tion, as does the polar material. The absorption band at 1790 cm.$^{-1}$ which characterizes the unknown material appears to be at a higher frequency than that usually associated with γ-lactones (saturated γ-lactones absorb at 1775 cm.$^{-1}$, α,β-unsaturated-γ-lactones absorb at 1750 cm.$^{-1}$ and β,γ-unsaturated-γ-lactones absorb at about 1800 cm.$^{-1}$).[12] In a KBr pellet, glucuronolactone exhibits an absorption maximum at 1775 cm.$^{-1}$.

From the evidence presented, it is reasonably certain that some of the substances occurring in this polar fraction were lactones. Assuming that the naturally occurring androsterone glucuronoside is a pyranoside, as are other uronic acids, lactones formed from it must have involved a conversion to the more stable furanoside. Ever since the demonstration[14] that glucurone is the γ-lactone of a furanoside and thus contains two five-membered rings, it has been recognized that a γ-lactone cannot form in a pre-existing pyranose structure. An analogous rearrangement of a pyranoside to a furanoside structure has been illustrated by the conversion of methyl 3,6-anhydro-α-D-glucopyranoside to methyl 3,6-anhydro-α-D-glucofuranoside by ethereal as well as methanolic HCl.[15] Protonation of androsterone glucuronoside probably produced an open chain carbonium ion which lactonized under the acidic conditions to the γ-lactone which, in turn, reverted to the strainless furanoside instead of returning to the sterically impossible pyranoside. An acid-catalyzed elimination reaction could have resulted in a subsequent formation of the α,β-unsaturated lactone.

The results described in this paper demonstrate that a gentle, chemical procedure for the hydrolysis of naturally occurring glycosides and glucuronosides is possible. To effect cleavage at low acid concentrations and low temperature requires that the glycosides first be solubilized in a suitable, nonionizing solvent. This requirement imposes a serious limitation since many glycosides are soluble only in polar media. Fortunately, the glucuronosides of the steroid hormone metabolites, as well as some other glycosides, can, under appropriate conditions, be extracted from aqueous solution into an organic solvent, such as ethyl acetate or tetrahydrofuran. Following reduction of the water content to tolerable levels (0.1–0.5%) by azeotropic distillation or other means, the hydrolysis can then be catalyzed by the addition of small amounts of $HClO_4$ (0.01–0.1 N). Whether this procedure will supplant the popular, albeit unreliable, hydrolysis using β-glucuronidase will depend upon the results of experiments presently being carried out to determine the extent of undesirable side reactions (acetate formation, dehydration, rearrangement, etc.), which the acidic conditions may produce simultaneously with cleavage.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CXXXIV.[1] Derivatives of 17α-Ethynyltestosterone and 17α-Ethynyl-19-nortestosterone

BY LAWRENCE H. KNOX, JOHN A. ZDERIC, J. PÉREZ RUELAS, CARL DJERASSI AND H. J. RINGOLD

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The reaction of enol ethers of Δ^4-androstene-3,17-dione and 19-nor-Δ^4-androstene-3,17-dione with propynylmagnesium bromide followed by acid hydrolysis gave 17α-propynyltestosterone (III) and the conjugated (VII) and unconjugated (VI) 17α-propynyl-19-nortestosterone. The syntheses of 6-fluoro and 6-chloro analogs in the ethynyl-, propynyl- and 19-norethynyltestosterone series are described.

In recent years considerable attention has been devoted to chemical modification of the orally active progestational agent 17α-ethynyltestosterone[2] in the hope of obtaining even more active compounds. Among the outstanding modifications leading to potentiated progestational activity have been replacement of the C-10 angular methyl group by hydrogen (17α-ethynyl-19-nortestosterone[3] and 17α - ethynyl - $\Delta^{5(10)}$- estren-17β-ol-3-one[4]), substitution by methyl at C-6α,[5,6] and conversion of the ethynyl group to a propynyl[6b] group. It has also been demonstrated that acetylation of the tertiary hydroxyl group[7] of 17α-ethynyl-19-nortestosterone further potentiates progestational activity. Finally, it has recently been reported that substitution of 17α-acetoxyprogesterone by fluorine,[8,9] chlorine[9] or bromine[9] at C-6 with and without additional double bond introduction at C-1 or C-6 leads to compounds of exceptional progestational potency. Thus it was of considerable interest to synthesize deriva-

