acid and 2.7 ml of triethylamine. The resulting solution was heated under reflux for 1 hr, cooled, and diluted with water. The crude product was filtered and recrystallized from aqueous acetone to afford 0.05 g (25%) of product, mp 102–110°. The analytical sample, recrystallized from aqueous acetone, had mp 115–117°, $[\alpha]^{28}D$ +220° (*c* 0.9, $CHCl_3$).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.57; H, 9.77.

20-Methylenepregn-4-en-3-one (XI).—A solution of 1.5 g (0.0042 mole) of X in 100 ml of acetone and 5 ml of 2 *N* HCl was refluxed for 1.5 hr. The acetone was evaporated under reduced pressure and water was added. The precipitate was filtered, washed with water, and dried, giving 1.0 g of product, mp 152–157°. Further recrystallization gave the analytical sample: mp 157–158°; $[\alpha]^{28}D$ +105° (*c* 1, $CHCl_3$); nmr, 0.62 (C-18 H) (3 H), 1.18 (C-19 H) (3 H), 1.75 (C-21 H) (3 H), 4.68 (1 H), 4.80 (20-methylene) (1 H), 5.68 (C-4 H) (1 H).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.73; H, 10.35.

3-Methylenepregn-4-en-20-one (XIV).—A solution of 1.0 g (0.003 mole) of XIII in 80 ml of acetone was treated dropwise with 8 *N* chromic acid reagent at 0°. Thin layer chromatography was used to monitor the course of the reaction. The excess chromic acid was decomposed with 2-propanol and the solvent was removed under reduced pressure. A gummy residue was obtained. It was extracted with ether, washed, and dried (Na_2SO_4). On evaporation of the ether and recrystallization from methanol there was obtained 0.30 g of product, mp 140–148°. Further recrystallizations from methanol gave the analytical sample, mp 148–149°, $[\alpha]^{18}D$ +268° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.24; H, 9.97.

20,20-Ethylenedioxypregn-5-ene-3β,21-diol 21-Acetate.—A solution of 4.2 g of 3β,21-dihydroxypregn-5-en-20-one 21-acetate in a mixture of 100 ml of ethylene glycol and 100 ml of benzene containing a trace of *p*-toluenesulfonic acid was heated under reflux for 3 hr. The benzene layer was washed with water and $NaHCO_3$ solution and dried ($CaSO_4$), and the benzene was removed *in vacuo*. The precipitate obtained was recrystallized from methanol giving 3.7 g of product: mp 135.5–136.5°; $[\alpha]^{26}D$ −33° (*c* 0.87, $CHCl_3$); nmr, 0.78 (C-18 H) (3 H), 1.00 (C-19 H) (3 H), 2.03 (acetate) (3 H), 3.98 (ethylenedioxy and C-21 H) (6 H), and 5.29 (C-6 H) (1 H).

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.61; H, 9.23.

20,20-Ethylenedioxy-21-hydroxypregn-4-en-3-one 21-Acetate.—To a solution of 3.0 g of 20,20-ethylenedioxypregn-5-ene-3β,21-diol 21-acetate in 50 ml of toluene and 30 ml of cyclohexanone there was added 5.0 g of aluminum isopropoxide, and the solution was heated under reflux. After the reaction, 50 g of sodium potassium tartrate was added and the mixture was steam distilled. The residue was extracted with CH_2Cl_2, and the CH_2Cl_2 was evaporated giving 1.4 g of crude oil. Crystallization from methanol gave 0.8 g of colorless product, mp 139–140° (lit.[18] mp 140–141° when prepared in another way).

20β,21-Dihydroxypregn-4-en-3-one 20-Acetate.—A solution of 1.00 g (0.0027 mole) of 3β,20β,21-trihydroxypregn-4-ene 21-acetate,[18] and 0.90 g (0.004 mole) of dichlorodicyanobenzoquinone in 22 ml of dioxane was stirred for 66 hr and filtered. The solid was washed with CH_2Cl_2, and the filtrate was concentrated, affording dark brown oily material, which was dissolved in CH_2Cl_2, washed with 10% NaOH solution and water, and dried. The resulting yellow oil was chromatographed on alumina; the fraction obtained from 1% methanol–ether (1:99%) was recrystallized from benzene–hexane (1:1) affording 0.78 g (78%) of colorless crystals: mp 188–190° (lit.[19] mp 185–188° when prepared by another method); nmr, 0.71 (C-18 H) (3 H), 1.17 (C-19 H) (3 H), 2.10 (acetate) (3 H), 5.69 (C-4 H) (1 H).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.96; H, 8.97.

