(doublet, J = 9 c.p.s.); 16β-proton at 3.76 p.p.m. (multiplet); 3α-proton at 5.10 p.p.m.

Further elution of the column with 5% ether in benzene gave 120 mg. of the thiol Va, crystallized from hexane, m.p. 168–171°; λ_{max}^{KBr} 5.86, 6.91, 7.40, and 9.70 μ, etc.; R_f 0.73 in system Ia, 0.70 in system IIIa.

Anal. Calcd. for $C_{21}H_{34}O_2S$: C, 71.95; H, 9.66; S, 9.15. Found: C, 71.83; H, 9.60; S, 8.80.

Both thiols Va and Vb gave a violet-red color with sodium nitroprusside solution and decolorized a carbon tetrachloride solution of iodine.

Acetylation of Va with excess acetic anhydride in pyridine in the usual manner gave the acetoxy thioester VIIb, m.p. 154–157°, identical in infrared and chromatographic properties with VIIb prepared from IVb.

16α,16α'-Dithiobis(3β-hydroxy-5β-pregnan-20-one) (VI).—A solution of 400 mg. of the thiol–disulfide mixture (Va and VI) dissolved in 100 ml. of benzene and 50 ml. of water was treated with a solution of iodine in benzene until a slight excess of iodine was present. Aqueous sodium thiosulfate was added to destroy the excess of iodine and the organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a gum which was crystallized from benzene–hexane, yielding 140 mg. of disulfide, m.p. 171–178°; λ_{max}^{KBr} 5.90, 6.92, 7.40, 8.12, and 9.71 μ, etc.; R_f 0.70 in system Ia, 0.18 in system IIIa.

Anal. Calcd. for $C_{42}H_{66}O_4S_2$: C, 72.16; H, 9.52; S, 9.17. Found: C, 72.27; H, 9.28; S, 9.20.

Nuclear magnetic resonance spectra: C-18 methyl at 0.60 p.p.m.; C-19 methyl at 0.95 p.p.m.; C-21 methyl at 2.18 p.p.m.; 17α-proton at 2.71 p.p.m. (doublet, J = 8 c.p.s.); 16β-proton at 3.88 p.p.m. (multiplet); 3α-proton at 4.13 p.p.m. (broad).

3β-Hydroxy-16α-mercapto-5α-pregnan-20-one (IXb).—A solution of 1.0 g. of 3β-hydroxy-5α-pregn-16-en-20-one in 25 ml. of pyridine and 0.09 ml. of piperidine was alternately flushed with nitrogen and evacuated four times. Hydrogen sulfide was bubbled through the solution at room temperature for 2.5 hr. (efficient stirring). The solvents were removed under vacuum, the solid residue was extracted with hot ethyl acetate, and the solids remaining crystallized from 2-propanol, yielding 150 mg. of pure IXb, m.p. 175–180 and 251–256° (Kofler); $[\alpha]_D$ +81.5°; λ_{max}^{KBr} 2.95 and 5.85 μ, etc.; R 0.44 in system III.

Anal. Calcd. for $C_{21}H_{34}O_2S$: C, 71.96; H, 9.66; S, 9.15. Found: C, 71.78; H, 9.92; S, 8.80.

Nuclear magnetic resonance spectra: C-18 methyl at 0.61 p.p.m.; C-19 methyl at 0.80 p.p.m.; C-21 methyl at 2.13 p.p.m.; 17α-proton at 2.58 p.p.m. (doublet, J = 9 c.p.s.); 3α- and 16β-protons at 3.6–3.9 p.p.m. (multiplets).

16α-Acetoxy-3β-hydroxy-5β-pregnan-20-one (X).—A solution of 350 mg. of 3β,16α-dihydroxy-5β-pregnan-20-one in 0.5 ml. of dry pyridine and 0.5 ml. of dry benzene was treated with 100 μl. of acetic anhydride. After standing overnight methanol was added, and the solvents were removed under vacuum. The residue obtained was crystallized from ethyl acetate–hexane, yielding 200 mg. of 16α-monoacetate X containing traces of the 3β,16α-diol by thin layer chromatography. Several recrystallizations from ethyl acetate–hexane and from hexane gave the pure sample, m.p. 86.5–92.0°, resolidifying and remelting 129.5–130.5° (Kofler); λ_{max}^{KBr} 2.93, 5.78, 5.84, 8.04, and 9.68 μ, etc.[33]; R_f 0.48 in system Ia, 0.26 in system IIIa; see also Table II.[34]

Nuclear magnetic resonance spectra: C-18 methyl at 0.65 p.p.m.; C-19 methyl at 0.97 p.p.m.; 16α-acetoxyl methyl at 2.00 p.p.m.; C-21 methyl at 2.18 p.p.m.; 17α-proton at 2.66 p.p.m. (doublet, J = 6 c.p.s.); 3α-proton at 4.15 p.p.m. (multiplet); 16β-proton at 5.50 p.p.m. (octuplet).

