, **79**, 3131 (1957).

(12) The carbon–carbon double bond stretching frequency of the enol-ether portion of this structure would be expected to have its principal absorption at wave lengths above 5.95 μ (*cf.* G. D. Meakins, *J. Chem. Soc.*, 4170 (1953)).

(13) F. L. Weisenborn, D. C. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(14) T. L. Jacobs and N. Takahashi, *ibid.*, **80**, 4865 (1958).

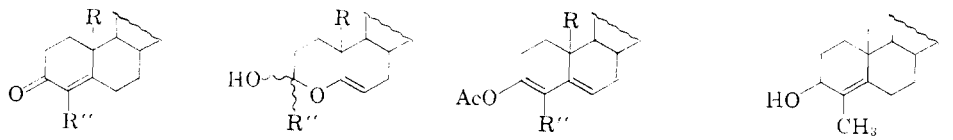


I, R = CH_3
II, R = H

III, R = CH_3
IV, R = H

V, R = CH_3
VI, R = H

VII, R = R'' = CH_3
VIII, R = CH_3, R'' = C_6H_5

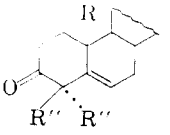


IX, R = R'' = CH_3
X, R = CH_3, R'' = C_2H_5
XI, R = CH_3, R'' = C_6H_5
XII, R = CH_3, R'' = $CH_2CH{:}CH_2$
XIII, R = CH_3, R'' = C_4H_9
XIV, R = H, R'' = CH_3

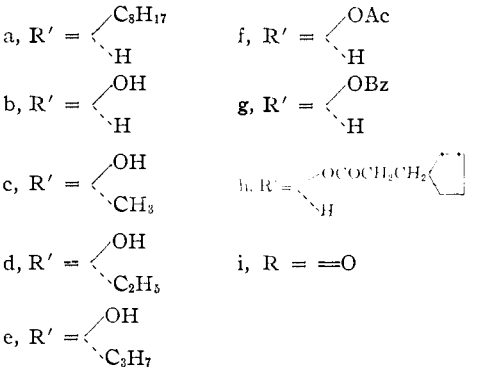
XIX

XX, R = R'' = CH_3
XXI, R = H, R'' = CH_3

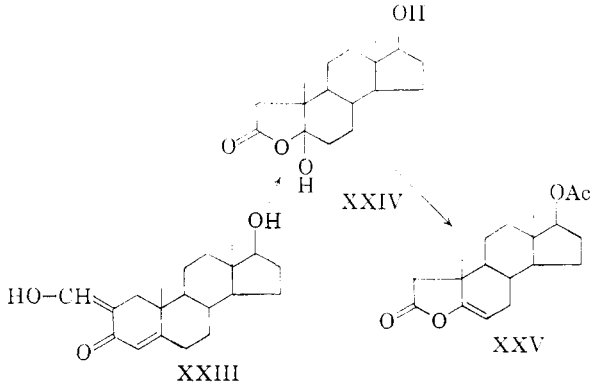
XXII



XV, R = R'' = CH_3
XVI, R = CH_3, R'' = $CH_2CH{:}CH_2$
XVII, R = CH_3, R'' = C_4H_9
XVIII, R = H, R'' = CH_3



a, R' = C_8H_{17}
b, R' = OH
c, R' = OH
d, R' = OH
e, R' = OH
f, R' = OAc
g, R' = OBz
h, R' = $OCOCH_2CH_2$
i, R = =O



XXIII

XXIV

XXV

of 33 and 15%, respectively, were obtained. Since there must be competition between the unalkylated and the monoalkylated material for the limited quantity of alkyl halide present, the above result indicates that the rate of the first alkylation is enhanced to a greater degree by increasing temperature than is the rate of the second. This may be due to increased hindrance by the first alkyl substituent to approach of the second mole of alkylating agent at higher temperatures.

An excess of alkyl halide was used in most cases to make up partially for its loss due to the competing reaction with *t*-butoxide ion. The halide was added slowly as a dilute solution in *t*-butyl alcohol to minimize loss of the volatile reagent through the condenser.

In no instance were products of oxygen alkylation at either position 3 or 17 noted, but unreacted starting material and the dialkylation product at C-4 were always present in the crude reaction mixtures. The method, therefore, depended for success on a good procedure for separation. This was found in adsorption chromatography using silica gel as adsorbent and mixtures of benzene and ethyl acetate as elution solvents. The compounds were eluted in order of decreasing degree of alkylation. Table I summarizes the

TABLE I

	Alkylating agent	Moles	Conv., %, to[a] Mono-alkyl	Di-alkyl	Recovered[a] starting mat., %
Ib	Methyl iodide	1.00	44	9	33
Ib	Butyl iodide	1.00	62	10[b]	
Ib	Allyl bromide	1.00	55	11	16
Ic	Methyl iodide	1.15	49	15	
IIb	Methyl iodide	1.25	47	14	
IId	Methyl iodide	1.25	53[b]	17	
IIe	Methyl iodide	1.15	17[c]		15

