duction only to the alcohol stage prior to dehydrogenation, is much more efficient than the previously reported method *via* the Clemmensen reduction of the ketone group.[6] This sample melted at 144–146° alone or when mixed with that prepared from ketone XI.

NEW BRUNSWICK, N. J.

[CONTRIBUTION OF THE RESEARCH LABORATORIES, THE UPJOHN CO.]

6-Methyl Steroids in the Androstane Series[1]

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Methylmagnesium bromide cleaved the epoxy group of 3-hydroxy- and 3-ethylenedioxy-5α,6α-epoxyandrostanes to give the corresponding 5α-hydroxy-6β-methyl derivatives. Dehydration of the 3-keto-5α-hydroxy intermediates afforded 6β-methylandrostenedione, testosterone, methyltestosterone and ethinyltestosterone, while dehydration and isomerization gave the corresponding 6α-methyl compounds.

An earlier communication from these laboratories[2] described 6-methyl derivatives of the cortical hormones and the potentiating effect of this modification on biological activity. This paper is a continuation of these studies and describes the 6-methylandrostenes.

More than seventeen years ago Madaeva, Ushakov and Kosheleva[3] synthesized 6α-methyl-4-androstene-3,17-dione without assigning a configuration to the 6-methyl group. The androgenic activity was reported to be about the same as that of the parent compound. During the preparation of this manuscript a preliminary announcement by Ringold, *et al.*,[4] and a more detailed study by Petrow, *et al.*,[5] appeared describing portions of the material covered in this work.

The 6-methyl group was introduced into the steroid molecule by cleavage of the 5α,6α-epoxides with methylmagnesium bromide. High yields of cleavage products were obtained from 3-ethylenedioxy-5α,6α-epoxides. However, when a 3-hydroxyl or a 3-acetoxyl group was present the 5α,6α-epoxide was cleaved with some difficulty.

Thus, although 5α,6α-epoxyandrostane-3β,17β-diol (Ib) was treated with methylmagnesium bromide in boiling tetrahydrofuran for 24 hours, the product (m.p. 115–120°, lit.[3] m.p. 117–120°), which seemed to be a dihydrate of IIb by analysis and infrared absorption, was shown to contain a considerable amount of starting material. Chromium trioxide oxidation of the crude Grignard product gave a mixture of ketones which could not be separated by chromatography over Florisil. Evidence that the Grignard reaction (Ib → IIb) did not proceed to completion was obtained by treating the crude oxidation product with piperidine and chromatographing the resulting mixture to give 6α-hydroxy-4-androstene-3,17-dione (Xa)[6a] (presumably arising from 5α,6α-epoxyandrostane-3,17-dione (IXa)) along with the expected 5α-hydroxy-6β-methyl-3-ketone IIIa. Although the 6α-hydroxyandrostenedione (Xa) melted somewhat higher than reported,[6b] its structure was confirmed both by acetylation to the 6α-acetate and by isomerization to the 3,6-dione. Further evidence that the Grignard reaction (Ib → IIb) did not proceed to completion was obtained by treating the crude reaction product with *p*-toluenesulfonic acid in pyridine. The acetone-insoluble pyridinium salt XIIb thus produced could be separated from the 5α-hydroxy-6β-methyl compound IIb and reverted to the starting epoxide Ib by treatment with alcoholic potassium hydroxide.

The reaction of methylmagnesium bromide with 5α,6α-epoxy-17α-methylandrostane-3β,17β-diol (Ic) and its 3-acetate gave products of variable melting points (165–190°) and rotations (−41 to −52°).[7] Recrystallization gave less than 40% yield of the triol IIc, m.p. 205–215°, having a characteristic strong hydrate band at 1635 cm.$^{-1}$ in the infrared spectrum. Analysis indicated it to be a monohydrate. Oxidation of the triol IIc with chromium trioxide in acetic acid gave the corresponding 3-ketone IIIc in about 50% yield.

The reaction of the epoxides of androstenedione-3-ketal (Va), testosterone ketal (Vb) and methyltestosterone ketal (Vc) with methylmagnesium bromide in boiling tetrahydrofuran proceeded without difficulty in yields of 70–85%. Although some of the 5-hydroxy-6-methyl-3-ketals resisted crystallization, after removal of the ketal groups in dilute acidic methanol nicely crystalline products (IIIa, b, c and d) were obtained.