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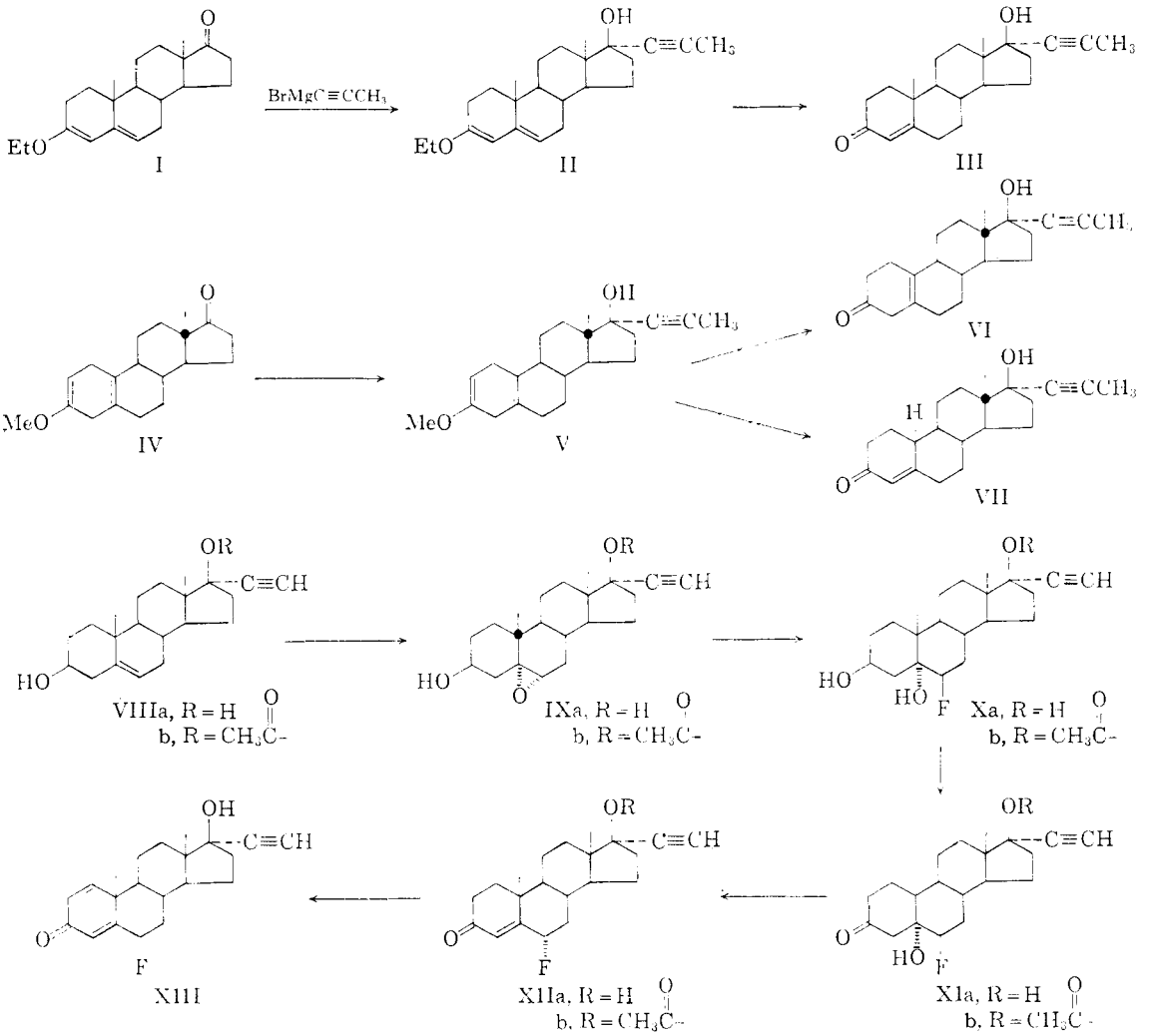

tives of 17α-ethynyltestosterone incorporating a number of these newer modifications.

Our attention was first turned to preparation of 17α-propynyl-19-nortestosterone (VII) and the $\Delta^{5(10)}$-isomer VI. Petrow,[6] in several cases, had converted the 17α-ethynyl-17β-hydroxyl group into 17α-propynyl-17β-hydroxyl by blocking the 17β-hydroxy as the dihydropyran adduct, alkylating the active hydrogen of the ethynyl group with methyl iodide–lithium amide in liquid ammonia and finally hydrolyzing the blocking group. For our purposes a more convenient route appeared to be reaction of the suitable 17-keto compound with propynylmagnesium bromide. As a model reaction, the 3-ethyl enol ether[10] (I) of Δ^4-androstene-3,17-dione dissolved in benzene was treated with propynylmagnesium bromide which had been prepared *in situ* by the reaction of propyne gas with methylmagnesium bromide in ether–tetrahydrofuran. The 3-enol ether of 17α-propynyltestosterone (II) thus obtained in good yield was hydrolyzed by hydrochloric acid in aqueous methanol to afford 17α-propynyltestosterone (III). Similarly, 1,4-dihydroestrone methyl ether[11] (IV) on reaction with propynylmagnesium bromide furnished the 17-propynylcarbinol (V) which on mild hydrolysis with oxalic acid[12] in methanol gave the desired unconjugated keto compound 17α-propynyl-$\Delta^{5(10)}$-estren-17β-ol-3-one (VI) while more vigorous hydrolysis with hydrochloric acid in methanol gave the conjugated 17α-propynyl-19-nortestosterone (VII).

To prepare 6α-fluoro-17α-ethynyltestosterone[13] (XIIa) and the corresponding 17-acetate XIIb the key step of boron trifluoride[14] opening of a 5α,6α-epoxide was utilized. Thus 17α-ethynyl-Δ^5-androstene-3β,17β-diol[15,16] (VIIIa) was converted to the 5α,6α-oxide IXa by oxidation with monoperphthalic acid. Fission of IXa with boron trifluoride etherate in benzene–ether yielded the 5α-hydroxy-6β-fluoro compound Xa which was