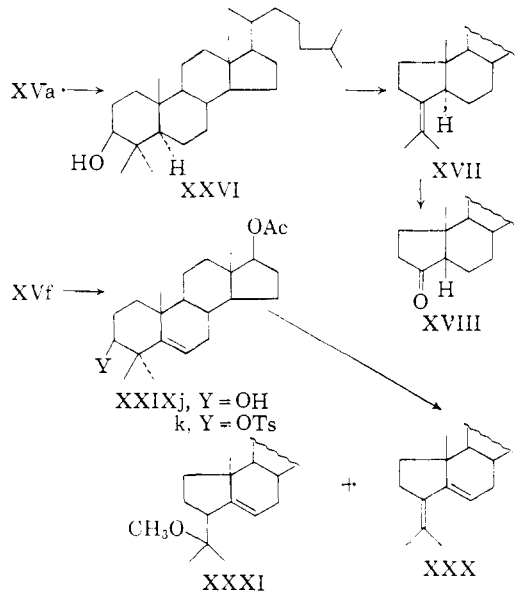
[a] Conversions and recoveries based on weights of well separated chromatography peaks before further purification. [b] Not completely characterized. [c] Exclusive of fractions which were mixtures with dialkylated material.

results of the application of this method to various testosterone and 19-nortestosterone derivatives.

In addition, a number of esters and other simple transformation products were prepared from the parent 4-alkyl-Δ^4-3-keto-steroids. The benzoate

IXg and cyclopentylpropionate IXh were prepared from 4-methyltestosterone (IXb) and the acetate XIVf[15] from 4-methyl-19-nortestosterone (XIVb). The enol-acetates XXa, XXf and XXIf were also made. 4-Methyltestosterone on oxidation with chromium trioxide–pyridine gave the diketone IXi and on reduction with lithium aluminum hydride gave the diol XXIIb.

The 4,4-dialkyl-Δ^5-3-ketones were available in some quantity as by-products of monoalkylation and could be prepared easily in good yield by deliberate dialkylation. Some attempts were therefore made to explore the chemistry of the A:B ring system in these compounds. 4,4-Dimethylcholest-5-en-3-one (XVa)[6] was hydrogenated directly to 4,4-dimethyl-5α-cholestan-3β-ol (XXVI).



This compound on treatment with phosphorus pentachloride in petroleum ether gave the rearranged isopropylidene-A-nor compound XXVII in good yield. Similar rearrangement in the pentacyclic triterpene series is considered diagnostic for the presence of a 3β-hydroxyl-5α-system and hence these configurations at C-3 and C-5 are assigned to XXVI. The structure of the rearranged product was established by ozonolysis[16] to the known A-norcoprostan-3-one (XXVIII).[17]

17β-Acetoxy-4,4-dimethylandrost-5-en-3-one (XVf) was converted to the 3β-tosylate XXIXk in two steps and the latter solvolyzed in methanol containing potassium acetate. The crude reaction product was separated by chromatography into three weight peaks which were identified as follows. The least polar material was deduced to be a mixture of 17β-acetoxy steroidal dienes consisting, at least, of two conjugated compounds as shown by ultraviolet spectral changes which occurred during unsuccessful attempts to obtain the pure components. The work of Moriarty and Wallis[18] as well as that of Haddad and Summers[19] suggest that 17β-acetoxy-3-isopropylidene-A-norandrost-5-ene (XXX) is present, but no evidence is at hand which would allow assignment of structure to the other member(s) of the mixture. The products of methyl migration, the double bond isomers of XXX and the simple elimination product bear consideration.

The second weight peak was comprised of 17β-acetoxy-3-(2-methoxy-2-propyl)-A-norandrost-5-ene (XXXI) (*cf.* Moriarty and Wallis[18]) as shown by the following facts which rule out both the i-ether and the normal 3β-methoxy structures. The substance was unsaturated as demonstrated by its ready absorption of bromine in carbon tetrachloride and the strong color it produced with tetraanitromethane in ethanol. Furthermore, it underwent elimination of the methoxyl group on treatment with dilute sulfuric acid to give a mixture of 17β-hydroxy-dienes.

The last substance isolated was XXIXj presumably formed by simple hydrolysis from traces of water present in the reaction mixture.

Bioassays[20] indicate that compounds IXb and XIVb are 30% and 20% as anabolic and 10% and 5% as androgenic, respectively, as testosterone propionate. The analogous substances with larger groups at C-4 and the 4,4-dialkylsteroids were inactive in these catagories. Weight increases in the rat levator-ani muscle,[2b] seminal vesicle and ventral prostate were used to measure these effects.