3,3-Ethylenedioxy-21-hydroxypregn-5-en-20-one Acetate.— A mixture of 5.20 g (0.014 mole) of deoxycorticosterone acetate, 30 ml of 2-methyl-2-ethyldioxolane, and 50 mg of *p*-toluenesulfonic acid was refluxed for 3.5 hr and allowed to stand for 18 hr at 27°. The precipitate was filtered and purified by alumina chromatography (the benzene eluate contained the product), followed by recrystallization from ethanol affording 1.0 g of colorless crystals: mp 203–203.5° (lit.[18] mp 209–211° when prepared by another method); nmr, 0.68 (C-18 H) (3 H), 1.04 (C-19 H) (3 H), 2.16 (acetate) (3 H), 3.95 (ethylenedioxy) (4 H), 4.65 (C-6 H) (1 H). A total of 2.3 g of starting material was recovered.

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.20; H, 9.00.

21-Hydroxy-20-methylenepregn-4-en-3-one (XVII).—To a solution of 0.54 g (0.0015 mole) of XVI in 90% aqueous acetone there was added 0.5 ml of trifluoroacetic acid. The mixture was refluxed for 1.5 hr and the acetone was removed *in vacuo*. The precipitate was filtered and the resulting solid was recrystallized twice from methanol, affording 456 mg (92%) of colorless crystals: mp 155–156°; $[\alpha]^{28}D$ +122° (*c* 1.03, $CHCl_3$); nmr, 0.65 (C-18 H) (3 H), 1.19 (C-19 H) (3 H), 4.07 (C-21 H) (3 H), 4.94 (1 H), 5.25 (1 H), 5.73 (C-4 H) (1 H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.29; H, 9.63.

Anabolic Agents. 19-Nor- and 19-Substituted 5α-Androst-2-ene Derivatives

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A series of 19-nor- and 19-substituted 5α-androst-2-ene derivatives were synthesized as part of a continuing program aimed at the preparation of potentially useful anabolic steroids. The anabolic and androgenic properties associated with some of these compounds and their synthetic intermediates are described.

The growth-promoting or anabolic property of the male hormone, testosterone, has been known for many years.[2] Clinical use of testosterone for this purpose, however, is limited by its inherent androgenic properties. As a result, this past decade has witnessed the synthesis of a wide variety of structural modifications of testosterone in an effort to separate the desirable anabolic properties from the masculinizing features of the molecule.[3]

(1) The work conducted in these laboratories was supported by National Institutes of Health predoctoral fellowship 5-F1-GM-24992-02 and American Cancer Society Grant PRA-18.

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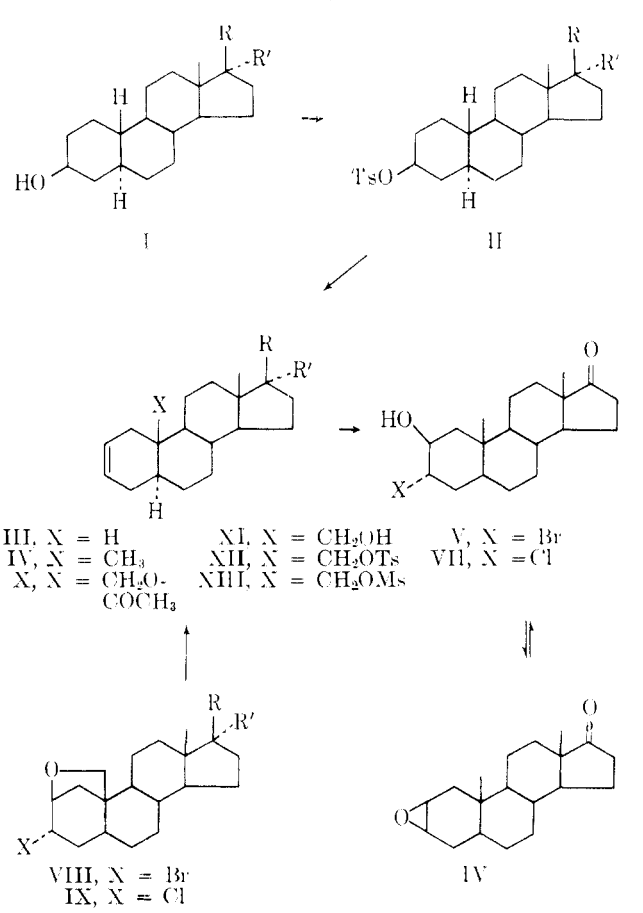
In the androstane series, several investigators[4-8] have noted that a C-3 oxygenated function is not essential for high biological activity. In particular, Edwards and Bowers[6] found that 17α-methyl-5α-androst-2-en-17β-ol (IVd) exhibited a favorable separation of anabolic and androgenic activities. They reported that this compound was two to five times as anabolic and only one-half as androgenic as methyltestosterone when given orally to rats. Prior to this report, similar findings had been made in our own laboratories.[9] In our bioassays, however, IVd was found to have twelve times the anabolic but less than twice the androgenic activity of methyltestosterone.