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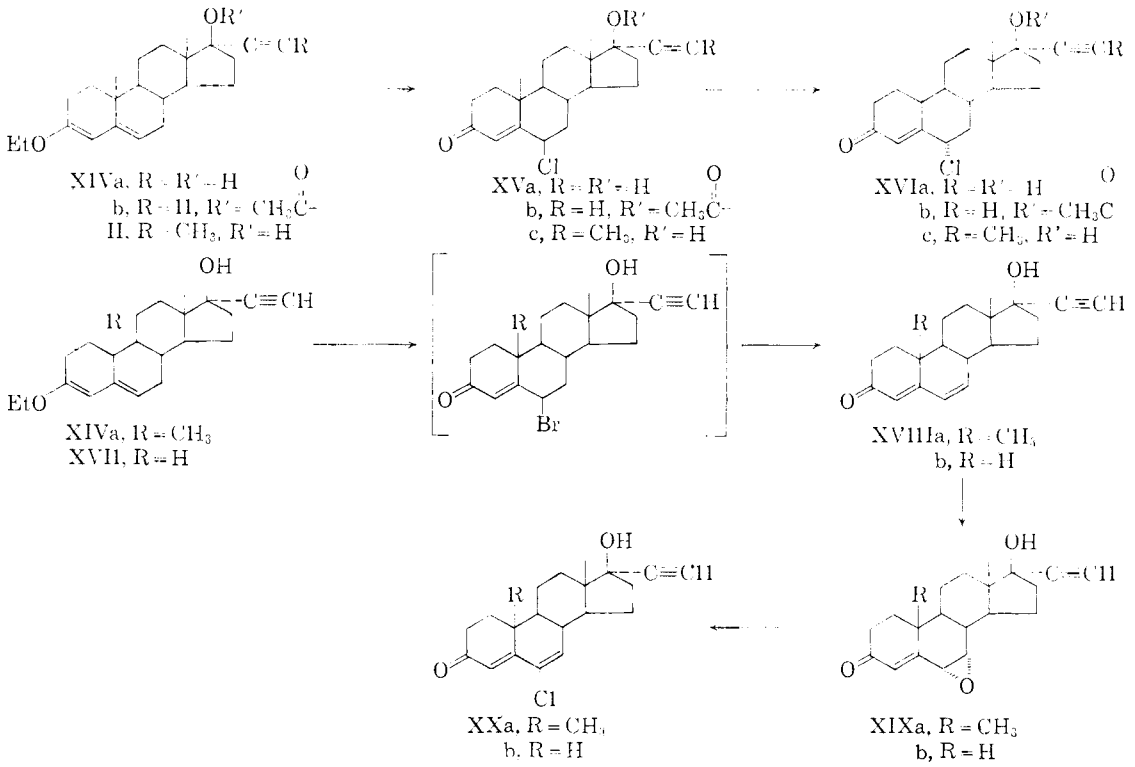

oxidized with chromic acid to the 3-keto compound XIa. Treatment of XIa with anhydrous hydrogen chloride in acetic acid then smoothly dehydrated the 5α-hydroxyl group and inverted the 6β-fluorine to yield 6α-fluoro-17α-ethynyltestosterone (XIIa). Similarly 17α-ethynyl-Δ^5-androstene-3β,17β-diol 17-monoacetate[16] (VIIIb), prepared by selective hydrolysis of the diacetate,[16] was converted to the α-epoxide IXb, fluorohydrin Xb, 3-ketofluorohydrin XIb and 6α-fluoro-17α-ethynyltestosterone 17-acetate (XIIb). Oxidation of XIIa with selenium dioxide[17] in *t*-butyl alcohol effected dehydrogenation at C-1,2 and afforded 6α-fluoro-17α-ethynyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one (XIII).

Application of our recently described addition[9,18] of hypochlorous acid to a $\Delta^{3,5}$-enol ether led to the desired 6-chloro derivatives. Thus the 3-ethyl enol ethers (XIVa, XIVb and II) of 17α-ethynyltestosterone, 17α-ethynyltestosterone 17-acetate and 17α-propynyltestosterone were respectively treated with N-chlorosuccinimide in aqueous buffered acetone to yield the 6β-chloro-Δ^4-3-keto compounds (XVa,b,c). Compounds XVa and XVb were inverted to the 6α-chloro derivatives XVIa and XVIb by treatment with hydrogen chloride in acetic acid. Some difficulties were encountered in the inversion of 6β-chloro-17α-propynyltestosterone (XVc) to the α-isomer by this method and thus this transformation was accomplished in two steps; XVc was converted to its ethyl enol ether which on very mild hydrolysis gave 6α-chloro-17α-propynyltestosterone (XVIc).

Since we had previously found that in the 17α-acetoxyprogesterone series the most marked increase in progestational activity was obtained by introduction of the 6-chloro-6-dehydro grouping,[9] it was clearly of interest to prepare the corresponding ethynyl derivatives.

Thus 17α-ethynyltestosterone and its 19-nor analog were converted to their 3-ethyl enol ethers (XIVa and XVII) which on treatment with N-bromosuccinimide in aqueous buffered acetone yielded the corresponding 6β-bromo-Δ^4-3-ketones.[9] Dehydrobromination of these compounds with calcium carbonate in boiling dimethylformamide furnished the 3-keto-$\Delta^{4,6}$-dienones (XVIIIa,b), and these were epoxidized with monoperphthalic acid to the 6α,7α-oxido-Δ^4-3-ketones.[19] Treatment of the latter with anhydrous hydrogen chloride in acetic acid yielded the desired 6-chloro-6-dehydro-17α-ethynyltestosterone (XXa) and -19-nortestosterone (XXb).

Table I lists the approximate oral progestational activity in the Clauberg assay of some of these compounds compared to 17α-ethynyl-19-nortestosterone (Norlutin) = 1.[20]

Experimental[21]

17α-Propynyl-3-ethoxy-$\Delta^{3,5}$-androstadien-17β-ol (II).—A cold solution of 26 g. of propyne gas in 500 ml. of dry tetrahydrofuran was added with stirring to 100 ml. of ethereal 3 *N* methylmagnesium bromide cooled to 0° and the solution

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(20) Bioassays by the Endocrine Laboratories, Madison, Wisc.

(21) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 96% ethanol. We are grateful to Dr. L. Throop for the determination of physical constants.

