Nonclassical and Other sp^2-Hybridized Steroids. Methano-, Spirocyclopropyl-, and Methylenepregnane Derivatives[1]

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Progesterone, deoxycorticosterone, and cortisol each have carbonyl groups at C-3 and C-20, and methylene and cyclopropane analogs at these positions were prepared in an effort to establish the function of these moieties in eliciting biological effects. The Simmons–Smith and Wittig reactions were used to prepare various methano, methylene, and spirocyclopropyl analogs of progesterone, deoxycorticosterone, and ethisterone. In the case of cortisol and deoxycorticosterone derivatives difficulties encountered in the removal of protecting groups prevented the synthesis of these analogs. Every substitution of a methylene group or cyclopropane ring gave an analog essentially devoid of progestational or mineralocorticoid activity, in contrast to earlier results in the androstane series. The nmr spectra are discussed.

In a previous study[2] from this laboratory evidence was presented leading to the view that the androgen molecule functions as a conformational cam or wedge and is bound to its receptor by means of a π bond involving C-2 and/or C-3. The high activity found in the nonclassical sp^2-hybridized system, $2\alpha,3\alpha$-methano-5α-androstan-17β-ol, provided important support for this concept.

We now describe work intended to extend this analysis to progestational, mineralocorticoid, and glucocorticoid systems. Progesterone, deoxycorticosterone, and cortisol each have carbonyl groups at C-3 and C-20, and the present work was carried out in an effort to establish the function of these moieties in eliciting the biological effects of the hormones. If these groups also are involved in π-bond formation with a receptor, it should be possible for other nonclassical sp^2 systems to assume their role, as in the case of the androgen analogs. The preparation of derivatives of these steroids containing methylene groups and/or cyclopropane rings in place of the carbonyl groups was therefore undertaken.

Conversion of steroidal ketones to the corresponding methylene groups by means of the Wittig reaction has been described,[3-5] and this method was utilized in the present study (Table I). In our previous work[2] the Simmons–Smith reaction[6] was employed for the preparation of steroidal cyclopropanes. In contrast to the earlier experiments, where the zinc–copper couple made by the method of Shank and Shechter[7] was utilized, the highly active zinc–copper couple of Le Goff[8] was used in the present case. It was found that these reactions took place with greater facility when the highly active couple was employed.

Treatment of I[9] with the Simmons–Smith reagent gave the methano steroid II in 30% yield. The configuration of the cyclopropane ring in II is assumed to be $2\alpha,3\alpha$, as in the case of our previous work. A single isomer was isolated from the Simmons–Smith reaction, which is known[6] to be highly subject to steric control, and the most reasonable product on this basis would arise from attack on the α face of the steroid. By treatment of II in redistilled tetrahydrofuran solution with iodine in the presence of calcium oxide and azobisisobutyronitrile,[10,11] the corresponding 21-iodo compound was obtained. Displacement of the halide with triethylammonium acetate solution gave the DOCA analog III. It is noteworthy that the yield of the product (25%) was no lower than a previous similar reaction in our hands[12] involving a steroid without a cyclopropane ring; this suggests that the cyclopropane ring is not attacked under these conditions.

Application of the Wittig reaction to I, employing methyltriphenylphosphonium bromide and phenyllithium in ether–tetrahydrofuran solution, gave the 20-methylene compound IV. The nmr spectrum of IV shows a broad singlet at 5.56 ppm (half-band width, 5 cps) which is due to the two protons at C-2 and C-3, coupled to each other and to other protons attached to the A ring. Although vicinal olefinic protons in six-membered rings have coupling constants of 8–10 cps,[13] no multiplet is seen here because of the high $J/\Delta\delta$ ratio. The olefinic protons at C-22, on the other hand, produce two broad peaks (half-band width, 5 cps) at 4.65 and 4.80 ppm. These are due to the AB system at C-22, for which J_{gem} is only about 1.5 cps. The chemical shift of the two protons is different owing to their different relationship to C-18 and ring D. The broadness of the peaks results from allylic coupling of the C-22 protons to C-21; the C-21 resonance at 1.73 ppm has a half-band width of 4 cps owing to this coupling. The spectra of V, VII, X, XI, XVI, and XVII display similar features in these regions for the same reasons.