The observation of pronounced anabolic activity in association with a 3-deoxy steroid prompted us to synthesize and evaluate a number of structural analogs of IVd. Since previous studies from these and other laboratories[10-12] had shown that removal of the C-19 methyl group increases the anabolic:androgenic ratio in certain instances, the synthesis of the 19-nor congenor of IVd (IIId) and related compounds was undertaken. In addition, several 19-substituted analogs were prepared as part of an effort to obtain a better understanding of the structure–activity relationships associated with 19-functionalized androstane derivatives.

Recently, Wolff, Ho, and Kwok[8] reported on the synthesis of 17α-methyl-5α-estr-2-en-17β-ol (IIId) as part of an extensive program designed to elucidate the mode of combination of steroids with receptor sites. We used two approaches to this compound which differed slightly from the one used by Wolff's group. In one case, 3β-hydroxy-5α-estran-17-one (Ia) was converted to the tosylate (IIa) in 85% yield and this product was dehydrotosylated in refluxing collidine to give 5α-estr-2-en-17-one (IIIa) (see Scheme I). Reduction of the latter with sodium borohydride or alkylation with methyl Grignard furnished IIIb and IIId, respectively. The 17α-methylated product, IIId, was also obtained by selective tosylation of 17α-methyl-5α-estrane-3β,17β-diol followed by dehydrotosylation.

As a means of access to the desired 19-substituted analogs of IVd, the hypoiodite oxidation of 3α-halo-2β-hydroxy-5α-androstanes was investigated. Since this work was initiated, several other groups[13-15] have oxidized other 2β-hydroxyandrostanes under similar conditions. For our experiments the 3α-bromo- (V) and 3α-chloro-2β-hydroxy (VII) compounds were desired. The former was readily obtained by the addition of hypobromous acid to the olefin IVa. Addition of hypochlorous acid to IVa, however, was not as successful. For example, treatment of IVa with N-

SCHEME I



chlorosuccinimide and perchloric acid in dioxane afforded only starting material. Similarly, generation of hypochlorous acid *in situ* from isocyanuric chloride and acetic acid according to the method of Mukawa[16] furnished after chromatography less than a 12% yield of VII. The chlorohydrin was obtained in essentially quantitative yield, however, by cleavage of the 2,3β-epoxide (VI)[17] with hydrogen chloride in chloroform.

Hypoiodite oxidation of the halohydrins V and VII gave the expected 2β,19-oxido products VIIIa and IXa in 54 and 51.5% yield, respectively. The nmr spectra of these compounds showed typical *AB* absorption patterns for the nonequivalent C-19 geminal protons.[18] In both cases the J_{gem} was in the range of 8–9 cps which is in good agreement with values reported for 6β,19-oxido steroids.[19,20] Several by-products from this reaction have been isolated and identified and have been reported on elsewhere.[21]

In contrast with the ease by which 5α-bromo 6β,19-oxides are reductively cleaved by refluxing with zinc dust and isopropyl alcohol,[22] VIIIa was unaffected by such treatment. Transformation to the 19-acetoxy olefin Xa, however, was achieved in excellent yield

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(16) F. Mukawa, *J. Chem. Soc. Japan*, **78**, 452 (1957); *Chem. Abstr.*, **53**, 5338 (1959).
(17) The epoxide was obtained in 81% yield by treating the bromohydrin V with K_2CO_3 in aqueous DMF.
(18) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 42.
(19) J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963).
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when VIIIa was refluxed with zinc dust in acetic acid. Surprisingly, similar treatment of the chloro ether IXa did not give Xa but another acetate in which the 2,19-oxide bridge remained intact. This reaction has been studied in greater detail and will form the subject of a subsequent report. Saponification of Xa afforded the corresponding alcohol (XIa) from which the tosylate (XIIa) and mesylate (XIIIa) esters were prepared.

In contrast with the ready conversion of sulfonate esters of various 19-hydroxyandrost-5-ene derivatives to the corresponding C-19 halides under certain conditions,[23-25] attempts to form 19-halo analogs from XIIa or XIIIa have been unsuccessful. The products resulting from the treatment of these sulfonates with various nucleophiles are currently under investigation.