Experimental[21]

Treatment of Enol-lactone Va[7b] with Ethylmagnesium Bromide.—A solution of Grignard reagent was made from ethyl bromide (2.5 g.) and magnesium turnings (0.28 g.) in a total of 25 ml. of ether. This was added to a solution of Va (3.5 g.) in benzene (25 ml.) and ether (25 ml.) and the mixture refluxed 2 hr. After hydrolysis with dil. hydrochloric acid the aqueous phase was ether extracted and the combined organic layers were washed, dried with anhydrous sodium sulfate and evaporated. The residue on crystallization from methanol and then petroleum ether gave 1.40 g. of 3a,6-dimethyl-12-ethyl-3(6-methyl-2-heptyl)-12-hydroxy-6,8-propanoperhydrobenz[e]inden-7-one (VIIa), m.p. 145–147°. Recrystallization from petroleum ether gave the analytical sample, m.p. 148.5–150°, $[\alpha]D$ + 32°; λ_{max}^{KBr} 2.90, 5.88 μ.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.88; H, 11.49.

Treatment of Enol-lactone Vg[7b] with Ethylmagnesium Bromide.—The reaction was carried out as above on 3.25 g. of Vg and the crude material was chromatographed on silica gel. The desired product along with starting material was eluted with benzene-ethyl acetate (19:1). Crystallization of the later fractions from petroleum ether gave 0.53 g. of 3a,-6-dimethyl-12-ethyl-3-benzoyloxy-12-hydroxy-6, 8-propanoperhydrobenz[e]inden-7-one (VIIg), m.p. 156–158°. Further crystallization from petroleum ether gave the analytical

(15) J. A. Hartman, A. J. Tomasewski and A. S. Dreiding, THIS JOURNAL, **78**, 5662 (1956).

(16) D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(17) A. Windaus, *Ber.*, **52**, 170 (1919); B. B. Smith and H. R. Nace, THIS JOURNAL, **76**, 6119 (1954); D. E. Evans, A. C. de Paulet, C. W. Shoppee and F. Winternitz, *Chemistry & Industry*, 355 (1955).

(18) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1274 (1959).

(19) Y. M. Y. Haddad and G. R. H. Summers, *J. Chem. Soc.*, 769 (1959).

(20) Bioassays performed under the direction of F. J. Saunders in the Division of Biological Research, G. D. Searle and Co., and at the Worcester Foundation for Experimental Biology.

(21) Melting points were determined on a Fisher–Johns apparatus and are corrected. Rotations were measured in chloroform at about 23°. Analyses and spectra were determined by the analytical department of this company in the charge of Dr. R. T. Dillon. The term petroleum ether refers to the hydrocarbon fraction boiling between 60 and 71° supplied by the Skelly Oil Co. with the designation "B."

sample, m.p. 156.5–158.5°, $[\alpha]_D$ + 29°; λ_{max}^{KBr} 2.92, 5.83, shoulder 5.88 μ.

Anal. Calcd. for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.44; H, 8.73.

Treatment of Enol-lactone Vg with Benzylmagnesium Chloride.—A Grignard solution prepared from benzyl chloride (2.74 g.) and magnesium (0.53 g.) in ether (25 ml.) was added to a solution of Vg (7.10 g.) in dry benzene (50 ml.). After stirring at room temperature for 18 hr. the reaction was worked up as before and the crude product chromatographed on silica gel. A peak of solid material (2.6 g.) was eluted with benzene–ethyl acetate (19:1) and a center fraction on two recrystallizations from ethyl acetate gave material with m.p. 197–198°; λ_{max}^{KBr} 2.82, 5.82, 5.87 μ.

Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 79.07; H, 7.82.

The remaining solid was recrystallized from ethyl acetate to give an additional 1.50 g. of 3a,6-dimethyl-12-benzyl-3-benzoyloxy-12-hydroxy-6,8-propanoperhydrobenz[e]inden-7-one (VIIIg) in several crops all melting in the range 190–194°.

4-Methylcholest-4-en-3-one (IXa).—Slightly impure VIIa (0.70 g.) was refluxed in 4% methanolic potassium hydroxide (100 ml.) for 2 hr. The reaction mixture was diluted with water and the product extracted into ether. After washing the ether solution with water and drying it with anhydrous sodium sulfate the solvent was removed at reduced pressure and the residue crystallized from methanol. There was obtained 0.47 g. (70%) of IXa, m.p. 94–96°. The analytical sample prepared by recrystallization from methanol melted at 103–104° (lit.[3b,8] 102–103°), $[\alpha]_D$ +117°; $\lambda_{max}^{CH_3OH}$ 251 mμ, ϵ 16,000; λ_{max}^{KBr} 6.01, 6.24 μ.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.60; H, 11.86.

4-Methyltestosterone (IXb). A. From VIIg.—Compound VIIg (0.28 g.) was refluxed 16 hr. in a solution composed of potassium hydroxide (1 g.), methanol (70 ml.) and water (30 ml.). After acidification and removal of the methanol by vacuum distillation the solid product was collected by filtration. Recrystallization from acetone–water gave 0.16 g. (80%) of IXb, m.p. 165–168°. The analytical sample prepared by recrystallization melted at 167–168.5° (lit.[3,9] 167–168.5°), $[\alpha]_D$ +137°; $\lambda_{max}^{CH_3OH}$ 250.5 mμ, ϵ 14,800; λ_{max}^{KBr} 2.89, 6.05, 6.22 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.21; H, 10.29.