Treatment of IV with the Simmons–Smith reagent gave a mixture of the 2,3-olefin 20-spirocyclopropyl derivative V and the biscyclopropyl derivative VI, as

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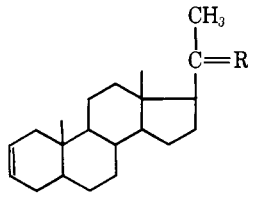
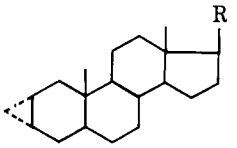
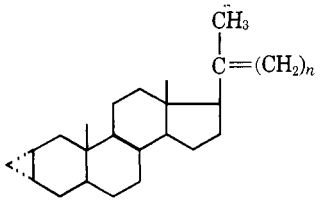


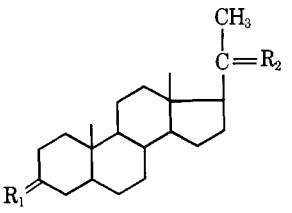
I, R = O
IV, R = CH_2



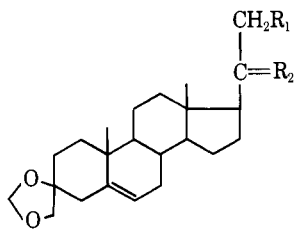
II, R = $\overset{H}{<}COCH_3$
III, R = $\overset{H}{<}COCH_2OAc$



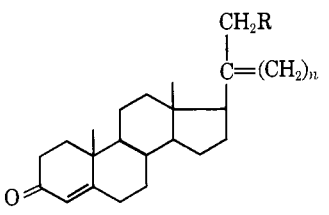
V, $n = 1$
VI, $n = 2$



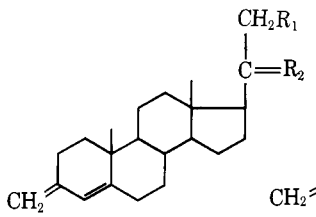
VII, $R_1 = CH_2$; $R_2 = CH_2$
VIII, $R_1 = CH_2$; $R_2 = O$
IX, $R_1 = (CH_2)_2$; $R_2 = (CH_2)_2$

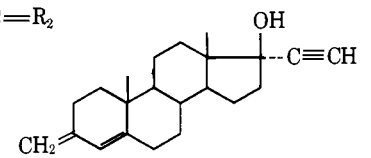


X, $R_1 = H$; $R_2 = CH_2$
XVI, $R_1 = OH$; $R_2 = CH_2$



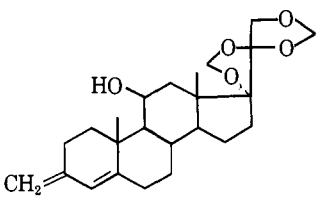
XI, R = H; $n = 1$
XII, R = H; $n = 2$
XVII, R = OH; $n = 1$





XIII, $R_1 = H$; $R_2 = OH$
XIV, $R_1 = H$; $R_2 = O$
XVIII, $R_1 = OH$; $R_2 = O(CH_2)_2O$

XV



XIX

judged from the olefinic proton signals in the nmr spectrum of the crude product. The crude material was allowed to react again with the Simmons–Smith reagent and gave a mixture which was inseparable by column chromatography and thin layer chromatography. Gas chromatography gave a clean separation of the mono- and biscyclopropane derivatives because of the difference in molecular weight. A pure sample of VI was obtained by repeated recrystallization from acetonitrile–ethanol while monitoring purity by gas chromatography.

The nmr spectrum of VI is of interest with respect to the width of the C-21 peak. The half-band width of this peak is only 2 cps indicating that the cyclopropane ring is more like a carbonyl group than an olefin in its ability to transmit spin couplings. The spectra of compounds IX and XII are similar in this respect.

Compound V was obtained by application of the Wittig reaction to II. Treatment of 5α-pregnane-3,20-dione with the Wittig reagent gave the reported[14] VII and also the 20-ketone VIII, which could be separated by chromatography. The two products could be distinguished readily by the C-21 peak frequencies and band widths in the nmr spectra as well as by the olefinic peak patterns as already indicated. On treatment of VII with the Simmons–Smith reagent, the bis-spirocyclopropyl derivative IX was obtained.

Treatment of 3,3-ethylenedioxypregn-5-en-20-one[15] with the Wittig reagent gave X which on hydrolysis gave the progesterone analog XI. The "reverse" of this analog, XIV, was obtained by a Wittig reaction of 20β-hydroxypregn-4-en-3-one[16] to give XIII followed by oxidation at C-20 to give XIV. Compound XII was obtained from XI by means of the Simmons–Smith reaction.