Biological Results.[26]—Table I compares the androgenic and anabolic activities for the compounds evaluated in this study. The procedures used in this evaluation were similar to that described previously by Nutting, *et al.*[27] The relative potencies are given in terms of per cent activity of testosterone propionate (intramuscular) or methyltestosterone (oral) and were determined from the minimal levels at which significant increases in ventral prostate and seminal vesicle or levator ani muscle weights were obtained.

TABLE I
RELATIVE ANDROGENIC AND ANABOLIC ACTIVITIES

Compd	Parenteral activity		Oral activity	
	Androgenic[a]	Anabolic	Androgenic[a]	Anabolic
IIIb	2.2	20	I[b]	I
IIId	1.9	6.5	34	110
IVb	5.8	17		
IVd	4.8	11	187	1200
Xb	I (<0.17)	I (<0.33)		
XIb	0.2	0.67	I	I
XId	<0.62	1.3	I	I
Testosterone propionate	100	100	40	67
Methyltestosterone	40	34	100	100

[a] The half-value of the sum of the ventral prostate and seminal vesicle response has been used as the criteria of androgenicity. [b] I = inactive at dose levels tested.

All of the compounds were much less active than testosterone propionate by parenteral administration. Similar to findings in the testosterone series,[10-12] conversion of IVb to its 19-nor analog (IIIb) caused a decrease in androgenic activity without affecting the anabolic activity. In addition, 19-acetoxylation or 19-hydroxylation (Xb or XIb) all but eliminated androgenic or anabolic activity.

Our results confirmed the earlier reports for the high oral activity for IVd. This compound was found to have approximately twice the androgenic and 12 times the anabolic activity of methyltestosterone and represents one of the most potent anabolic steroids studied to date. In this case, conversion to the 19-nor analog decreased both androgenic and anabolic activity. 19-Hydroxylation virtually eliminated the oral activity of IVd.

The 3α-bromo-2β,19-oxido compounds VIIIc and VIIId were found to be essentially devoid of anabolic and androgenic activity.

Experimental Section[28]

3β-Hydroxy-5α-estran-17-one *p*-Toluenesulfonate (IIa).—A solution of 3β-hydroxy-5α-estran-17-one (Ia, 10 g) and *p*-toluenesulfonyl chloride (10 g) in pyridine (30 ml) was allowed to stand at room temperature for 24 hr. The solution was poured into water and the resulting mixture was extracted with chloroform. The chloroform extract was washed successively with dilute HCl (1:3), 10% Na_2CO_3 solution, and water. The organic phase was dried (Na_2SO_4) and the solvent was removed by distillation under partially reduced pressure. The resulting crystalline product was triturated with hexane and collected by filtration. Recrystallization from chloroform–ethyl acetate gave 13.3 g (85%) of tosylate, mp 159–161.5° dec (lit.[29] mp 152–154.5° dec). Additional recrystallizations from the same solvent system furnished an analytical sample, mp 169–170° dec, $[\alpha]^{26}D$ +56°, λ_{max} 225 mμ (log ε 4.10).

Anal. Calcd for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.96. Found: C, 70.04; H, 8.11.

17α-Methyl-5α-estrane-3β,17β-diol 3-*p*-Toluenesulfonate (IId).—Tosylation of Id (0.55 g) as described above and recrystallization of the crude product from methylene chloride–hexane gave pure IId (0.72 g, 86%), mp 136–139° dec, λ_{max} 224.5 mμ (log ε 4.11).

Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.92; H, 8.58. Found: C, 70.00; H, 8.64.

5α-Estr-2-en-17-one (IIIa).—A solution of IIa (8.6 g) in collidine (100 ml) was stirred at reflux for 4 hr. The solution was allowed to cool and poured slowly into an ice–water mixture (1.5 l.) containing concentrated H_2SO_4 (100 ml). The precipitate was collected, washed with water, and air dried. The crude product (5.0 g) was dissolved in acetone (20 ml) and a mixture of ether–hexane (2:1, 150 ml) was added. The solution was decolorized with Darco and concentrated on the steam bath. The solution was allowed to cool and the resulting crystalline product was collected by filtration to furnish pure IIIa (3.5 g), mp 125–126.5°, $[\alpha]^{27}D$ +168.5° (lit.[29] mp 123.5–124.5°, $[\alpha]^{28}D$ +170°), nmr 55 (18-methyl) and 325–350 cps (C-2 and C-3 protons). A second crop (1.0 g), mp 120–124°, was collected.