The epoxide of testosterone ketal (Vb) was a convenient intermediate since it was prepared easily, and from it the whole series of 6-methyl C_{19}-steroids could be made. Thus, it reacted with methylmagnesium bromide to give the 5α-hydroxy-6β-methyl intermediate VIb which, after removal of the ketal and dehydration, gave the 6-methyltes-

(1) Presented before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society, New York, N. Y., September 8–13, 1957.

(2) 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).

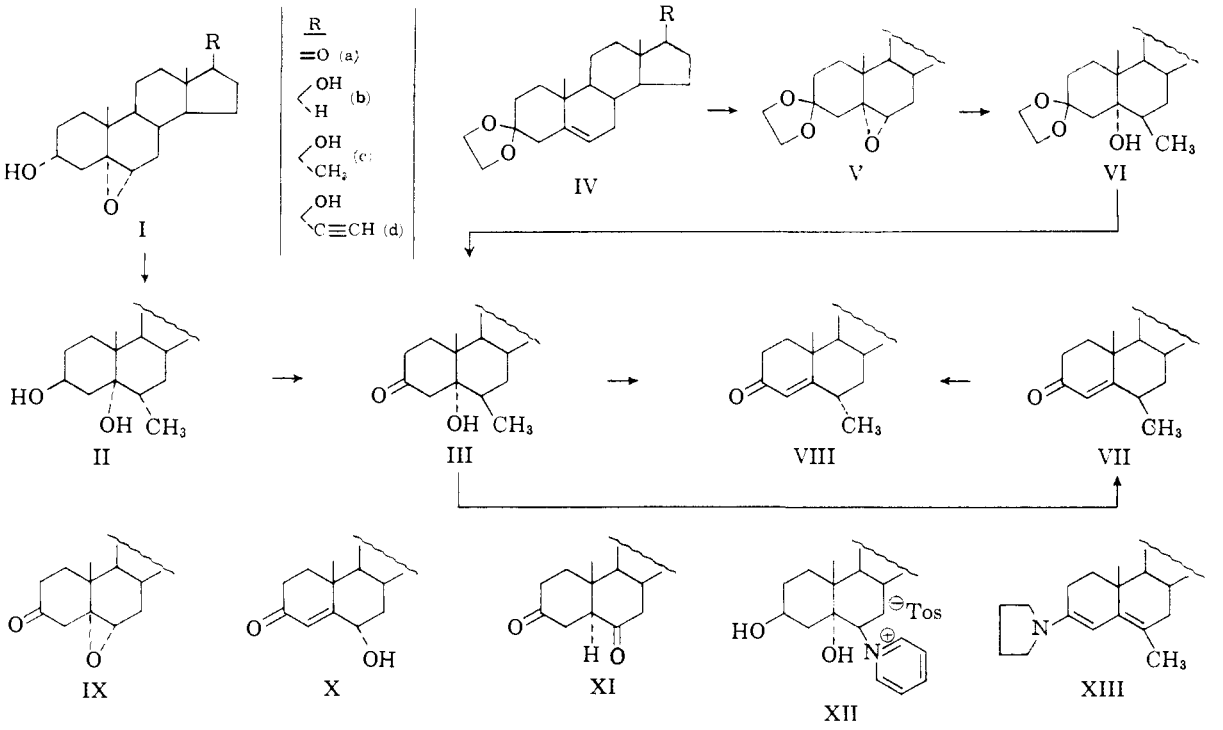
(3) O. S. Madaeva, M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem. (USSR)*, **10**, 213 (1940); *C. A.*, **34**, 7292 (1940).

(4) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(5) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957); V. Greenvill, D. K. Patel, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *ibid.*, 4105 (1957); G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *ibid.*, 4112 (1957).

(6) (a) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952). (b) We are very grateful to Prof. Ehrenstein for determining a "mixed melting point"; there was no depression.

(7) Reference 4 gives m.p. 191–192° and $[\alpha]_D$ −45° and states that satisfactory analysis could not be obtained apparently due to solvent of crystallization.



tosterones (VIIb and VIIIb). Oxidation of VIb with chromium trioxide in pyridine[8] gave the 17-ketone VIa. Hydrolysis and dehydration then afforded the 6-methylandrostenediones VIIa and VIIIa, while addition of methylmagnesium bromide to VIa led to members of the 17-methylcarbinol series VIc and ethinylation with commercial sodium acetylide[9] in dimethyl sulfoxide led to the members of the 17-ethinyltestosterone series VId.