B. From Testosterone.—See below.

4-Phenyltestosterone (XIb).—Compound VIIIg (1.49 g.) was treated as above in boiling aqueous methanolic potassium hydroxide. The crude product gave 0.72 g. (51%) of analytical material after two recrystallizations from benzene-petroleum ether; m.p. 180–182° (lit.[9] 176–178°), $[\alpha]_D$ +133°; $\lambda_{max}^{CH_3OH}$ 240–245 mμ, ϵ 15,800; λ_{max}^{KBr} 3.10, 6.00, 6.31 μ.

Anal. Calcd. for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85. Found: C, 82.08; H, 8.71.

4-Ethyltestosterone (Xb).—Compound Vg[7b] (6.7 g.) was treated with propylmagnesium bromide in the same manner as for the preparation of VIIIg. The total crude product was treated with aqueous methanolic potassium hydroxide as above and the crude product chromatographed on silica gel. The fractions eluted with benzene–ethyl acetate (9:1) were recrystallized from ether–petroleum ether to obtain 1.65 g. (31%) of Xb, m.p. 141.5–142° (lit.[9] 128–130°), $[\alpha]_D$ +117°, $\lambda_{max}^{CH_3OH}$ 250 mμ, ϵ 18,600.

Anal. Calcd. for $C_{21}H_{32}O_2$: C ,79.69; H, 10.19. Found: C, 79.66; H, 10.14.

4-Methyl-19-nortestosterone (XIVb). A. From VIf.—17β-Acetoxy-4-oxa-19-norandrost-5-en-3-one (VIf) prepared by acetic anhydride–sodium acetate treatment of IVf had physical constants (m.p. 110–112°, $[\alpha]_D$ −4°) indicating major contamination with the $\Delta^{5(10)}$-isomer.[15,22] The analysis was correct. This material (1.81 g.) was treated with ethylmagnesium bromide in the same manner as in the preparation of VIIIg. The crude gummy reaction product was refluxed for 5 hr. in 150 ml. of a methanol–water mixture (5:1) containing potassium hydroxide (1.0 g.). After acidification the reaction mixture was distilled to a small volume under reduced pressure, diluted with water and extracted with chloroform. The extracts were shaken with 2% aqueous sodium hydroxide and then with water. They were dried with sodium sulfate and evaporated to dryness leaving 0.84 g. of a yellow gum.

Chromatography of this material on 30 g. of silica gel gave 0.31 g. of material eluted with benzene–ethyl acetate (9:1). Crystallization from acetone–water gave analytical material, m.p. 154–158.5°, $[\alpha]_D$ +58°; $\lambda_{max}^{CH_3OH}$ 250 mμ, ϵ 16,000; λ_{max}^{KBr} 3.01, 6.04, 6.23 μ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.99; H, 9.63.

B. From 19-Nortestosterone.—See below.

17β-Acetoxy-3-oxa-A-norandrost-5-en-2-one XXV.—Compound XXIV[13a] (1.04 g.) was refluxed for 24 hr. in a mixture of acetic anhydride (15 ml.) and acetyl chloride (10 ml.). The mixture was then distilled to dryness under reduced pressure and the oily residue was made to solidify by trituration with water. The crude product after two recrystallizations from ethanol–water gave 0.76 (68%) of XXV, m.p. 102.5–105.5°. The analytical sample obtained by recrystallization from petroleum ether exhibited a double m.p. 108° and 123–125°, $[\alpha]_D$ −76°; λ_{max}^{KBr} 5.50, 5.57, 5.77, 5.86 μ.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.77; H, 8.43.

General Alkylation Procedure.—Freshly cut potassium metal (15 milliatoms) was dissolved with heating and stirring in *t*-butyl alcohol (33 ml.). A solution of the Δ^4-3-keto-steroid (10 millimoles) in the same solvent was heated to the boiling point and added to the boiling solution of base. The refluxing mixture was then treated dropwise over a 2.5-hr. period with a solution of alkyl halide (10 to 12.5 millimoles) in 165 ml. of *t*-butyl alcohol. After a further 0.5-hr. reflux period the turbid solution was cooled and acidified with concd. hydrochloric acid. Water was added to dispel the turbidity and the resulting solution stripped of *t*-butyl alcohol at reduced pressure. The organic material was extracted into benzene and the extracts washed with water and dried by distillation to about half volume. This solution was then poured onto a column of 100–200 mesh silica gel (100 times the weight of steroid starting material) and fractions eluted with benzene and benzene–ethyl acetate mixtures (19:1, 9:1 and 4:1). The following alkylation experiments were run using this procedure unless noted to the contrary.

Methylation of Testosterone (Ib). 4-Methyltestosterone (IXb). B.—Compound Ib (1.77 g.) was alkylated with 1 mole of methyl iodide. The dialkylated product XVb (9%) was the first eluted from the column. The analytical sample obtained by crystallization from acetone had m.p. 184–185.5° (lit.[3a] 198–201°), $[\alpha]_D$ −5°; λ_{max}^{KBr} 3.03, 5.82, 6.03 μ.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.35, H, 10.21.