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.78; H, 9.98.

5α-Estr-2-en-17β-ol (IIb).—Sodium borohydride (1.0 g) was added in portions to a solution of IIIa (2.0 g) in ethanol (50 ml). The solution was allowed to stand at room temperature for 20 hr and then poured slowly with stirring into 10% NH_4Cl solution (500 ml). The crystalline product was collected by filtration and recrystallized from ethyl acetate–heptane. This afforded IIIb (1.6 g), mp 108–112°. An additional recrystallization gave an analytical sample, mp 111.5–113.5, $[\alpha]^{27}D$ +85.5° (lit.[8] mp 111–113°, $[\alpha]^{28}D$ +100°).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.35; H, 10.89.

The acetate (IIIc) was prepared in the usual manner from acetic anhydride and pyridine. Recrystallization from methanol furnished an analytical sample, mp 97–98°, $[\alpha]^{25}D$ +56.6° (lit.[8] mp 96–98°, $[\alpha]^{28}D$ +68°).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.23; H, 9.78.

17α-Methyl-5α-estr-2-en-17β-ol (IIId). A. From IIIa.—A solution of IIIa (1.5 g) in dry tetrahydrofuran (20 ml) was added dropwise with stirring to a 3 *M* solution of methylmagnesium bromide in ether (10 ml). The mixture was refluxed

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(24) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *ibid.*, **4**, 1 (1964).

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(26) We are grateful to Drs. F. J. Saunders and E. F. Nutting of G. D. Searle and Co. for furnishing us with this information.

(27) E. F. Nutting, P. D. Klimstra, and R. E. Counsell, *Acta Endocrinol.*, in press.

(28) The optical rotations, spectra, and analytical data were furnished by Dr. R. T. Dillon, Mr. E. Zelinski, and Mr. J. Damascus of the G. D. Searle analytical department. The optical rotations were obtained in $CHCl_3$ and the ultraviolet spectra in methanol. The nmr spectra were obtained in $CDCl_3$ with a Varian A-60 spectrometer and are reported in cycles per second downfield from tetramethylsilane which was used as the internal standard. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

(29) D. K. Fukushima and S. Dobriner, *J. Org. Chem.*, **26**, 3022 (1961).

for 5 hr and allowed to stand overnight at room temperature. Ammonium chloride solution (2.5 ml, 10%) was added dropwise with stirring and the mixture was allowed to cool. Anhydrous Na_2SO_4 and THF (20 ml) was added and the mixture was filtered. The filtrate was concentrated to a syrup and the product crystallized from methanol–water (1.2 g), mp 133–135°. Recrystallization from methanol gave an analytical sample, mp 142–144° (lit.[8] mp 135–137°).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.85; H, 10.89.

B. From IId.—Dehydrotosylation of IId (1 g) in collidine (15 ml) as described above gave a crude product which was purified by chromatography over silica gel (60 g). Elution with benzene–ethyl acetate (19:1) gave IIId which upon recrystallization from methanol afforded a pure product (275 mg), mp 141–143.5°, identical with that above.

3α-Bromo-2β-hydroxy-5α-androstan-17-one (V).—To a cooled solution of 5α-androst-2-en-17-one[30] (IVa, 25 g) in purified dioxane (500 ml) was added dropwise with stirring a mixture of N-bromosuccinimide (17.6 g), 60% $HClO_4$ (17 g), and water (170 ml). The reaction mixture was stirred at room temperature for 3.5 hr and poured slowly into an ice–water mixture (2 l.). The mixture was stirred for 2 hr and the precipitate was collected. The crude product was washed well with water, dried, and recrystallized from methanol to give V (15.5 g), mp 194–196°. An analytical sample was prepared from acetone–hexane, mp 195–196°, $[\alpha]^{25}D$ +124°.

Anal. Calcd for $C_{19}H_{29}BrO_2$: C, 61.78; H, 7.91. Found: C, 61.91; H, 7.91.

2,3β-Epoxy-5α-androstan-17-one (VI).—A mixture of V (40 g), K_2CO_3 (16 g), DMF (500 ml), and water (75 ml) was stirred at 60° for 2.5 hr. Water (200 ml) was added slowly with stirring to the reaction mixture which was externally cooled with a cold-water bath. The resulting precipitate was collected, washed well with water, and air dried to give VI (25.3 g, 81%), mp 121–123°. Recrystallization of a sample from methanol afforded pure material, mp 121–123°, $[\alpha]^{25}D$ +132° (lit.[30] mp 121–122°, $[\alpha]^{20}D$ +144°).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.91; H, 9.68.