Dehydration of the 5α-hydroxy-6β-methyl-3-ketones (IIIa, b, c and d) was accomplished in nearly quantitative yields in very dilute alkali (0.00475 *N*) in about 90% ethanol. Stronger base gave the 6α-isomers in inferior yields. Dehydration and isomerization in cold chloroform saturated with hydrogen chloride[3] gave the 6α-methyl compounds (VIIIa, b, c and d). A summary of the physical constants is given in Table I. The two 6-methyl-Δ^4-3-ketones were epimeric at carbon atom 6 since they formed the same enamine (XIIIa). This enamine also was prepared directly from the 5α-hydroxy-6β-methyl ketone IIIa.

Biological tests[10] carried out in the Endocrinology Department of these laboratories showed the 6α- and 6β-methyl derivatives of testosterone and methyltestosterone to be somewhat less active than their parent compounds as androgenic and "anabolic" agents.[11,12]

6α-Methyl-17α-ethinyltestosterone is a potent oral progestational agent[13] with about two times the activity of ethinyltestosterone. The 6β-isomer is about half as active as the α-isomer.

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Experimental[14]

5α,6α-Epoxy-17α-methylandrostane-3β,17β-diol (Ic) and its 3-Acetate.—A solution of 64 g. of 17α-methyl-5-androstene-3β,17β-diol and 8.0 g. of sodium acetate in 1.5 l. of chloroform was stirred and cooled to 20° during the addition of 80 ml. of 40% peracetic acid solution. After 1.25 hours the temperature was lowered to 5° and the precipitated product was collected, washed with fresh chloroform and water and dried; yield 37.8 g., m.p. 242°. The filtrate was washed with dilute sodium hydroxide and water, dried over magnesium sulfate and the solvent removed. The residue was recrystallized from 95% alcohol; yield 11.4 g., m.p. 239–242°.

Acetylation in pyridine with acetic anhydride at 55° gave the 3-acetate which after recrystallization from ethyl acetate showed m.p. 168–171°, $[\alpha]D$ −89° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.13; H, 9.20.

6β,17α-Dimethylandrostane-3β,5α,17β-triol (IIc). From 5α,6α-Epoxy-17α-methylandrostane-3β,17β-diol (Ic).—A solution (under N_2) containing 10 g. of Ic, 100 ml. of 3 *M* methylmagnesium bromide in ether and 500 ml. of tetrahydrofuran was distilled until the boiling point reached 58°. The solution was heated under reflux for 3 days. About 750 ml. of toluene was added and the solution distilled until all the tetrahydrofuran was removed and the boiling point

(8) R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns and L. H. Sarett, THIS JOURNAL, **75**, 1707 (1953).

(9) Kindly supplied by Air Reduction Chemical Co.

(10) L. E. Barnes, R. O. Stafford, M. E. Guild, L. C. Thole and K. J. Olson, *Endocrinol.*, **55**, 77 (1954).

(11) These results are not in accord with data reported by Ringold, *et al.*,[4] who report 6α-methyltestosterone to have 4.6 times the myotrophic activity of testosterone.

(12) Both androstenedione and its 6-methyl derivatives are too inactive to give a measurable response at the standard dosage level (2 mg./day orally or 0.1 mg./day subcutaneously) in this assay.

(13) Progestational assays were carried out at the Endocrine Laboratories, Madison, Wisc.

(14) Melting points were determined on a Kofler block. Infrared spectra were determined as Nujol mulls or in chloroform solution, ultraviolet spectra in 95% ethanol, and rotations in 1-dcm. tubes at concentrations of 0.8–1.2 mg./ml. unless indicated otherwise. The tetrahydrofuran used throughout was freshly redistilled from lithium aluminum hydride; SSB = Skellysolve B.