TABLE I

ORAL PROGESTATIONAL ACTIVITY—CLAUBERG ASSAY

17α-Ethynyl-19-nortestosterone	1
17α-Propynyl-19-nortesterone	1.2
6α-Fluoro-17α-ethynyltestosterone	1
6α-Fluoro-17α-ethynyltestosterone 17-acetate	<0.2
1-Dehydro-6α-fluoro-17α-ethynyltestosterone	0.5
6α-Chloro-17α-ethynyltestosterone	1
6α-Chloro-17α-ethynyltestosterone 17-acetate	0.5
6-Dehydro-17α-ethynyl-19-nortestosterone	0.4
6-Chloro-6-dehydro-17α-ethynyltestosterone	0.3
6-Chloro-6-dehydro-17α-ethynyl-19-nortestosterone	2

then stirred for 2 hours (methane evolution was visible). A solution of 3-ethoxy-$\Delta^{3,5}$-androstadien-17-one[10] (I) (25 g.) in 100 ml. of dry benzene was added and the solution boiled for 3 hours under nitrogen. The cooled solution was treated with 25 g. of ammonium chloride in 250 ml. of water, ether (500 ml.) was added, the organic phase separated and the aqueous phase extracted with 3 portions of ether. The dried extract was evaporated under reduced pressure at room temperature and the residue crystallized from acetone affording crude II, 22 g., m.p. 146–153°. Recrystallization from acetone yielded 17.6 g. of pure II, m.p. 160–162°, λ_{max} 241 mμ, log ε 4.28, $[\alpha]_D$ −234°.

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.09; H, 9.60.

17α-Propynyltestosterone (III).—A suspension of 500 mg. of enol ether II in 9 ml. of methanol containing 0.6 ml. of concentrated hydrochloric acid and 0.4 ml. of water was stirred at room temperature with complete solution occurring after 45 min. After standing for an additional hour at room temperature, the product was precipitated in ice-water, the product collected, washed and dried yielding 0.42 g. of IX, m.p. 149–151°. The analytical specimen from acetone exhibited m.p. 182–184°, λ_{max} 241 mμ, log ε 4.20, $[\alpha]_D$ +18°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.20; H, 9.43.

17α-Propynyl-3-methoxy-$\Delta^{2,5(10)}$-estradien-17β-ol (V).—1,4-Dihydroestrone methyl ether[11] (IV) (25 g.) was treated with propynylmagnesium bromide exactly as described above. Crystallization from acetone gave 16.9 g. of V, m.p. 175–180°, and 5.38 g., m.p. 163–165°. A sample recrystallized from acetone had m.p. 183–185°, $[\alpha]_D$ +47°, no absorption maximum in the ultraviolet.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.58; H, 8.94.

17α-Propynyl-$\Delta^{5(10)}$-estren-17β-ol-3-one (VI).—A solution of 3.0 g. of the enol ether V (m.p. 175–180°) in 240 ml. of methanol containing 3.9 g. of oxalic acid and 15 ml. of water was held at 20–25° for 40 min. and then precipitated in ice-water. The filtered and dried residue was taken up in benzene and absorbed on 150 g. of neutral (ethyl acetate-washed) alumina whereupon elution with benzene–ether (1:1) furnished 1.24 g. of 3-keto-$\Delta^{5(10)}$ compound VI, m.p. 130–141°. Recrystallization from acetone raised the m.p. to 147–149°, $[\alpha]_D$ +117°, no absorption in the ultraviolet (λ_{max} 240 mμ in presence of acid or alkali).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03: Found: C, 80.47; H, 9.20.

17α-Propynyl-19-nortestosterone (VII).—A solution of enol ether V (1.5 g.) in methanol (100 ml.) containing 1.8 ml. of concentrated hydrochloric acid and 1.2 ml. of water was boiled for 20 minutes and then precipitated in water. The filtered and dried product, 1.2 g., m.p. 152–156°, afforded pure VII after recrystallization from acetone, m.p. 160–163°, λ_{max} 240 mμ, log ε 4.24, $[\alpha]_D$ −32°.

Anal. Calcd. for $C_{21}H_{28}O_2 \cdot {}^1/_2C_3H_6O$: C, 79.13; H, 9.15. Found: C, 79.57; H, 9.30.

17α-Ethynyl-5α,6α-oxidoandrostane-3β,17β-diol (IXa).—A cold solution of 50 g. of 17α-ethynyl-Δ^5-androstene-3β, 17β-diol[15,16] (VIIIa) in 1.2 l. of chloroform–tetrahydrofuran (1:1) was treated with 420 ml. of an ether solution containing 35 g. of monoperphthalic acid and the mixture allowed to stand for 18 hours at 0–5° before washing with sodium carbonate solution and water. The dried solution was concentrated *in vacuo* and the residue crystallized from methanol to yield 30 g. of α-epoxide IXa, m.p. 229–231°, $[\alpha]_D$ −115°. The analytical specimen from acetone melted at 242–244°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.08; H, 9.32.

6β-Fluoro-17α-ethynylandrostane-3β,5α,17β-triol (Xa).—To a solution of 7.1 g. of epoxide IXa in 700 ml. of dry benzene–ether (1:1), 10 ml. of freshly distilled boron trifluoride etherate was added. After standing for 4 hours at 25° the solution was washed successively with 5% sodium carbonate solution and water, dried and concentrated to dryness. The residue was crystallized from methanol to yield 2.0 g. of fluorohydrin Xa, m.p. 245–248°, and the mother liquors in benzene solution were chromatographed on 400 g. of neutral alumina. Elution with benzene–ether (1:1, 1 l.) afforded 2.76 g. of starting epoxide IXa while further elution with the same solvent mixture (1.5 l.) yielded an additional 1.61 g. of fluorohydrin, m.p. 240–252°, for a total yield of 3.61 g. of Xa (78.4% based on recovered epoxide). Recrystallization from acetone gave the analytical sample, m.p. 251–253°, $[\alpha]_D$ −54°.