3α-Chloro-2β-hydroxy-5α-androstan-17-one (VII).—To an ice-cold saturated solution of HCl in chloroform (250 ml) was added dropwise with stirring a solution of VI (5.0 g) in $CHCl_3$ (100 ml). The solution was allowed to come to room temperature. After 2 hr, the solution was washed (5% $NaHCO_3$, H_2O) and dried (Na_2SO_4). Removal of the solvent afforded crude VII (5.7 g), mp 198–202°. Recrystallization from methanol gave needles (3.9 g), mp 201–203°, unraised by additional recrystallizations.

Anal. Calcd for $C_{19}H_{29}ClO_2$: C, 70.24; H, 9.00; Cl, 10.91. Found: C, 70.08; H, 8.89; Cl, 11.00.

3α-Bromo-2β,19-oxido-5α-androstan-17-one (VIIIa).—To a solution of V (18.5 g) in CCl_4 (1 l.) was added lead tetraacetate (67 g) and iodine (25.4 g). The mixture was refluxed with stirring for 8 hr and allowed to stand overnight at room temperature. The insoluble salts were removed by filtration and washed with methylene chloride. The filtrate was washed with two 300-ml portions of 10% sodium thiosulfate solution and water (500 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed by distillation *in vacuo*. The residue was dissolved in hexane–benzene (1:1, 100 ml) and adsorbed onto silica gel (1 kg). The column was eluted with benzene followed by benzene containing increasing amounts of ethyl acetate. Elution with benzene–ethyl acetate (19:1) gave crude VIIIa which upon recrystallization from methanol afforded pure material (10.3 g): mp 130–132°; $[\alpha]^{25}D$ +87°; nmr 48 (18-methyl), 218, 227, 228, 237 (C-19 protons), and 245–265 cps (C-2 and C-3 protons).

Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 62.12; H, 7.41; Br, 21.76. Found: C, 62.43; H, 7.77; Br, 21.76.

3α-Bromo-2β,19-oxido-5α-androstan-17β-ol (VIIIb).—To a solution of VIIIa (2.0 g) in ethanol (40 ml) was added $NaBH_4$ (1.0 g) in portions with stirring. The mixture was allowed to stand at room temperature for 20 hr and then poured into 2% NH_4Cl solution (100 ml). The precipitate was collected, washed with water, and air dried (2.0 g). Recrystallization from methanol–acetone gave an analytical sample, mp 165–167°, $[\alpha]^{25}D$ +24°.

Anal. Calcd for $C_{19}H_{29}BrO_2$: C, 61.78; H, 7.91. Found: C, 61.53; H, 7.63.

Acetylation of VIIIb (0.1 g) with acetic anhydride (0.2 ml) in pyridine (2 ml) and recrystallization of the product from methanol gave 3α-bromo-2β,19-oxido-5α-androstan-17β-ol acetate (VIIIc), mp 138–140°, $[\alpha]^{25}D$ +20°.

Anal. Calcd for $C_{21}H_{31}BrO_3$: C, 61.31; H, 7.60. Found: C, 61.63; H, 7.73.

3α-Bromo-17α-methyl-2β,19-oxido-5α-androstan-17β-ol (VIIId).—A solution of VIIIa (1.0 g) in anhydrous ether (90 ml) was added dropwise with stirring to 3 *M* methylmagnesium bromide in ether (35 ml). The mixture was refluxed overnight and saturated NH_4Cl solution (10 ml) was added dropwise with stirring. Water (30 ml) was added and the organic phase separated. The ether solution was washed with water and dried (Na_2SO_4 containing Darco). The solvent was removed *in vacuo* and the resulting solid was recrystallized from methanol–water. This afforded pure VIIId (0.6 g), mp 174–175°, $[\alpha]^{25}D$ +7°.

Anal. Calcd for $C_{20}H_{31}BrO_2$: C, 62.65; H, 8.15. Found: C, 62.65; H, 8.29.

3α-Chloro-2β,19-oxido-5α-androstan-17-one (IXa).—Hypoiodite oxidation of VII (3.7 g) as described above for V afforded a crude product which was purified by chromatography over silica gel (100 g). The column was eluted consecutively, with benzene–hexane (1:1), benzene, and benzene containing increasing amounts of ethyl acetate. Elution with benzene–ethyl acetate (19:1) gave IXa (1.9 g), mp 139–141°. Recrystallization from methanol–water and then from heptane afforded an analytical sample: mp 142–143°; nmr 50 (18-methyl), 217, 225, 227.5, 235.5 (C-19 protons), and 240–265 cps (C-2 and C-3 protons).