TABLE I

6-METHYL C_{19}-STEROIDS

Name	M.p., °C.	a_M 242 mμ	$[\alpha]_D$, $CHCl_3$	$M_D\beta - M_D\alpha$	Analyses, % Calcd. C	Calcd. H	Found C	Found H
6β-Methylandrostene-3,17-dione	207–212	16,200	+139°	−123	79.95	9.39	79.43	9.62
6α-Methylandrostene-3,17-dione	164–167	15,650	+180		79.95	9.39	80.31	9.72
6β-Methyltestosterone	214–216	16,200	+ 60	−103	79.42	10.00	79.88	10.22
6α-Methyltestosterone	159–160	15,150	+ 94		79.42	10.00	79.35	10.26
6β,17α-Dimethyltestosterone	160–161	15,500	+ 28	−101	79.69	10.19	79.15	10.27
6α,17α-Dimethyltestosterone	138–141	15,600	+ 60		79.69	10.19	79.74	10.11
6β-Methyl-17α-ethinyltestosterone	223–226	15,950	− 11	−121	80.93	9.26	81.05	9.13
6α-Methyl-17α-ethinyltestosterone	191–195	15,475	+ 26		80.93	9.26	80.53	9.10

reached 108°. After refluxing two more days the reaction mixture was poured into dilute hydrochloric acid and ice. The precipitate was collected, washed with water and dried. It was recrystallized twice from 95% ethanol; yield 4.9 g., m.p. 205–215°, $[\alpha]_D$ −41° (C_2H_5OH). Infrared analysis shows a strong band at 1635 $cm.^{-1}$ which is attributed to a hydrate.

Anal. Calcd. for $C_{21}H_{36}O_3 \cdot H_2O$: C, 71.14; H, 10.80. Found: C, 71.42; H, 10.80. After thorough drying: Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.97; H, 10.82.

Starting with the 3-acetate the same product was obtained in about the same yield.

From 5α,6α-Epoxy-3β-hydroxyandrostan-17-one (Ia).—To a solution of 100 ml. of 4 *M* methylmagnesium bromide in ether and 100 ml. of tetrahydrofuran was added 6.7 g. of the 5α,6α-epoxide of dehydroepiandrosterone (Ia) dissolved in 150 ml. of tetrahydrofuran while stirring under nitrogen. The solution was distilled until the b.p. reached 58° and then heated under reflux overnight. During this time about 70% of the solvent escaped. The reaction mixture was poured into dilute hydrochloric acid and ice. The precipitate was collected, washed with water and dried. It was recrystallized from 95% ethanol; yield 2.4 g., m.p. 192–210°. It was identical with the product isolated above.

6β-Methylandrostane-3β,5α,17β-triol (IIb) and its 3,17-Diacetate.—To a solution of 500 ml. of 4 *M* methylmagnesium bromide in ether and 250 ml. of tetrahydrofuran was added a solution of 30.6 g. of 5α,6α-epoxyandrostane-3β,17β-diol (Ib) in 900 ml. of tetrahydrofuran with stirring. (A precipitate which formed almost immediately did not seem to redissolve.) The solution, concentrated until the b.p. reached 58°, was heated under reflux for 22 hours. After concentration to about 700 ml. the mixture was poured into dilute hydrochloric acid and ice. The product separated as an oil but soon crystallized. The solid was collected, washed well with water and dried; yield 29.4 g., m.p. 115–120°. This product is about a 1–1 mixture of starting epoxide Ib and the desired 6-methyltriol IIb.

A solution of 1.25 g. of the above mixture and 0.2 g. of *p*-toluenesulfonic acid in 5 ml. of pyridine was warmed on the steam-bath overnight. Most of the pyridine was allowed to evaporate under a stream of nitrogen. The residue was triturated with two portions of acetone. The acetone extracts were combined, concentrated to dryness, taken up in ethyl acetate and washed with water, dilute acid, dilute sodium hydroxide and brine, dried over magnesium sulfate and concentrated to dryness. The residue was recrystallized from methylene chloride containing a small amount of methanol to give the 6-methyltriol IIb, m.p. 115–125°. Papergram analysis did not show any impurities. It was acetylated in pyridine with acetic anhydride to give the 3,17-diacetate of IIb, m.p. 174–179°, $[\alpha]_D$ −35° ($CHCl_3$).

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.52; H, 9.25.

The above acetone insoluble portion was made strongly alkaline with 40% aqueous sodium hydroxide, heated on the steam-bath overnight and extracted with ethyl acetate. The extract was washed with dilute acid and water and dried. The solvent was removed and the residue triturated with ethyl acetate to give 5α,6α-epoxyandrostane-3β,17β-diol (Ib).