Compound IXb was eluted next (44%). The analytical sample obtained by crystallization from acetone–water had m.p. 168.5–170.5°. Mixture m.p. with material obtained by procedure A was 167.5–169.5°. The infrared spectra of the two samples were identical. Starting material (33%) was eluted last, $\lambda_{max}^{CH_3OH}$ 241 mμ, ϵ 15,100.

Alkylation of Testosterone (Ib) with Butyl Iodide.—Testosterone (3.00 g.) was treated with 1 mole of butyl iodide. 4-Butyltestosterone (XIIIb) (62%) was recrystallized from isopropyl ether to give the analytical material, m.p. 127.5–128.5°, $[\alpha]_D$ +113°; $\lambda_{max}^{CH_3OH}$ 251 mμ, ϵ 15,000; λ_{max}^{KBr} 3.11, 6.00, 6.23.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.24; H, 10.73.

17β-Hydroxy-4,4-dibutylandrost-5-en-3-one (XVIIb) (10%) which was eluted from the column ahead of XIIIb had $\lambda_{max}^{CHCl_3}$ 2.74, 5.85, 6.01 μ and no discernible ultraviolet absorption in the 220–260 mμ region. This material was not further purified.

Alkylation of Testosterone (Ib) with Allyl Bromide.—Compound Ib was treated with 1 mole of allyl bromide. 17β-Hydroxy-4,4-diallylandrost-5-en-3-one (XVIb) (11%), m.p. 108–109.5°, $[\alpha]_D$ −12°; λ_{max}^{KBr} 2.92, 5.84, 6.04, 6.11 μ, was obtained pure by recrystallization from acetone–water.

Anal. Calcd. for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85. Found: C, 81.13; H, 9.84.

4-Allyltestosterone (XIIb) (46%) was also purified by recrystallization from acetone–water, m.p. 124.5–125° with

(22) S. Kushinsky, *J. Biol. Chem.*, **230**, 31 (1958).

presoftening, $[\alpha]D$ +125°; $\lambda_{max}^{CH_3OH}$ 250 mμ, ε 15,000; λ_{max}^{KBr} 2,87, 2.94, 6.04, 6.25 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.64; H, 9.99.

Testosterone (16%) was recovered as the last solid material to be eluted from the column.

Methylation of 17α-Methyltestosterone (IXc). A. At 83°.—Compound Ic (20.0 g.) was treated with 1.15 moles of methyl iodide. 17β-Hydroxy-4,4,17-trimethylandrost-5-en-3-one (XVc) (3.28 g., 15%) was eluted first from the column. Crystallization from acetone and isopropyl ether gave the analytical sample, m.p. 182–188° (lit.[3a] 194–196°), $[\alpha]D$ −25°; λ_{max}^{KBr} 2.83, 2.94, 5.87, 6.04 μ.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H,10.37. Found: C, 79.77; H, 10.19.

4,17α-Dimethyltestosterone (IXc) (10.10 g., 49%) was eluted next. Recrystallizations from acetone–water and then isopropyl ether gave the analytical material, m.p. 143–144°, $[\alpha]D$ +96°; λ_{max}^{KBr} 2.85, 6.02, 6.14 μ.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.62; H, 10.19.

B. At 23°.—Compound Ic (13 g.) was treated with 1.25 moles of methyl iodide as in the general procedure except that the reactants were mixed at room temperature. Compound XVc (4.66 g., 33%), having an identical infrared spectrum to that obtained above was eluted first from the column and IXc (2.08 g., 15%) was eluted next. The latter substance after 2 recrystallizations from acetone–water had a m.p. of 145.5–146.5° and when mixed with a sample of the material from the reaction above melted at the same temperature (145.5–146.5°).

These experiments bear comparison even though different molar proportions of methyl iodide were used since approximately the same proportion was utilized for steroid alkylation (0.79 and 0.81 mole, respectively).

Methylation of 19-Nortestosterone (IIb). 4-Methyl-19-nortestosterone (XIVb). B.—Compound IIb (5.00 g.) was treated with 1.25 moles of methyl iodide. There was obtained from the column 0.74 g. (14%) 17β-hydroxy-4,4-dimethyl-19-norandrost-5-en-3-one (XVIIb)[23] which after recrystallization from isopropyl ether gave material of m.p. 149–149.5°, $[\alpha]D$ +33°; λ_{max}^{KBr} 3.01, 5.84, 6.06 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H,10.00. Found: C, 79.02; H, 9.96.

The monomethyl product XIVb comprised 2.44 g. (47%). After crystallization from acetone–water it melted at 157–159.5° and its infrared spectrum was identical to that of a sample prepared by the alternate route.

Methylation of 17α-Ethyl-19-nortestosterone (IId).—Compound IId (2.74 g.) was treated with 1.25 moles of methyl iodide. 17β-Hydroxy-17-ethyl-4,4-dimethyl-19-norandrost-5-en-3-one (XVIIId, 0.51 g., 17%), the first compound eluted, was recrystallized from acetonitrile to give material of m.p. 163–169.5°. The ultraviolet spectrum showed no absorption attributable to an α,β-unsaturated ketone.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.30; H, 10.50.