Anal. Calcd for $C_{19}H_{27}ClO_2$: C, 70.66; H, 8.43. Found: C, 70.89; H, 8.45.

3α-Chloro-2β,19-oxido-5α-androstan-17β-ol (IXb).—Reduction of IXa (1.0 g) with $NaBH_4$ (0.5 g) as described above for VIIIa gave crude IXb. Recrystallization from methanol–water gave platelets (1.0 g), mp 164–166° unchanged by an additional recrystallization from heptane.

Anal. Calcd for $C_{19}H_{29}ClO_2$: C, 70.24; H, 9.00. Found: C, 70.32; H, 9.02.

Acetylation of IXb with acetic anhydride in pyridine and recrystallization of the product from methanol gave the corresponding acetate IXc, mp 139–141°.

Anal. Calcd for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.52. Found: C, 68.99; H, 8.39.

19-Hydroxy-5α-androst-2-en-17-one Acetate (Xa).—A mixture of VIIIa (50 g) and zinc dust (50 g) in glacial acetic acid (500 ml) was stirred under reflux for 7 hr. The mixture was allowed to cool and the salts were removed by filtration. The salts were washed with isopropyl alcohol, and the filtrate was poured into an ice–water mixture (3 l.). The mixture was refrigerated overnight and the product was collected by filtration, washed with water, and dried. This gave crude Xa (43.7 g) which was satisfactory for subsequent experiments. Recrystallization of a sample from methanol–water afforded pure Xa as needles: mp 72–74°; $[\alpha]^{28}D$ +107.5°; nmr 52 (18-methyl), 123 (acetate methyl), 237, 249, 256.5, 268.5 (C-19 protons), and 340 cps (C-2, C-3 protons).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.43; H, 9.12.

5α-Androst-2-ene-17β,19-diol 19-Acetate (Xb).—A solution of Xa (2.0 g) and lithium tri-*t*-butoxyaluminohydride (6.0 g) in THF (45 ml) was stirred for 1.5 hr in an ice–water bath. The solution was poured into 10% acetic acid (200 ml) and the mixture was refrigerated. The product was collected by filtration, washed with water, and air dried to give crude Xb (2.0 g), mp 99–101°. Recrystallization from methanol–water gave needles, mp 100.5–101.5°, $[\alpha]^{26}D$ +43.5°.[31]

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.97; H, 9.85.

Acetylation of Xb with acetic anhydride and pyridine and recrystallization of the product from methanol gave the diacetate Xc, mp 138–140°, $[\alpha]^{25}D$ +23°.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.96; H, 9.00.

19-Hydroxy-5α-androst-2-en-17-one (XIa).—A solution of Xa (40 g) and KOH (10 g) in methanol (480 ml) and water (20 ml) was refluxed on the steam bath for 3 hr. The solution was al-

(30) J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **24**, 3115 (1959).

(31) This product was also obtained by reduction of Xa with sodium borohydride in isopropyl alcohol at room temperature.

lowed to cool and poured into an ice–water mixture (1.5 l.) with stirring. The mixture was refrigerated for 30 min and the product was collected by filtration, washed with water, and dried. Recrystallization of the crude product (31.2 g) from acetone–hexane gave a first crop (23.0 g) melting at 137.5–140° and a second crop (5.0 g) melting at 132–135°. Recrystallization of a sample from methylene chloride–hexane gave pure XIa: mp 138–140°; $[\alpha]^{26}D$ +152.5°; nmr 54 (C-18 methyl), 228 (C-19 methylene), and 341–343 cps (C-2, C-3 protons).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.83; H, 9.67.

5α-Androst-2-ene-17β,19-diol (XIb).—A solution of Xb (0.3 g) and KOH (0.5 g) in methanol (10 ml) and water (4 ml) was refluxed for 1.5 hr. The mixture was filtered while still hot and the filtrate was poured slowly with stirring into cold water. The precipitate was collected, washed with water, and air dried. Recrystallization from acetone–hexane gave pure XIb (0.25 g), mp 152–152.5°, $[\alpha]^{26}D$ +76°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.59; H, 10.41. Found: C, 78.71; H, 10.65.