5α-Hydroxy-6β-methylandrostane-3,17-dione (IIIa) and 6α-Hydroxy-4-androstene-3,17-dione (Xa).—To a slurry of 26 g. of the mixture of epoxy diol Ib and the 6-methyltriol IIb obtained from the previous experiment in 190 ml. of acetic acid cooled to 10° was added dropwise with stirring and cooling a solution of 10 g. of chromium trioxide in 10 ml. of water and 50 ml. of acetic acid. The cooling bath was removed and after 45 minutes enough methanol was added to react with the excess chromium trioxide. The acetic acid was partly neutralized with 250 ml. of 20% sodium hydroxide with cooling. The precipitate was collected, washed with water and dried; yield 11.7 g., m.p. about 150° dec.

About 8 g. of this mixture, which contained 5α-hydroxy-6β-methylandrostane-3,17-dione (IIIa) and 5α,6α-epoxyandrostane-3,17-dione (IXa), was dissolved in a minimum amount of piperidine at room temperature. After one hour the solution was diluted with water and carefully neutralized with hydrochloric acid. The precipitate was collected, washed with water and dried; yield 7.2 g. It was dissolved in methylene chloride and chromatographed over 200 g. of Florisil. The material eluted by 12–14% acetone in SSB was recrystallized from acetone–SSB to give 1.1 g. of 5α-hydroxy-6β-methylandrostane-3,17-dione (IIIa), m.p. 215–225°, $[\alpha]_D$ + 69° ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.26; H, 8.97.

The material eluted by 25% acetone in SSB was recrystallized twice from acetone to give 1.1 g. of 6α-hydroxy-4-androstene-3,17-dione (Xa), m.p. 238–246° dec.,[15] $[\alpha]_D$ +184° (CH_3Cl_3), λ_{max}^{alc} 239 mμ, a_M 15,300.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.49; H, 8.66.

It was acetylated to give 6α-acetate,[6] m.p. 172–174°, $[\alpha]_D$ +164° ($CHCl_3$), λ_{max}^{alc} 236 mμ, a_M 15,350. Treatment with sodium hydroxide in aqueous methanol in a nitrogen atmosphere gave 5α-androstane-3,6,17-trione (XIa),[6] m.p. 191–194°.

5α,6α-Epoxyandrostane-3,17-dione (IXa).[16]—To a solution of 1.9 g. of 5α,6α-epoxyandrostane-3β,17β-diol (Ib) in 20 ml. of pyridine was added with stirring 1.9 g. of chromium trioxide complexed with 20 ml. of pyridine. After stirring overnight the mixture was diluted with water and extracted 6 times with ether. The ether extracts were combined and washed with brine and dried over magnesium sulfate. The solvent was removed under vacuum and the residue recrystallized from acetone–ether to give 0.73 g. of the dione IXa, m.p. 195–201°, $[\alpha]_D$ −2° ($CHCl_3$). (This may be a polymorphic modification of material, m.p. 265°, reported by Ruzicka and Bosshard.[16]) Infrared analysis showed a trace of OH impurity.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.34; H, 9.13.

It was isomerized to 6α-hydroxy-4-androstene-3,17-dione (Xa) on treatment with piperidine as described above.

1-(3β,5α,17β-Trihydroxyandrostan-6β-yl)-pyridinium *p*-Toluenesulfonate (XIIb).—A solution of 2.0 g. of 5α,6α-epoxyandrostane-3β,17β-diol, 1.0 g. of *p*-toluenesulfonic acid and 10 ml. of pyridine was heated on the steam-bath for 8 hours. Most of the pyridine was allowed to evaporate under a stream of nitrogen. Acetone was added and the crystalline product was collected and recrystallized from methanol–acetone; yield 2.45 g., m.p. 206–208° dec., $[\alpha]_D$ −13° (95% alcohol).

(15) Reference 6 gives m.p. 229–230°.

(16) L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937)

Anal. Calcd. for: C, 66.76; H, 7.77; N, 2.51. Found: C, 66.76; H, 7.97; N, 2.57.

Testosterone 3-Ethyleneacetal (IVb).[17]—In a 1-l. flask equipped with a distillation head, thermometer and a mechanical stirrer were placed 50 g. of testosterone, 660 ml. of ethylene glycol and 2.5 g. of *p*-toluenesulfonic acid. The solution was distilled rapidly under high vacuum (below 0.5 mm.) at 80–81°. About 200–250 ml. of distillate was collected in 15 minutes. During this time crystals of the ketal formed. During the next 10 minutes the temperature was lowered to 74° and after a total of 35 minutes the temperature was lowered to 71°. A total of 310 ml. of distillate was collected. The reaction mixture was cooled to about 50° and filtered. The crystals were washed with a little warm glycol, saturated sodium bicarbonate solution and water, and dried; yield 43 g. Ultraviolet absorption analysis showed the presence of 3.9% testosterone.