Anal. Calcd. for $C_{21}H_{31}FO_3$: C, 71.96; H, 8.92; F, 5.42. Found: C, 71.75; H, 8.85; F, 5.30.

6β-Fluoro-17α-ethynylandrostane-5α,17β-diol-3-one (XIa).—A solution of 3.0 g. of fluorohydrin Xa in 75 ml. of acetone held at 0° was treated dropwise with stirring with 4 ml. of 8 *N* chromic acid in sulfuric acid[22] over a period of 5 min. After an additional 2 minutes stirring the mixture was diluted with water and the sparingly soluble product isolated by ether extraction. Recrystallization from acetone yielded 1.77 g. of ketofluorohydrin XIa, m.p. 250–252°, $[\alpha]_D$ −21°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.39; H, 8.39. Found: C, 72.60; H, 8.44.

6α-Fluoro-17α-ethynyltestosterone (XIIa).—A solution of 0.58 g. of XIa in 30 ml. of glacial acetic acid was saturated with dry hydrogen chloride at 15°, the reaction mixture stoppered and allowed to stand at room temperature for 16 hours. Precipitation in water and ether extraction gave crude XIIa, crystallized from acetone–ether to yield 0.22 g. of pure 6α-fluoro-17α-ethynyl testosterone, m.p. 236–238°, λ_{max} 236 mμ, log ε 4.20, $[\alpha]_D$ ± 0° (reported[13] m.p. 237–239°, $[\alpha]_D$ +30°.

Anal. Calcd. for $C_{21}H_{27}FO_2$: C, 76.33; H, 8.24; F, 5.75. Found: C, 76.69; H, 8.50; F, 5.31.

17α-Ethynyl-Δ^5-androstene-3β,17β-diol-17-Acetate (VIIIb).—A solution of 5.0 g. of 17α-ethynyl-Δ^5-androstene-3β, 17β-diol diacetate,[16] m.p. 166–167°, in 50 ml. of tetrahydrofuran and 200 ml. of methanol was treated with 0.94 g. of potassium carbonate in 10 ml. of water. The solution was held at 28° for 3 hours, neutralized with acetic acid, diluted with water and the product isolated by ether extraction. Crystallization of the residue from acetone–hexane afforded the 17-monoacetate VIIIb, 3.04 g., m.p. 193–195°, raised to 203–208° by further crystallization from the same solvent pair, $[\alpha]_D$ −109°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.26; H, 9.32.

17α-Ethynyl-5α,6α,-oxidoandrostane-3β,17β-diol 17-Acetate (IXb).—A stirred solution of 4.5 g. of VIIIb in 50 ml. of chloroform was treated at −70 to −80°, and over a 30-min. period with 3.5 g. of monoperphthalic acid in 44 ml. of ether. The mixture was then allowed to stand for 16 hours at 0–5° before washing with sodium carbonate and water and evaporating to dryness. Crystallization from ether afforded 3.59 g. of α-epoxide IXb, m.p. 141–154°, raised to 157–158° by two further crystallizations from ether, $[\alpha]_D$ −99°.

Anal. Calcd. for $C_{23}H_{32}O$: C, 74.16; H, 8.66. Found: C, 74.53; H, 8.95.

6β-Fluoro-17α-ethynylandrostane-3β,5α,17β-triol 17-Acetate (Xb).—The epoxide IXb (4.4 g.) was treated with boron trifluoride exactly as described for the preparation of Xa. The total crude reaction product was then chromatographed on 200 g. of neutral alumina, whereupon elution with benzene–acetone (4:1, 400 ml.) afforded 2.0 g. of recovered epoxide IXb and continued elution with the same mixture (1.1 l.) yielded 2.1 g. of fluorohydrin Xb, m.p. 212–215°. The analytical sample, from methanol, exhibited m.p. 226–229°, $[\alpha]_D$ −60°.

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Anal. Calcd. for $C_{23}H_{33}FO_4$: C, 70.38; H, 8.47; F, 4.84. Found: C, 70.32; H, 8.48; F, 4.62.

6β-Fluoro-17α-ethynylandrostane-5α,17β-diol-3-one 17-Acetate (XIb).—Oxidation of 0.9 g. of Xb was carried out as described in the preparation of XIa. Crystallization from acetone–ether gave 0.44 g. of XIb, m.p. 243–246°, $[\alpha]_D$ −39°.

Anal. Calcd. for $C_{23}H_{31}FO_4$: C, 70.79; H, 8.00; F, 4.87. Found: C, 70.48; H, 8.21; F, 4.36.

6α-Fluoro-17α-ethynyltestosterone 17-Acetate (XIIb).—Dehydration and inversion of 300 mg. of XIb as described for the preparation of XIIa, followed by ether crystallization afforded 210 mg. of 6α-fluoro-17α-ethynyltestosterone 17-acetate, m.p. 188–190°. Further crystallization from ether raised the m.p. to 200–202°, λ_{max} 236 mμ, log ε 4.14, $[\alpha]_D$ +69°.

Anal. Calcd. for $C_{23}H_{29}FO_3 \cdot H_2O$: C, 70.79; H, 8.00; F, 4.87. Found: C, 71.27; H, 8.09; F, 4.26.