A derivative (XV) of ethinyltestosterone was obtained by reaction of this compound with the Wittig reagent.

In the DOCA series, ketalization of DOCA with methyl ethyl dioxolane gave the monoketal[17] which on treatment with the Wittig reagent lost the acetate function and gave XVI. All attempts to carry out the Simmons–Smith procedure on XVI failed, and only starting material was recovered. Hydrolysis of XVI gave the 20-methylene analog of DOC, XVII.

Efforts to secure C-3 analogs of DOCA and cortisol were less successful. DOCA was reduced with lithium tri-*t*-butoxyaluminohydride to give the 3β,20β-diol 21-acetate[18] which on selective oxidation of the allylic alcohol with 2,3-dichloro-5,6-dicyanoquinone and isolation under alkaline conditions gave 20β,21-dihydroxypregn-4-en-3-one 20-acetate *via* migration of the ester group.[19] The last compound gave no isolable product in the Wittig reaction.

In another attempt, ketalization of 3β,21-dihydroxypregn-5-en-20-one 21-acetate gave the corresponding ketal which on Oppenauer oxidation gave the conjugated 3-ketone.[18] Application of the Wittig reaction gave XVIII, but mixtures containing no exocyclic olefin as shown by nmr were obtained on removal of the ketal group. Similarly, bismethylenedioxycortisol[20] gave the Wittig product XIX, but the protecting group could not be removed without affecting the exocyclic olefin.

Pharmacological Results.[21]—Compounds I, II, IV–IX, XI, XII, XIV, and XV were inactive or nearly

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(21) Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis. Statistical analyses were made in part with a machine program kindly supplied by Dr. Bertram Katzung and were supported in part by U. S. Public Health Service Grant FR-00122 for computing services on this campus.

TABLE I

WITTIG REACTION PRODUCTS[a]

No.	Starting material	Yield, %	Mp, °C	$[\alpha]^{25}D$,[b] deg	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nmr spectra, chemical shifts, ppm C-18	C-19	C-21	C-3 Methylene	C-20 Methylene
IV	I	55	115–117	+53	$C_{22}H_{34}$	88.52	88.25	11.48	11.23	0.57	0.75	1.73	...	4.65, 4.80
V	II	..	103–104	+17	$C_{23}H_{36}$	88.39	88.44	11.61	11.42	0.57	0.80	1.75	...	4.67, 4.80
VII	c	40	98–99	+8	$C_{21}H_{36}$	88.39	88.09	11.61	11.41	0.57	0.87	1.73	4.58	4.69, 4.80
VIII	c	25	123–124	+104	$C_{20}H_{34}O$	84.02	84.18	10.90	10.81	0.62	0.87	2.10	4.58	...
X	d	90	165–166	−43	$C_{24}H_{36}O_2$	80.85	81.05	10.18	10.09	0.58	1.03	1.73	...	4.67, 4.80
XIII	c	45	124–125	+50	$C_{20}H_{34}O$	84.02	84.05	10.90	11.17	...	...			
XV	f	40	148–150	−150	$C_{20}H_{36}O$	85.11	84.88	9.74	9.92	0.86	1.07	...	4.65	...
XVI	g	..	200–202	+21	$C_{24}H_{36}O_3$	77.38	77.18	9.74	9.59	0.62	1.04	4.07	...	4.93, 5.25
XVIII	h	36	153–155	+148	$C_{24}H_{36}O_3$	77.38	77.43	9.74	9.66	0.81	1.04	3.47	4.58	...
XIX	i	..	182–184	−208	$C_{24}H_{34}O_5$	71.61	71.57	8.51	8.64	1.06	1.30	3.93	4.60	...