The second weight peak from the chromatography column (1.53 g., 53%), even though it could not be crystallized to analytical purity, was assigned structure XIVd on the basis of the physical characteristics of material crystallized from acetonitrile: m.p. 82–89°; $\lambda_{max}^{CH_3OH}$ 250 mμ, ε 16,000; λ_{max}^{KBr} 2.93, 6.07, 6.23 μ.

Methylation of 17α-Propyl-19-nortestosterone (IIe).—Compound IIe (3.20 g.) on reaction with 1.15 moles of methyl iodide gave after chromatography three weight peaks the first two of which were not completely resolved. Those fractions (all resinous) of the second peak with ultraviolet extinction coefficients above 15,000 at 250 mμ were combined. The 4-methyl-17α-propyl-19-nortestosterone (XIVe) composite had the following physical characteristics: $\lambda_{max}^{CH_3OH}$ 250 mμ, ε 15,200; $\lambda_{max}^{CHCl_3}$ 2.75, 6.03, 6.20 μ; $[\alpha]D$ +14°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.87; H, 10.54.

The third weight peak comprised unalkylated material (0.473 g., 15%); $\lambda_{max}^{CH_3OH}$ 240.5 mμ, ε 16,800.

4-Methyltestosterone Benzoate (IXg).—Compound IXb (0.50 g.) was dissolved in 25 ml. of dry benzene. The solution was treated with 0.6 ml. of pyridine and 0.6 ml. of benzoyl chloride. After standing at room temperatures for 16 hr. the mixture was shaken with water, dil. hydrochloric acid, dil. sodium hydroxide and then again with water. The residue obtained after drying and stripping the benzene at reduced pressure was crystallized from methanol to give 0.53 g. (79%) of IXg, m.p. 199.5–202°. The analytical sample obtained on recrystallization from methanol melted at 202–203°, $[\alpha]D$ +118°; $\lambda_{max}^{CH_3OH}$ 235 mμ, ε 22,000, shoulder at 250 mμ; λ_{max}^{KBr} 5.83, 6.03, 6.26 μ.

Anal. Calcd. for $C_{27}H_{34}O_3$: C, 79.76; H, 8.43. Found: C, 79.83; H, 8.22.

Ozonization of 4-Methyltestosterone Benzoate (IXg).—This material (0.53 g.) was ozonized in the same manner reported[7] for ozonization of testosterone benzoate (Ig). The acidic product after 2 crystallizations from methanol–water melted at 174.5–176° and the infrared spectrum of this sample was identical to that of 17β-benzoyloxy-5-hydroxy-4-oxaandrostan-3-one obtained from Ig.

4-Methyltestosterone β-Cyclopentylpropionate (IXh).—Compound IXb (0.50 g.) was treated with β-cyclopentylpropionyl chloride as described by Heyl and Herr.[24] The crude product crystallized from methanol–water gave 0.58 g. (82%) of material with m.p. 83–88°. Recrystallization from acetone–water gave the analytical sample, m.p. 91–92.5°, $[\alpha]D$ +100°; λ_{max}^{KBr} 5.78, 5.96, 6.23, 8.47 μ.

Anal. Calcd. for $C_{28}H_{42}O_3$: C, 78.82; H, 9.93. Found: C, 78.51; H, 9.90.

4-Methyl-19-nortestosterone Acetate (XIVf).—Compound XIVb (0.20 g.) was dissolved in 4 ml. of pyridine and 2 ml. of acetic anhydride. After standing for 16 hr. the reaction mixture was poured into water and the product was collected by filtration and crystallized from methanol. It melted 125.5–126.5° (lit.[15] 121.4–123°), $[\alpha]D$ +42°; $\lambda_{max}^{CH_3OH}$ 249.5 mμ, ε 17,100.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.03; H, 9.06.

3-Acetoxy-4-methylcholesta-3,5-diene (XXa).—Compound IXa (0.30 g.) was dissolved in 3 ml. of acetyl chloride and 3 ml. of acetic anhydride. The solution was heated at steam-bath temperature under a nitrogen atmosphere for 16 hr. and then the volatiles were removed at reduced pressure. After two recrystallizations from methanol, analytical material (0.16 g., 47%) was obtained, m.p. 114–116°, $[\alpha]D$ −102°; $\lambda_{max}^{CH_3OH}$ 236 mμ, ε 22,400; λ_{max}^{KBr} 5.69, 5.98, 8.14 μ.

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.70; H, 10.92.

3,17β-Diacetoxy-4-methylandrosta-3,5-diene (XXf).—Compound IXb (0.17 g.) was treated as in the case of the cholestane derivative above. After two crystallizations from methanol–methylene chloride, analytical material was obtained, m.p. 165–167.5°, $[\alpha]D$ −135°; $\lambda_{max}^{CH_3OH}$ 235 mμ, ε 19,000; λ_{max}^{KBr} 5.70, 5.79, 6.00, 6.11 μ.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.49; H, 8.80.