Optical rotatory dispersion: $[\alpha]_{600}$ +67°, $[\alpha]_{589}$ +70°, $[\alpha]_{310}$ +1720°, $[\alpha]_{264}$ −1890°, and $[\alpha]_{250}$ −1590°.

Acknowledgment.—The authors are grateful to Drs. R. Edgren and C. L. Nagra of these laboratories for the biological data reported, and to Prof. Kurt Mislow, New York University, for the optical rotatory dispersion data.

(33) Hirschmann and Daus (see ref. 9) report m.p. 134–135.5° and a double melting point 89 and 137° for X, with $\lambda_{max}^{CS_2}$ 2.77, 5.74, 5.84, 8.06, and 9.70 μ, etc. Recrystallization of our sample showing the double melting point from ethyl acetate–cyclohexane using a seed crystal of 16α-acetoxy-3β-hydroxy-5β-pregnan-20-one, m.p. 132.5–135.0° (Kofler), kindly supplied by Dr. Hirschmann gave the second crystalline form, m.p. 130.0–131.5°, with infrared spectra identical with that of the Hirschmann sample, λ_{max}^{KBr} 2.88, 5.82, 7.94, 8.13, and 9.68 μ, etc. Chromatographic identity of the two samples was also established.

(34) The greater mobility of the 16α-monoacetate X relative to the 3β-monoacetate (3β-acetoxy-16α-hydroxy-5β-pregnan-20-one) in several solvent systems is the reverse of the order found in the 5α-series, where 16α-acetoxy-3β-hydroxy-5α-pregnan-20-one is less mobile than 3β-acetoxy-16α-hydroxy-pregnan-20-one in the Bush A and B-3 systems.[18]

Some 20-Substituted 21-Norprogesterone Derivatives

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Several new analogs of progesterone have been prepared in which the acetyl side chain has been replaced by benzoyl, *o*-anisoyl, and propiolyl groups. They were prepared by allowing the appropriate aryl- or ethinyllithium or Grignard reagent to react with corticosterone or deoxycorticosterone and subsequently cleaving the 20,21-diol with periodic acid to give the corresponding 20-ketone. The 20-(*p*-anisyl)-20,21-diol underwent a facile pinacol rearrangement under mildly acidic conditions to give a 20-(*p*-anisyl)-21-aldehyde derivative.

The lengthening of the acetyl side chain of 20-ketopregnane steroids has been accomplished by the synthesis of several types of derivatives. Among these are the 21-alkyl,[1] 21-methylene,[2] 21-cyano,[3] 21-acyl,[4] 21-benzilidene,[5] and 21-ethoxyoxalyl[6] derivatives. Two groups of investigators have introduced a 20-(α-pyridyl) group[7,8] which in one case[8] afforded a 17β-picolinoylandrostane derivative by oxidative removal of the 21-methyl group. However, there have been no reports in the literature of 20-phenyl-21-nor-20-ketopregnanes (17β-benzoylandrostanes), and it seemed