6α-Fluoro-17α-ethynyl-Δ^{1,4}-androstadien-17β-ol-3-one (XIII).—A mixture of 6α-fluoro-17α-ethynyltestosterone (XIIa) (500 mg.), selenium dioxide (260 mg.), pyridine (0.07 ml.) and *t*-butyl alcohol (25 ml.) was boiled for 24 hours under nitrogen. The cooled solution, after filtration through Celite, was concentrated to dryness *in vacuo* and water added to the residue. The resultant gum, which solidified on rubbing, was filtered, washed, dried and chromatographed on 20 g. of washed alumina. The product, eluted by benzene, was recrystallized from acetone–ether to yield 100 mg. of Δ^{1,4}-dienone XIII, m.p. 209–213°, λ_{max} 243 mμ, log ε 4.24, $[\alpha]_D$ −15°.

Anal. Calcd. for $C_{21}H_{25}FO_2$: C, 76.80; H, 7.67; F, 5.80. Found: C, 76.53; H, 7.91; F, 5.52.

3-Ethoxy-17α-ethynyl-Δ^{3,5}-androstadien-17β-ol (XIVa).—A suspension of 17α-ethynyltestosterone (5 g.) in anhydrous dioxane (150 ml.) and ethyl orthoformate (10 ml.) was treated with 300 mg. of *p*-toluenesulfonic acid·H_2O and then stirred for 3 hours. The homogeneous solution was treated with pyridine (5 ml.) and 250 ml. of water added dropwise with stirring. The crystalline product which separated was filtered, washed with water, dried and recrystallized from hexane, yielding 4.2 g. of enol ether XIVa, m.p. 159–161°, λ_{max} 241 mμ, log ε 4.32, $[\alpha]_D$ −210°.

Anal. Calcd. for $C_{25}H_{32}O_2$: C, 81.12; H, 9.47. Found: C, 81.22; H, 9.30.

6β-Chloro-17α-ethynyltestosterone (XVa).—Enol ether XIVa (6 g.) was dissolved in 200 ml. of acetone containing 3.4 g. of sodium acetate dissolved in 34 ml. of water and the mixture cooled to 0°. N-Chlorosuccinimide (3.3 g.), immediately followed by glacial acetic acid (3.4 ml.), was added and the mixture stirred for 1.5 hours at 0–5° and then poured into ice-water. The filtered, washed and dried product was crystallized from acetone–ether, to yield in two crops, 4.42 g. of XVa, m.p. 197–198°. The analytical specimen from the same solvent pair exhibited m.p. 200–201°, λ_{max} 241 mμ, log ε 4.14, $[\alpha]_D$ −43°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 72.76; H, 7.76; Cl, 10.22. Found: C, 72.99; H, 7.89; Cl, 10.01.

6α-Chloro-17α-ethynyltestosterone (XVIa).—A solution of 6β-chloro-17α-ethynyltestosterone (3.34 g.) in glacial acetic acid (135 ml.) was treated with concentrated hydrochloric acid (11 ml.) and allowed to stand for 6 hours at room temperature. Water was added, the resultant precipitate washed, dried *in vacuo* and crystallized from acetone–ether yielding 1.14 g. of 6α-chloro-17α-ethynyltestosterone, m.p. 169–172°. Repeated recrystallization from acetone–ether raised the m.p. to 180–182°, λ_{max} 236 mμ, log ε 4.16, $[\alpha]_D$ +13°.

Anal. Calcd. for $C_{21}H_{27}ClO_2$: C, 72.76; H, 7.76; Cl, 10.22. Found: C, 72.99; H, 7.85; Cl, 9.70.

3-Ethoxy-17α-ethynyl-Δ^{3,5}-androstadien-17β-ol Acetate (XIVb).—A solution of 17α-ethynyltestosterone 17-acetate[23] (4.2 g.), dioxane (30 ml.), ethyl orthoformate (4.2 ml.) and *p*-toluenesulfonic acid·H_2O (130 mg.) was allowed to stand for 45 min. Pyridine (3.5 ml.) and water (60 ml.) were added, the precipitate filtered, washed and recrystallized from aqueous methanol containing a few drops of pyridine to yield 3.8 g. of XIVb, m.p. 181–183°, λ_{max} 241 mμ, log ε 4.30, $[\alpha]_D$ −198°.

Anal. Calcd. for $C_{25}H_{34}O_3$: C, 78.49; H, 8.95. Found: C, 78.19; H, 8.99.

6β-Chloro-17α-ethynyltestosterone Acetate (XVb).—Treatment of 3.5 g. of enol ether XIVb with N-chlorosuccinimide exactly as described for the preparation of XVa and treatment of the crude product with hexane gave 1.75 g. of amorphous XVb, m.p. 140–151°, λ_{max} 240 mμ, log ε 4.10, $[\alpha]_D$ −45°. Satisfactory elemental analyses could not be obtained.

6α-Chloro-17α-ethynyltestosterone Acetate (XVIb).—Anhydrous hydrogen chloride was slowly bubbled through a solution of 1.75 g. of XVb (m.p. 140–151°) in 40 ml. of glacial acetic acid for a period of 2 hours, the solution temperature being held between 15–18°. Precipitation in water gave the crude product which was chromatographed on 45 g. of silica gel. The benzene–ether (19:1) eluates were pooled and recrystallized from acetone–hexane to yield 170 mg. of XVIb, m.p. 155–160°. Recrystallization from ether gave material of m.p. 162–164°, λ_{max} 236 mμ, log ε 4.10, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{23}H_{29}ClO_3$: C, 71.02; H, 7.51; Cl, 9.11. Found: C, 71.05; H, 7.70; Cl, 9.00.