Methyltestosterone 3-ethyleneacetal could not be prepared by this method since the 17-hydroxyl group was eliminated. It was prepared in low yield by the usual benzene–ethylene glycol–*p*-toluenesulfonic acid procedure.[18,19]

5α,6α-Epoxy-17β-hydroxyandrostan-3-one 3-Ethyleneacetal (Vb) and the 5β,6β-Epoxide.—To a solution of 8.5 g. of the ketal of testosterone (IVb) in 140 ml. of chloroform was added 1.0 g. of sodium acetate and 10 ml. of peracetic acid (40%) with cooling in an ice–salt-bath and stirring. After 2 hours the solution was washed with dilute sodium hydroxide and water, dried over magnesium sulfate, filtered and concentrated to dryness. The α- and β-epoxides were separated by chromatography through Florisil (200 g.). The β-epoxide (3.4 g.) was eluted with 10% acetone–90% SSB and recrystallized from ether–SSB, m.p. 91–95°, $[\alpha]_D$ −3° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 72.38; H, 9.26. Found: C, 72.36; H, 9.76.

The α-epoxide Vb (4.0 g.) was eluted with 15% acetone–SSB and recrystallized from acetone–SSB, m.p. 205–208°, $[\alpha]_D$ −68° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.32; H, 9.31

The α-epoxide also was separated easily by recrystallizing the mixture from benzene.

5α,6α-Epoxy-17β-hydroxy-17α-methylandrostan-3-one 3-Ethyleneacetal (Vc).—The crude reaction mixture from the ketalization of methyltestosterone[18] was epoxidized as described above. The desired α-epoxide was crystallized from the reaction mixture after washing with dilute sodium hydroxide and water. It was collected and recrystallized from acetone, m.p. 206–209°, $[\alpha]_D$ −84° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.69; H, 9.37.

5α,6α-Epoxyandrostane-3,17-dione 3-Ethyleneacetal (Va).—To 500 ml. of pyridine in an indented round bottomed flask was added with stirring and cooling 48.5 g. of chromium trioxide. After the complex was of even consistency, 48.5 g. of 5α,6α-epoxy-17β-hydroxyandrostane-3-one 3-ethyleneacetal (Vb) was added. The reaction mixture was stirred at room temperature for 20 hours, diluted with 700 ml. of brine and extracted with six 500-ml. portions of ether. Each extract was washed with the same 300 ml. of brine and 300 ml. of water. The extracts were combined, dried and the solvent removed; yield 44.5 g., m.p. 165–182°. Recrystallization from acetone–SSB gave an analytical sample, m.p. 190–192°, $[\alpha]_D$ +10° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.72. Found: C, 72.83; H, 8.69.

6β,17α-Dimethyl-5α,17β-dihydroxyandrostan-3-one (IIIc).

a. **From 5α,6α-Epoxy-17β-hydroxy-17α-methylandrostan-3-one 3-Ethyleneacetal (Vc).**—To a solution of 90 ml. of 3 *M* methylmagnesium bromide and 100 ml. of tetrahydrofuran was added a solution of 5.0 g. of Vc in 150 ml. of tetrahydrofuran. The clear dark solution was distilled until the b.p. reached 58°. After refluxing about 20 hours, the solution was concentrated to about 50 ml., poured into a mixture of ice-water and ammonium chloride and extracted several times with ether. The combined extracts were washed with brine, dried and the solvent removed. The residue of 6β,17α-dimethyl-5α,17β-dihydroxyandrostane-3-one 3-ethyleneacetal (VIc) resisted crystallization. It was dissolved in 50 ml. of methanol and 5 ml. of 1 *N* sulfuric acid was added. After boiling with stirring for 15 minutes the solution was cooled and 5 ml. of water was added. The precipitate of 6β,17α-dimethyl-5α,17β-dihydroxyandrostan-3-one (IIIc) was collected and washed with a little cold methanol and water; yield 4.0 g. (86.5%), m.p. 235–243°. It was recrystallized from methanol–acetone, m.p. 253–257°, $[\alpha]_D$ −26° (95% alcohol).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.24. Found: C, 75.15; H, 9.92.

b. **From 6β,17α-Dimethyl-3β,5α,17β-triol (IIc).**—Oxidation of IIc with chromium trioxide in acetic acid gave a 50% yield of the 3-ketone IIIc identical with the product described above.

c. **From 5α,6α-Epoxyandrostane-3,17-dione 3-Ethyleneacetal (Va).**—The epoxy ketone Va was converted to IIIc by the procedure used in part a above in 59% yield.

d. **From 6β-Methyl-5α-hydroxyandrostane-3,17-dione 3-Ethyleneacetal (VIa).**—Again using the method described in part a, VIa was converted to IIIc in 60% yield.