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TABLE I

Name	No.	Yield, %	M.p., °C.	$[\alpha]^{25}D$	λ_{max}, mμ ($\epsilon \times 10^{-3}$)	Formula (mol. wt.)	% calcd. C	% calcd. H	% found C	% found H
3-(N-Pyrrolidyl)-pregna-3,5-dien-20-on-21-ol	I	90	158–161			$C_{25}H_{37}NO_2$ (383.6)	78.25	9.72	78.10	9.72
20-Phenylpregn-4-en-3-one-20,21-diol	IIIa	27	237–239	−9	241 (16.8)	$C_{27}H_{36}O_3$ (408.6)	79.35	8.88	79.04	8.98
20-(*o*-Anisyl)-pregn-4-en-3-one-20,21-diol	IIIb	24	134–137	+10	277 (2.01) 242 (15.6) 227 (14.5)	$C_{28}H_{38}O_4$ (438.6)	76.67	8.73	76.91	9.31
20-Ethinyl-3,3-ethylenedioxypregn-5-ene-20,21-diol	IV	87	239–242			$C_{25}H_{36}O_4$ (400.6)	74.96	9.06	75.05	9.08
17β-Benzoylandrost-4-en-3-one	Va	98	182–184	+178	242 (28.1)	$C_{26}H_{32}O_2$ (376.5)	82.91	8.51	82.61	8.70
17β-(*o*-Anisoyl)-androst-4-en-3-one	Vb	66	187–188	+121	297 (2.8) 242 (20.3)	$C_{27}H_{34}O_3$ (406.5)	79.75	8.43	79.49	8.39
17β-Propiolylandrost-4-en-3-one	Vc	84	182–185	+79	240 (16.9)	$C_{22}H_{28}O_2$ (324.5)	81.45	8.70	81.38	8.56
20-(*p*-Anisyl)-3-oxopregn-4-en-21-al	VI	13	196–199		240 (20.8)	$C_{28}H_{36}O_3$ (420.6)	79.96	8.63	79.54	8.91
11β-Hydroxy-17β-benzoylandrost-4-en-3-one	VIIa	8	247–249	+219	241 (27.5)	$C_{26}H_{32}O_3$ (392.5)	79.56	8.22	79.34	8.15
9α-Fluoro-11β-hydroxy-17β-benzoylandrost-4-en-3-one	VIIc	28	238–240	+199	240 (27.7)	$C_{26}H_{31}FO_3$ (410.5)	76.07	7.61	75.88	7.58
17β-Benzoylandrosta-4,9(11)-dien-3-one	VIII	58	157–158.5	+108	240 (30.0)	$C_{26}H_{30}O_2$ (374.5)	83.38	8.07	83.20	8.26
17β-Benzoylandrosta-1,4-dien-3-one	X	30	209–210	+181	252 (28.4)	$C_{26}H_{30}O_2$ (374.5)	83.41	8.08	83.16	8.03

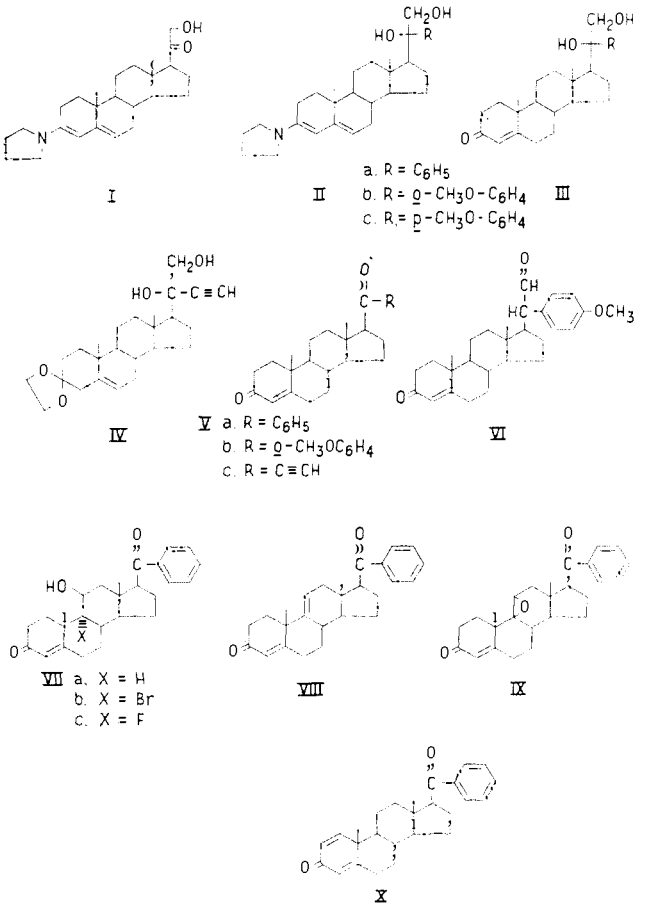
worthwhile to investigate the pharmacological activity of steroids substituted in this manner.

These compounds were synthesized from the 3-pyrrolidyl enamine of deoxycorticosterone (I) (see Table I). Addition of an aryl Grignard or aryllithium reagent to the ketol side chain afforded the corresponding diol (II). This intermediate was not isolated but was hydrolyzed to a 20-arylpregn-4-en-3-one-20,21-diol (III). Cleavage of the 20,21-glycol with periodic acid gave the corresponding 17β-benzoylandrost-4-en-3-one (V).