6β-Chloro-17α-propynyltestosterone (XVc).—Treatment of enol ether II (2.0 g.) exactly as described for the preparation of XVa and crystallization of the crude product from acetone afforded 1.41 g. of 6β-chloro-17α-propynyltestosterone (XVc), m.p. 200–202°, λ_{max} 240 mμ, log ε 4.15, $[\alpha]_D$ −49°.

Anal. Calcd. for $C_{23}H_{29}ClO_2$: C, 73.21; H, 8.09. Found: C, 72.90; H, 8.39.

6α-Chloro-17α-propynyltestosterone (XVIc).—A solution of 1 g. of XVc in 10 ml. of dioxane was treated with ethyl orthoformate (1 ml.) and *p*-toluenesulfonic acid·H_2O (30 mg.) and the mixture allowed to stand for 3.5 hours. Precipitation in water containing a few drops of pyridine gave 0.77 g. of crude 6-chloro-17α-propynyl-3-ethoxy-Δ^{3,5}-androstadien-17β-ol, exhibiting, after methanol crystallization, m.p. 145–150°, $[\alpha]_D$ −147°, λ_{max} 251 mμ, log ε 4.20. A suspension of 250 mg. of this enol ether in 4.5 ml. of methanol containing 0.3 ml. of 12 *N* hydrochloric acid and 0.2 ml. of water was stirred at room temperature for 3 hours and then poured into water. The product was filtered, washed, dried and recrystallized several times from acetone–hexane to yield the analytical specimen of 6α-chloro-17α-propynyltestosterone (XVIc), m.p. 118–121°, $[\alpha]_D$ +28°, λ_{max} 237 mμ, log ε 4.06.

Anal. Calcd. for $C_{23}H_{29}ClO_2$: C, 73.21; H, 8.10; Cl, 9.84. Found: C, 73.01; H, 8.42; Cl, 9.51.

6-Dehydro-17α-ethynyltestosterone (XVIIIa).—A solution of 17α-ethynyltestosterone enol ether (XIVa) (3 g.) was dissolved in 120 ml. of acetone containing 2.2 g. of sodium acetate dissolved in 15 ml. of water and the mixture cooled to 0°. N-Bromosuccinimide (3.2 g.), immediately followed by glacial acetic acid (2.5 ml.), was added and the mixture stirred for 3 hours at 0–5° and then poured into water. The crude 6-bromo-17α-ethynyltestosterone thus obtained (3.0 g., m.p. 151–153°) was heated for 45 min. in a boiling suspension of 2 g. of calcium carbonate in 30 ml. of dimethylformamide. The hot mixture was filtered, the precipitate washed with ethyl acetate, the combined solutions concentrated *in vacuo* to *ca.* 30 ml. and precipitated in water. The crude XVIIIa, 2.1 g., m.p. 260–262°, was collected, dried and recrystallized from chloroform–ether yielding 1.83 g. of pure 6-dehydro-17α-ethynyltestosterone, m.p. 262–265°, λ_{max} 284 mμ, log ε 4.43, $[\alpha]_D$ −85°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44; O, 10.31. Found: C, 81.51; H, 8.40; O, 10.51.

6α,7α-Oxido-17α-ethynyltestosterone (XIXa).—A solution of 2 g. of XVIIIa dissolved in 200 ml. of methylene dichloride was cooled to 5°, treated with 56 ml. of 1.15 *N* ethereal monoperphthalic acid and allowed to stand for 20 hours at room temperature. The mixture was then poured into excess sodium bicarbonate, the organic layer separated, washed with water, dried and evaporated. Crystallization from chloroform–ether yielded 0.98 g. of 6α,7α-oxide XIXa, m.p. 284–286°, raised by further crystallization to 289–291°, λ_{max} 241 mμ, log ε 4.23, $[\alpha]_D$ −28°.

(23) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03; O, 14.70. Found: C, 77.04; H, 8.22; O, 14.51.

6-Chloro-6-dehydro-17α-ethynyltestosterone (XX).—A suspension of 2.29 g. of epoxide XIXa in 150 ml. of glacial acetic acid was saturated at room temperature with anhydrous hydrogen chloride and allowed to stand for 4 hours before pouring into water. The product was isolated by methylene dichloride extraction and then purified by chromatography on 60 g. of neutral alumina. The hexane–benzene (1:4) fractions were crystallized from acetone–ether to yield 380 mg. of XX, m.p. 190–195°. The analytical specimen, from the same solvents, melted at 193–195°, λ_{max} 286 mμ, log ε 4.33, $[\alpha]_D$ −58°.

Anal. Calcd. for $C_{21}H_{25}ClO_2$: C, 73.13; H, 7.31; Cl, 10.30. Found: C, 73.40; H, 7.20; Cl, 10.25.

17α-Ethynyl-19-nor-3-ethoxy-$\Delta^{3,5}$-androstadien-17β-ol (XVII).—17α-Ethynyl-19-nortestosterone (2 g.) was treated with ethyl orthoformate as described for the preparation of XIVa. Crystallization of the water-precipitated product from hexane yielded 1.55 g. of still somewhat impure enol ether, m.p. 165–170°. The analytical specimen of XVIII (from hexane) melted at 187–189°, λ_{max} 242 mμ, log ε 4.35, $[\alpha]_D$ −228°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; O, 9.81. Found: C, 80.60; H, 9.02; O, 10.02.