3,17β-Diacetoxy-4-methyl-19-norandrosta-3,5-diene (XXIf).—Compound XIVb (0.50 g.) was dissolved in 20 ml. of isopropenyl acetate. After 50 mg. of toluenesulfonic acid monohydrate had been added the mixture was slowly distilled for 6 hr. while fresh isopropenyl acetate was added slowly to maintain the initial volume. An excess of solid sodium bicarbonate was then added and the volatile reagent was removed under vacuum. The residue was recrystallized from isopropyl ether to give 0.40 g. (62%) of XXIf, m.p. 174.5–177.5°. The analytical sample obtained on further crystallization from methanol melted at 176.5–178°; $[\alpha]D$ −148°; $\lambda_{max}^{CH_3OH}$ 236 mμ, ε 18,100; λ_{max}^{KBr} 5.68, 5.77, 6.01, 6.11 μ.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.78; H, 8.95.

4-Methylandrost-4-ene-3,17-dione (IXi).—Compound IXb (0.75 g.) in 10 ml. of pyridine was added to a slurry of chromium trioxide–pyridine complex prepared from 0.63 g. of chromium trioxide and 6 ml. of pyridine. After standing at room temperature for 16 hr. the mixture was poured into

(23) A. Bowers and H. J. Ringold, THIS JOURNAL, **81**, 424 (1959).

(24) F. W. Heyl and M. E. Herr, *ibid.*, **77**, 488 (1955).

water and the product extracted with ether. After washing, drying and stripping the solvent at reduced pressure the residue was recrystallized from acetone–water to give 0.54 g. (72%) of analytically pure material, m.p. 143.5–144.5°, $[\alpha]_D$ +216°; $\lambda_{max}^{CH_3OH}$ 249 mμ, ε 15,300; λ_{max}^{KBr} 5.74, 6.01, 6.22 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.40. Found: C, 79.57; H, 9.30.

4-Methylandrost-4-ene-3β,17β-diol (XXII).—Compound IXb (1.00 g.) in 15 ml. of dry tetrahydrofuran was added to a slurry of lithium aluminum hydride (0.5 g.) in 10 ml. of the same solvent and the mixture was refluxed for 0.5 hr. Acetone was added to decompose the excess reagent and then dil. hydrochloric acid was added until the mixture was acidic. Further dilution and filtration gave the solid product which was crystallized repeatedly from methanol–water and then isopropyl ether to obtain 0.39 g. (39%) of XXII, m.p. 138.5–140.5°, $[\alpha]_D$ +117.5°; λ_{max}^{KBr} 2.88, 9.42 μ.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 79.09; H, 10.23.

4,4-Dimethyl-5α-cholestan-3β-ol (XXVI).—4,4-Dimethylcholest-5-en-3-one (XVa)[6] (10 g.) was dissolved in 120 ml. of cyclohexane and the solution was added to a suspension of 1.0 g. of prereduced platinum oxide in 60 ml. of acetic acid. After shaking for 2 hr. in an atmosphere of hydrogen only 10% reduction had occurred so 2 drops of concd. hydrochloric acid and an additional 1.0 g. of catalyst were added. The reaction then proceeded rapidly to about 90% completion with no further uptake of hydrogen on shaking for 16 hr. The catalyst was filtered and the solvents removed under vacuum to leave solid material whose infrared spectrum showed that a small amount of acetylation had occurred. In addition this material gave a faint Liebermann–Burchard test and decolorized a bromine solution. Recrystallization once from acetic acid and twice from methanol gave 5.10 g. (50%) of XXVI, m.p. 156–157°, $[\alpha]_D$ +14°; λ_{max}^{KBr} 2.90, 9.58, 9.72 μ.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.58; H, 12.58. Found: C, 83.33; H, 12.18.

3-Isopropylidene-A-norcholestane (XXVII).—Compound XXVI (1.115 g.) in 500 ml. of petroleum ether at 0° was treated with phosphorus pentachloride (2.0 g.). After the solution was stirred at 0° for 0.5 hr. and for 1 hr. while warming to 23° it was washed with water, dil. sodium hydroxide and again with water. It was then dried over magnesium sulfate and reduced in volume to 200 ml. by vacuum distillation. The resulting solution was passed through a column containing alumina (150 g.) with more petroleum ether. All of the desired product (0.935 g., 88%) was eluted in the first 750-ml. fraction. Recrystallization from ethyl acetate gave 0.70 g. of XXVII, m.p. 98–100°, $[\alpha]_D$ +121°.

Anal. Calcd. for $C_{29}H_{50}$: C, 87.36; H, 12.64. Found: C, 86.99; H, 12.42.