In contrast with the compounds obtained when phenyllithium, phenylmagnesium bromide, or *o*-anisyllithium were employed as reagents, the products from the reaction with *p*-tolylmagnesium bromide or *p*-chlorophenylmagnesium bromide could not be isolated in a pure state. Diol IIIc obtained from *p*-anisyllithium was not isolated, for it underwent a pinacol rearrangement to 20-(*p*-anisyl)-3-oxo pregn-4-en-21-al (VI) under the mild conditions employed for the hydrolysis of the enamine.

Previously, 20-ethinylpregn-5-ene-3β,20-diol was obtained from the reaction of sodium acetylide with pregnenolone acetate.[9] When the 3-ethylene ketal of deoxycorticosterone[10] was treated with ethinylmagnesium bromide, the analogous diol (IV) was obtained. Periodate cleavage of this afforded 17β-propiolylandrost-4-en-3-one (Vc).

The reaction of the 3-pyrrolidyl enamine of corticosterone with phenyllithium, followed by periodate oxidation, yielded 11β-hydroxy-17β-benzoylandrost-4-en-3-one (VIIa). Dehydration with sulfur dioxide and N-bromacetamide in pyridine[11] afforded 17β-benzoylandrosta-4,9(11)-dien-3-one (VIII), which was converted into 9α-fluoro-11β-hydroxy-17β-benzoylandrost-4-en-3-one (VIIc).[12] Oxidation of 17β-benzoyl-



androst-4-en-3-one with 2,3-dichloro-5,6-dicyanobenzoquinone[13] gave 17β-benzoylandrosta-1,4-dien-3-one (X).

The 17β-benzoyl and 17β-propiolyl compounds were inactive as progestational agents in the Clauberg assay. However, some of these derivatives (IIIb, Va, VIIa, and VIII) were found to possess oral myotrophic activity, as measured by the modified Hershberger assay.[14] Daily oral doses of 2.0 mg. per rat increased

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the weight of the levator ani muscle without increasing the weight of either the seminal vesicles or the ventral prostate. In fact, no evidence of androgenicity was observed for Va even at doses of 5.0 mg./rat/day.

Experimental[15]

3-(N-Pyrrolidyl)-pregna-3,5-dien-20-on-21-ol (I).—A warm solution of 10.0 g. of pregn-4-ene-3,20-dion-21-ol in 25 ml. of methanol was treated with 6 ml. of pyrrolidine. After 10 min., the solution was placed in a refrigerator and left overnight. The precipitated product was filtered, washed with cold methanol, and dried.

Preparation of 20,21-Diols (III and IV).—A solution of 5.00 g. (13.0 mmoles) of 3-(N-pyrrolidyl)-pregna-3,5-dien-20-on-21-ol (I) in 1000 ml. of ether was added to a solution of 170 mmoles of the appropriate Grignard or organolithium reagent in 50 ml. of ether. The resulting solution was stirred and heated under reflux overnight. The cooled solution was then treated with a solution of 8 g. of sodium acetate and 60 ml. of acetic acid in 300 ml. of water, and the resulting two-phase mixture was stirred and refluxed for an additional 3 hr.[16] The reaction mixture was cooled and the layers were separated. The ether layer was washed with water, dilute hydrochloric acid, and water, and was then dried over magnesium sulfate. The ether solution was concentrated to dryness and the residue was recrystallized from methanol or ethyl acetate.

However, the product from the reaction of *p*-anisylmagnesium bromide with I was found to be 20-(*p*-anisyl)-3-oxopregn-4-en-21-al (VI) rather than the expected diol. The infrared spectrum of VI exhibited absorption at 2740 and 1716 (CHO), 1672 and 1616 cm.$^{-1}$ (Δ^4-3-one) and was transparent in the 3400 cm.$^{-1}$ region. The n.m.r. spectrum exhibited resonances at 0.83 (18-Me), 1.20 (19-Me), a quartet at 3.44 (20-H, J_{21H} = 4 c.p.s., J_{15H} = 11 c.p.s.), 3.80 (OCH_3), 5.76 (4-H), a quartet at 7.03 (p-C_6H_4), and a doublet at 9.62 p.p.m. (21-H, J_{20H} = 4 c.p.s.).

Preparation of 20-Ketones (V and VIIa).—A solution of 2.62 mmoles of the 20,21-diol in 85 ml. of dioxane was cooled to 0° and treated with a solution of 4.80 mmoles of periodic acid in 25 ml. of water. The solution was kept at 0° overnight, poured into dilute potassium carbonate solution, and filtered.[16] The precipitate was washed with water, dried, and recrystallized from methanol or ethyl acetate.