6-Dehydro-17α-ethynyl-19-nortestosterone (XVIIIb).—17α-Ethynyl-19-nortestosterone enol ether (XVII) (4.3 g.) was treated, according to the preparation of XVIIIa, with N-bromosuccinimide and the crude total 6β-bromo-17α-ethynyl-19-nortestosterone dehydrobrominated with calcium carbonate in dimethylformamide. Crystallization of the crude product from ethyl acetate gave 2.53 g. of XVIIIb, m.p. 243–247°. The analytical sample (from methanol) exhibited m.p. 251–252°, λ_{max} mμ, log ε 4.38, $[\alpha]_D$ −151°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; O, 10.80. Found: C, 80.79; H, 8.29; O, 11.20.

6α,7α-Oxido-17α-ethynyl-19-nortestosterone (XIXb).—A solution of 2.2 g. of 6-dehydro-17α-ethynyl-19-nortestosterone (XVIIIb) in 240 ml. of methylene dichloride was allowed to stand for 40 hours at room temperature with 65 ml. of 1.04 *N* monoperphthalic acid in ether. The solution was washed with aqueous saturated sodium carbonate and water to neutrality then dried and evaporated. Crystallization of the residue from acetone provided 380 mg. of XIXb, m.p. 260–264°, raised by further crystallization from acetone to 264–267°, λ_{max} 241 mμ, log ε 4.18, $[\alpha]_D$ −50°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; O, 15.37. Found: C, 76.71; H, 7.83; O, 15.60.

6-Chloro-6-dehydro-17α-ethynyl-19-nortestosterone (XXb).—A solution of 250 mg. of epoxide XIXb in 10 ml. of glacial acetic acid saturated with hydrogen chloride was kept at 20–25° for 3 hours and then diluted with ice-water. The resultant crystals, 150 mg., m.p. 108–112°, λ_{max} 284 mμ, log ε 4.16, were chromatographed on 3 g. of neutral alumina. Benzene elution gave 100 mg. of XXb, m.p. 145–150°, recrystallized several times from ether–pentane to give a pure sample of 6-chloro-6-dehydro-17α-ethynyl-19-nortestosterone, m.p. 156–158°, λ_{max} 283 mμ, log ε 4.35, $[\alpha]_D$ −83°.

Anal. Calcd. for $C_{20}H_{23}ClO_2$: C, 72.60; H, 7.00; O, 9.60. Found: C, 72.44; H, 7.02; O, 9.84.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. XIV.[1] 16α-Hydroxy-6α-methyl-corticoids. Part I

BY SEYMOUR BERNSTEIN AND RUDDY LITTELL

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The synthesis of a number of related 16α-hydroxy-6α-methyl-corticoids is described. 16α-Hydroxy-6α-methylprednisolone (XVI) has been prepared in an over-all yield of 2.3% *via* a seventeen-stage synthesis from cortisone (I). Compound XVI was also prepared in an over-all yield of 7.6% *via* a nine-stage synthesis from 6α-methylcortisone (XXII).

Recently this Laboratory has published on the preparation and biological properties of 16α-hydroxy-2-methyl-corticoids.[2] We now wish to report in part[3] on the preparation of 16α-hydroxy-6-methyl-corticoids, in particular the preparation of the 16α-hydroxy-derivatives of 6α-methylhydrocortisone and 6α-methylprednisolone.[4]

The chemical syntheses[5] elaborated utilized the 5α,6α-epoxide II of hydrocortisone 3,20-bis-ethylene ketal[6] as the starting material. Treatment of II with methylmagnesium bromide afforded in 75% yield 3,20 - bis - ethylenedioxy - 6β - methylpregnane-5α,11β,17α,21-tetrol (III).[7] Oxidation of the latter with chromium trioxide–pyridine complex[8] gave the desired 3,20-bis-ketal 11-one Va for which suitable elemental analyses could not be obtained. The compound on recrystallization gave variable melting points, probably ascribable to solvation. Acetylation provided the 3,20-bis-ketal 11-one 21-acetate Vb. This intermediate was also obtained by acetylation (90% yield) of III followed by oxidation (93% yield). This latter procedure was the preferred preparative route to Vb. Heat-

(1) Paper XIII, S. Bernstein, R. H. Lenhard, N. E. Rigler and M. A. Darken, *J. Org. Chem.*, in press.

(2) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen and I. Ringler, THIS JOURNAL, **81**, 1696 (1959).

(3) The preparation of the 16α-hydroxy-derivatives of 9α-halogeno-6-methylcorticoids will be described in the forthcoming Part II of this research.

(4) (a) 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); (b) G. B. Spero, J. L. Thompson, F. H. Lincoln, W. J. Schneider and J. A. Hogg, *ibid.*, **79**, 1515 (1957); (c) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957); (d) J. H. Fried, G. E. Arth and L. H. Sarett, THIS JOURNAL, **81**, 1235 (1959).

(5) Preliminary attempts to effect 16α-hydroxylation of 6α-methylhydrocortisone and 6α-methylprednisolone with *Streptomyces roseochromogenus* (Lederle AE 409) were not promising. This observation also pertains to 2-methyl-corticoids.

(6) The three stage-synthesis (24% over-all yield) of the bis-ketal epoxide II from cortisone (I) has been described by R. Littell and S. Bernstein, THIS JOURNAL, **78**, 984 (1956); see also, S. Bernstein and R. H. Lenhard, *ibid.*, **77**, 2233 (1955).

(7) This intermediate has been described by G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, ref. 4c. Its preparation was accomplished independently in this Laboratory prior to the British publication. In this connection see also ref. 4a.

(8) The stability of the C21-hydroxy group adjacent to a C20-ketal group under these oxidation conditions has been noted by W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954), and subsequently utilized by S. Bernstein and R. H. Lenhard, ref. 6 and R. Littell and S. Bernstein, ref. 6.