6β-Methyl-5α,17β-dihydroxyandrostan-3-one (IIIb).—Twenty two grams of the epoxy ketal Vb when treated with methylmagnesium bromide as described in part a of the preceding experiment gave 21 g. of crude 6β-methyl-5α,17β-dihydroxyandrostan-3-one 3-ethyleneacetal (VIb). It resisted crystallization from most solvents except methanol with which it formed a crystalline monoalcoholate, m.p. 80–105°, $[\alpha]_D$ −28° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4 \cdot CH_3OH$: C, 70.01; H, 9.71. Found: C, 69.74; H, 9.80.

The ketal group was removed as previously described to give 6β-methyl-5α,17β-dihydroxyandrostan-3-one (IIIb). It was recrystallized from methanol; yield 72% from Vb, m.p. 211–213°, $[\alpha]_D$ −9° ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.95; H, 10.07. Found: C, 74.96; H, 10.03.

6β-Methyl-5α-hydroxyandrostane-3,17-dione 3-Ethyleneacetal (VIa).—Two grams of 6β-methyl-5α,17β-dihydroxyandrostan-3-one 3-ethyleneacetal (VIb) was oxidized with pyridine–chromium trioxide as described previously. The crude product was recrystallized from acetone–SSB; yield 1.33 g., m.p. 175–179°, $[\alpha]_D$ +36° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 71.89; H, 9.45. Found: C, 73.01; H, 9.51.

It was hydrolyzed to the diketone IIIa, m.p. 225–235°, identical to that described previously.

6α-Methyl-17α-ethinyl-5α,17β-dihydroxyandrostan-3-one (IIId).—A suspension (30 ml.) of sodium acetylide (20% in xylene) was centrifuged. The solid brown sodium acetylide was taken up in 25 ml. of dimethyl sulfoxide. To this was added a solution of 5.0 g. of 5α-hydroxy-6β-methylandrostane-3,17-dione 3-ethyleneacetal (VIa) in 85 ml. of dimethyl sulfoxide. After stirring at room temperature overnight, ice was added and the solution diluted to about 250 ml. The tan precipitate of VId was collected, washed with water and dried; yield 4.8 g., m.p. 202–204°. It was recrystallized from ethyl acetate, m.p. 204–206°.

Hydrolysis with methanol–HCl as described previously gave IIId, m.p. 218–221°; λ_{max}^{Nujol} 3580, 3320, 2105 and 1686 cm.$^{-1}$.

6β-Methyl-Δ^4-3-ketones (VIIa, b, c and d). General Procedure.—To a solution of 5 g. of the steroid (IIIa, b, c and d) in 200 ml. of 95% ethanol under nitrogen was added 10 ml. of 0.10 *N* sodium hydroxide. After 5.5–6 hours at room temperature the base was neutralized with acetic acid and concentrated under vacuum to about 25 ml. About 10 ml. of water was added and the precipitate of the 3-keto-Δ^4-6β-methyl derivative was collected, washed with water–ethanol and dried. The yield in all cases was nearly quantitative when the starting material was pure. See Table I for constants and analyses.

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(19) ADDED IN PROOF.—Crystalline methyltestosterone 3-ethyleneacetal (m.p. 178–180°, $[\alpha]_D$ −53° ($CHCl_3$). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 76.24; H, 9.89. Found: C, 76.16; H, 10.12) has since been prepared by D. G. Martin of these laboratories in 75% yield using a modification of the procedure in ref. 18; 1% *p*-toluenesulfonic acid and 16–20 hours reflux.

6α-Methyl-Δ⁴-3-ketones (VIIIa, b, c and d). General Procedure.—One gram of 3-keto-5α-hydroxy-6β-methyl derivative (IIIa, b, c and d) was dissolved (or slurried) in 50 ml. of chloroform, cooled in an ice–salt-bath and saturated with hydrogen chloride gas. After 25 minutes nitrogen was bubbled through to remove some of the hydrogen chloride. The solution was washed 3 times with water, dried over magnesium sulfate, filtered and the solvent removed. The residue was recrystallized from acetone–SSB to give from 55–75% yield of the 6α-methyl derivatives in Table I.