17β-Benzoylandrosta-4,9(11)-dien-3-one (VIII).—A solution of 0.20 g. of 11β-hydroxy-17β-benzoylandrost-4-en-3-one (VIIa) in 3 ml. of anhydrous pyridine was treated with 0.12 g. of recrystallized N-bromoacetamide and allowed to stand at room temperature for 35 min. Sulfur dioxide was then bubbled into the reaction mixture until acidified starch–iodide paper gave a negative test. The reaction mixture was covered with an atmosphere of sulfur dioxide, stirred an additional 30 min., and poured into water. The precipitate was filtered and dried, affording 0.15 g. of crude product, m.p. 149–157°. This was chromatographed on Merck alumina, and was eluted with methylene chloride–petroleum ether. Recrystallization from ether afforded 0.06 g. of product, m.p. 157–158.5°. A second crop of 0.05 g., m.p. 154–157°, was obtained for an over-all yield of 0.11 g. of material sufficiently pure for the next step. This material was homogeneous as determined by vapor phase chromatography.

9α-Fluoro-11β-hydroxy-17β-benzoylandrost-4-en-3-one (VIIc).—A solution of 0.20 g. of 17β-benzoylandrosta-4,9(11)-dien-3-one (VIII) and 0.20 g. of recrystallized N-bromoacetamide in 2 ml. of water and 10 ml. of dioxane was cooled in ice, and 4 drops of 72% perchloric acid was added with shaking. The reaction mixture was allowed to stand at room temperature for 1 hr. and then excess sodium thiosulfate was added. The mixture was poured into water, and the precipitate was filtered and dried. The solid was recrystallized from ether, affording 0.14 g. (56%) of **9α-bromo-11β-hydroxy-17β-benzoylandrost-4-en-3-one** (VIIb), m.p. 164–166°.

A solution of 0.20 g. of 9α-bromo-11β-hydroxy-17β-benzoylandrost-4-en-3-one and 0.20 g. of potassium acetate in 10 ml. of absolute ethanol was heated under reflux for 4 hr. The solution was concentrated under reduced pressure and the residue was dissolved in ether and water. The ether layer was separated, washed with water, dried over magnesium sulfate, and concentrated. The dark brown residue was recrystallized from ether, affording 0.07 g. (42%) of **9β,11β-oxido-17β-benzoylandrost-4-en-3-one** (IX), m.p. 185–190°.

A mixture of 1.33 g. of tetrahydrofuran and 3 ml. of chloroform was cooled to −60° and hydrogen fluoride gas was bubbled into the solution until two layers were visible. A solution of 0.24 g. of 9β,11β-oxido-17β-benzoylandrost-4-en-3-one (IX) in 6 ml. of chloroform was added and the reaction mixture was maintained at −30 to −40° for 4 hr. It was then made basic with aqueous sodium bicarbonate solution, and this mixture was extracted with ether–methylene chloride. The extracts were combined, washed with water, dried over magnesium sulfate, and concentrated to dryness. The residue was crystallized from ether, yielding 0.10 g. of crude product, m.p. 229–231°. The solid was recrystallized from ether, after treatment with charcoal, affording 0.07 g. of 9α-fluoro-11β-benzoylandrost-4-en-3-one.

17β-Benzoylandrosta-1,4-dien-3-one (X).—A solution of 3.25 g. of 17β-benzoylandrost-4-en-3-one (Va) in 70 ml. of benzene was treated with 3.20 g. of 2,3-dichloro-5,6-dicyanobenzoquinone, and the mixture was heated under reflux for 24 hr. The cooled solution was diluted with an equal volume of ether and filtered. The filtrate was washed well with water, 2 *N* sodium hydroxide solution, and water, was dried over magnesium sulfate, and was evaporated to dryness. The residue was recrystallized from methanol, affording 0.98 g. of product.

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(15) The melting points were determined on a Fisher-Johns block and are corrected. The infrared spectra were recorded on a Beckman IR-7 in KBr disks. The ultraviolet spectra were obtained in methanol solution and the optical rotations were determined as a 1% solution in chloroform. The n.m.r. spectra were determined in deuteriochloroform solution with a Varian A-60 instrument; resonances are reported as parts per million downfield from tetramethylsilane, used as an internal reference.

(16) In the preparation of IV from the reaction of 3,3-ethylenedioxypregn-5-en-20-on-21-ol (see ref. 10) with ethinylmagnesium bromide, the excess Grignard reagent was decomposed with 5% aqueous ammonium chloride solution, leaving the 3-ketal intact. This ketal was removed after the periodic acid cleavage by treatment with 0.5% sulfuric acid in aqueous methanol at room temperature overnight.