A-Norcoprostan-3-one (XXVIII).—Compound XXVII (0.255 g.) was dissolved in 30 ml. of methylene chloride and the solution was ozonized at −78° until it assumed a blue color. Acetic acid (10 ml.) and zinc dust (0.5 g.) were added at 0° and the slurry was stirred for 1 hr. at this temperature. The reaction mixture was filtered and the filtrate washed with water, dil. sodium hydroxide and again with water. Drying and evaporation left a yellow gum which was dissolved in benzene and passed through an alumina column (10 g.) with more benzene. The first 250 ml. of eluate contained 91 mg. of solid and the following 750 ml. contained 8 mg. The initial fraction gave analytical material after two recrystallizations from methanol, m.p. 71–72° (lit.[17] 73–74°), λ_{max}^{KBr} 5.77 μ.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found: C, 83.60; H, 11.84.

Semicarbazone, m.p. 266–267° (lit.[17] 267–268°).

17β-Acetoxy-4,4-dimethylandrost-5-en-3β-ol (XXIXj).—17β-Acetoxy-4,4-dimethylandrost-5-en-3-one (XVf)[3a] (5.00 g.) in 300 ml. of 95% ethanol was treated at 10° with a solution of 2.5 g. of sodium borohydride in 200 ml. of the same solvent. After 20 minutes at 10°, acetic acid was added cautiously to destroy the excess reducing agent and the mixture was diluted with water to 2 l. Filtration and recrystallization from methanol gave 4.47 g. (89%) of XXIXj, m.p. 194–198°. The analytical sample prepared by further crystallization from methanol melted at 200–202°, $[\alpha]_D$ −93°; λ_{max}^{KBr} 2.83, 2.91, 5.80, 7.97 μ.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.56; H, 10.32.

17β-Acetoxy-3β-toluenesulfonyloxy-4,4-dimethylandrost-5-ene (XXIXb).—Compound XXIXk (3.00 g.) was dissolved in pyridine (15 ml.) and was treated with toluenesulfonyl chloride (3.0 g.). The solution stood for 40 hr. at 23° and was then diluted to 100 ml. with methylene chloride and washed with water, several times with dil. hydrochloric acid, then dil. sodium bicarbonate and finally again with water. After drying, the solvent was removed and the residue was crystallized from acetone to give 2.40 g. of XXIXk, m.p. 103–106° (dec.), $[\alpha]_D$ −52°.

Anal. Calcd. for $C_{30}H_{42}O_5S$: C, 70.00; H, 8.23. Found: C, 70.25; H, 8.06.

Solvolysis of Tosylate XXIXk.—Compound XXIXk (2.25 g.) was refluxed in 120 ml. of methanol containing 6.4 g. of freshly fused potassium acetate for 6 hr. The mixture was then diluted with water and extracted with ether. The extracts were washed, dried, and evaporated to leave a resinous residue which was chromatographed on 200 g. of silica gel. The first material eluted (1:1 petroleum ether–benzene) (0.58 g.) had $\lambda_{max}^{CH_3OH}$ 242 mμ, ε 12,800, shoulder 250 mμ.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.88; H, 9.82.

The second material eluted (0.47 g.) was recrystallized twice from acetone–water to give pure XXXI, m.p. 118.5–119°, $[\alpha]_D$ −42°; λ_{max}^{KBr} 5.77, 7.99, 9.24, 9.69 μ.

Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 77.10; H, 10.20.

The third weight peak (0.17 g.) (benzene-ethyl acetate, 19:1) had an infrared spectrum identical to XXIXj.

In a second reaction using 11.65 g. of XXIXk under the same conditions, 3.60 g. of material was eluted from the silica gel column with a 1:1 mixture of petroleum ether–benzene. This, on careful chromatography using silica gel and increasingly more concentrated solutions of petroleum ether in benzene, gave 12 fractions containing solid with no indication of separation into weight peaks. The ultraviolet spectra and optical rotations of a number of these were determined: fraction 1, $\lambda_{max}^{CH_3OH}$ 224 mμ, ε 7,200, $[\alpha]_D$ −195°; fraction 3, $\lambda_{max}^{CH_3OH}$ 245 mμ, ε 7,000, shoulders at 238 and 253 mμ, $[\alpha]_D$ −14°; fractions 5, $\lambda_{max}^{CH_3OH}$ 245 mμ, ε 11,400, $[\alpha]_D$ −108°, fraction 7 and 9, $\lambda_{max}^{CH_3OH}$ 242–243 mμ, ε 15,200–16,400, shoulders at 235 and 250 mμ, $[\alpha]_D$ −190 to −196°; fraction 12, $\lambda_{max}^{CH_3OH}$ 242 mμ, ε 16,200, shoulder at 236 and 239 mμ, $[\alpha]_D$ −172°.

Acid Treatment of Ether XXXI.—Compound XXXI (0.20 g.) in 10 ml. of purified dioxane was treated with 1 ml. of water containing a drop of concd. sulfuric acid and the solution was refluxed for 16 hr. Solid sodium bicarbonate was added and the slurry was taken to dryness under reduced pressure. The residue was diluted with water and the gummy organic material was filtered and crystallized twice from acetone–water to obtain 0.12 g. of solid in 2 crops melting at 78–103° and 99–103° with presoftening. This latter material had λ_{max}^{MeOH} 245 and 251 mμ, ε 9,000, shoulders at 235 and 260 mμ.