The 6β-methyl isomers VII also can be epimerized using this procedure.

3-(1-Pyrrolidinyl)-6-methyl-3,5-androstadien-17-one (XIIIa).—To 100 mg. of 5α-hydroxy-6β-methylandrostane-3,17-dione (IIIa) in 2 ml. of boiling methanol was added 0.1 ml. of pyrrolidine. The solution was heated for about one minute and part of the methanol was allowed to evaporate under a stream of nitrogen. The crystals were collected, washed with fresh methanol and dried, m.p. 172–180° dec., λ_{max}^{MeOH} 281 mμ, a_M 17,900; λ_{max}^{ether} 284 mμ, a_M 23,150.

Anal. Calcd. for $C_{24}H_{34}NO$: C, 81.79; H, 9.72; N, 3.97. Found: C, 81.46; H, 10.15; N, 3.90.

Using the above procedure 6α- and 6β-methyl-4-androstene-3,17-diones (VIIa and VIIIa) were converted to the same enamine.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Leuckart Reduction of Cholestan-3-one

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Leuckart reductive amination of cholestan-3-one gave 39–57% yields of several 3β-alkylaminocholestanes: piperidino, dimethylamino, benzylamino, pyrrolidino, diethylamino and N-methylbenzylamino. Smaller amounts (5–9%) of the 3α-isomers were isolated in some cases.

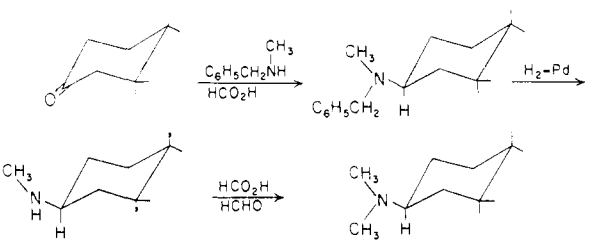
In connection with another project it was desirable to develop a convenient synthetic procedure for the preparation of relatively large amounts of 3β-mono- and dialkylaminocholestanes. The present methods for the preparation of 3β-aminoalkyl steroids suffer from marked limitations caused by undesirable side reactions, uncertain stereochemistry or unduly long synthetic procedures. For example, 3β-alkylamino steroids have been prepared from the corresponding 3α-tosylates (or halides) by heating with an amine.[1–3] In addition to the inconvenience involved in the preparation of 3α-tosylates, this method is also limited by the ease of diaxial elimination of toluenesulfonic acid.

Another general synthesis of 3β-alkylamino steroids involves, for example, reaction of amines with 3β-chlorocholest-5-ene to give 3β-alkylaminocholest-5-enes. Catalytic reduction of the Δ⁵-double bond leads to 3β-alkylaminocholestanes.[1–4] The success of this method depends largely on the nucleophilicity of the amine involved. Poor nucleophiles react *via* the homoallylic cation to give products of retained configuration, whereas the more nucleophilic amines react by the SN2 mechanism to give inverted products. Further, 3,5-cycloamines also have been isolated from this reaction.[5–10]

Finally, 3β-dimethylamino steroids have been prepared by formic acid–formaldehyde methylation of the corresponding 3β-amines. Preparation of the 3β-amines is tedious, however, involving sodium–alcohol reduction of the oximes of 3-ketosteroids.[11–13]

It appeared that Leuckart reductive amination might prove to be a useful method for the preparation of steroidal amines not only because of the high degree of stereospecificity expected (*vide infra*) but also because of the availability of the starting materials (*i. e.*, steroidal ketones). These expectations were realized experimentally when it was found that reaction of cholestan-3-one with secondary amines and formic acid gave 40 to 57% yields of 3β-dialkylaminocholestanes. Smaller amounts (5–9%) of the corresponding 3α-isomers could sometimes be isolated by chromatography of the crystallization liquors. The stereochemistry of the products was deduced from comparisons of the physical constants with literature values, and/or comparisons with the physical constants and infrared spectra of unambiguously prepared samples of the 3α-isomers.

The configuration of 3β-(N-methyl)-benzylaminocholestane was demonstrated by its conversion to the known 3β-dimethylaminocholestane.



The preparation of 3β-dimethylaminocholestane

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