17α-Methyl-5α-androst-2-ene-17β,19-diol (XId).—To a refluxing mixture of 3 *M* methylmagnesium bromide in *n*-butyl ether (30 ml) and THF (50 ml) was added dropwise with stirring a solution of XIa (1.45 g) in THF (50 ml). The entire process was performed under an atmosphere of nitrogen. The mixture was then refluxed with stirring for 7 hr and allowed to stand at room temperature overnight. The vessel was surrounded with an ice–water bath and 10% NH_4Cl solution (50 ml) was added dropwise with stirring. The contents was transferred to a separatory funnel, ether (10 ml) was added, and the aqueous phase separated. The ether solution was washed successively with dilute HCl (1:4, 75 ml) and two 75-ml portions of water and dried (Na_2SO_4, Darco). The solvent was removed under reduced pressure and the solid residue (1.4 g) was recrystallized from ethyl acetate. This gave pure XId (0.66 g), mp 165–166°, $[\alpha]^{27}D$ +26.3°. A second crop (0.44 g) was also obtained, mp 163–166°.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.76; H, 10.63.

19-Hydroxy-5α-androst-2-en-17-one *p*-Toluenesulfonate (XIIa).—A solution of XIa (10 g) and *p*-toluenesulfonyl chloride (7.0 g) in pyridine (100 ml) was warmed on the steam bath for 4 hr and allowed to stand at room temperature for 48 hr. The solution was poured into water (600 ml) and the mixture was allowed to stand for 30 min whereupon the initial oil crystallized. The mixture was refrigerated for 1 hr and the product was collected. After washing the product successively with water, dilute HCl (1:10), and water, it was recrystallized from acetone–water to give XIIa as needles (12.0 g), mp 145.5–147.5°. Recrystallization of a sample from acetone–hexane gave pure XIIa, mp 145–147.5°, $[\alpha]^{26}D$ 67.5°, λ_{max} 225 mμ (log ε 4.09).

Anal. Calcd for $C_{26}H_{34}O_4S$: C, 70.55; H, 7.74. Found: C, 70.20; H, 7.72.

19-Hydroxy-5α-androst-2-en-17-one Methanesulfonate (XIIIa).—A solution of XIa (10 g) in methanesulfonyl chloride (15 ml) and pyridine (160 ml) was stirred for 5 hr and allowed to stand at room temperature for 48 hr. The mixture was poured into water (600 ml) and allowed to stand at room temperature for 30 min whereupon the initial oil became crystalline. The mixture was refrigerated for 1 hr. The product was collected and washed with water, dilute HCl (1:10), and water. The brown product was dissolved in ether and the solution was decolorized with Darco. The solvent was removed *in vacuo* and the oily residue crystallized from ether–pentane to give XIIIa (9.5 g), mp 117.5–119°. Recrystallization of a sample from acetone–hexane afforded pure XIIIa, mp 120–122°, $[\alpha]^{27}D$ +91°.

Anal. Calcd for $C_{20}H_{30}O_4S$: C, 65.54; H, 8.25. Found: C, 65.68; H, 8.42.

Chemical and Biological Properties of Some 17-Substituted Estradiol Derivatives

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A series of 17-substituted estradiol derivatives were prepared with the hope of introducing progestational properties into an estrogenic molecule. The methods for synthesizing these compounds are described along with some of the striking biological properties exhibited by some of the derivatives.

It has been known for many years that some of the naturally occurring sex hormones such as testosterone, progesterone, and estrone are capable of inhibiting ovulation in women. For various reasons, however, these hormones are unsuitable for clinical use as oral contraceptives. In an effort to overcome some of the shortcomings associated with these substances, various laboratories have been involved in extensive programs directed toward the chemical modification of natural hormones.[2] In most instances, these modifications have dealt with testosterone (*e.g.*, 17α-ethynyltestosterone and 19-nor analogs) and progesterone (*e.g.*, 17-acetoxyprogesterones). On the other hand, few investigations have involved modification of estrogens such as estrone. This is true despite the fact that estrogens such as ethynylestradiol or its 3-methyl ether are components of most contraceptive medications. Moreover, it has been noted that these estrogens when given alone have ovulation inhibitory properties in women.[3]

Clinical experience indicates that the estrogen–progestin combination therapy provides the most effective means for control of fertility.[4] As a result, our attempts to find a single agent useful for fertility control has involved a search for substances that would mimic the biological effects produced by the estrogen–progestin combinations.

In 1957, studies by Saunders, *et al.*,[5] dealing with 17-alkylated 19-nortestosterone derivatives indicated that progestational activity was related to the length of the side chain at C-17. Maximum activity was achieved with the 17-(2-methylallyl)-substituted compounds. It seemed reasonable, therefore, that one might be able to incorporate progestational activity into the estradiol molecule by alkylating at C-17 with appropriate groups. To test this hypothesis, a series

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