[a] The experimental procedure was similar to the method described in ref 5. Compound IV was recrystallized from ethanol, V from methanol–acetone, VII, VIII, XIII, XV, XVIII, and XIX from methanol, X from acetonitrile, and XVI from acetone. [b] All rotations at 1% concentration except XIII (1.19%), XV (0.5%), XVI (1.25%), XVIII (1.25%), and XIX (1.16%). [c] Compounds VII and VIII were both isolated from the Wittig reaction on 5α-pregnane-3,20-dione. [d] 3,3-Ethylenedioxypregn-4-en-20-one.[15] [e] 20β-hydroxypregn-4-en-3-one.[16] [f] Ethisterone. [g] 3,3-Ethylenedioxy-21-hydroxypregn-5-en-20-one acetate.[17] [h] 20,20-Ethylenedioxy-21-hydroxypregn-4-en-3-one acetate. [i] 17α,20,20,21-Bismethylenedioxy-11β-hydroxypregn-4-en-3-one.[20]

inactive in the progestational assay.[22] Compounds III and XVII were inactive or nearly inactive in the sodium retention test.[12]

Unlike the situation in the testosterone series,[2,3] the 2α,3α-methano steroids II and III are inactive as are the methylene steroids XIV and XV. In the side chain also, active compounds cannot be obtained by conversion of the 20-ketone to a cyclopropane or methylene group, as in XI, XII, and XVII. Although these negative data allow few conclusions to be drawn, it is clear that we still have no real understanding of the role of the carbonyl group in steroid action. It seems likely, however, that the function of this group in the A ring involves more than simple π-bond interaction in the case of progesterone and the corticoids. Oxidation–reduction and hydrogen-bond acceptance are other possible mechanisms by which the carbonyl group in ring A could exert an effect, and the preparation of hormone analogs to test these possibilities is in progress.

Experimental Section[23]

2α,3α-Methano-5α-pregnan-20-one (II) (General Simmons–Smith Procedure).—A mixture of 9.0 g (0.12 mole) of Zn–Cu couple,[8] 32.0 g (0.12 mole) of diiodomethane, and 0.08 g of iodine in 150 ml of anhydrous ether was heated under reflux for 1 hr. Then 3.0 g (0.01 mole) of I dissolved in anhydrous ether was added. The mixture was heated under reflux for 1 week, filtered through alumina, washed with 5% HCl and water, and dried (Na_2SO_4). On evaporation to dryness, a gummy substance was obtained and was passed through 100 g of neutral alumina. The benzene fraction furnished 0.9 g (30%) of the product, mp 94–99°. Recrystallization from acetonitrile gave the analytical sample: mp 115–117°; $[\alpha]^{25}D$ +121° (c 1, $CHCl_3$); nmr, 0.58 (C-19 H) (3 H), 0.80 (C-18 H) (3 H), 2.10 (C-21 H) (3 H).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 84.27; H, 10.82.

2α,3α-Methano-20-spirocyclopropyl-5α-pregnane (VI) was obtained from the general Simmons–Smith procedure using 3.0 g (0.045 g-atom of Zn) of Zn–Cu couple, 12.0 g (0.045 mole) of CH_2I_2, a few crystals of iodine, 80 ml of anhydrous ether, and 1.0 g (0.003 mole) of IV in 30 ml of anhydrous ether. The residue after evaporation of the solvent was a mixture of products which showed no terminal olefin infrared absorption but showed olefinic protons in the nmr spectrum. Fractional recrystallization failed to separate the two products. It was subjected to the Simmons–Smith procedure a second time. After working up as described above, the residue, which showed two peaks in gas chromatography, was recrystallized ten times from acetonitrile–ethanol solution to afford 45 mg of colorless crystals: mp 129–130°; $[\alpha]^{25}D$ +17° (c 1, $CHCl_3$); nmr, 0.72 (C-18 H) (3 H), 0.80 (C-19 H) (3 H), 1.07 (C-21 H) (3 H).

Anal. Calcd for $C_{23}H_{38}$: C, 88.27; H, 11.73. Found: C, 88.21; H, 11.91.

3,20-Bisspirocyclopropyl-5α-pregnane (IX) was obtained from the general Simmons–Smith procedure using 3.0 g (0.023 mole) of Zn–Cu couple, 12.0 g (0.02 mole) of CH_2I_2, a few crystals of iodine, 100 ml of anhydrous ether, and 0.7 g (0.0022 mole) of VII in ether. Chromatography on 50 g of neutral alumina gave, from the petroleum ether (bp 30–60°) fractions, a total of 0.35 g of product, mp 107–112°. Recrystallization from acetone gave the analytical sample: mp 118–120°; $[\alpha]^{25}D$ 0° (c 1, $CHCl_3$); nmr, 0.72 (C-18 H) (3 H), 0.82 (C-19 H) (3 H), 1.07 (C-21 H) (3 H).

Anal. Calcd for $C_{24}H_{36}$: C, 88.16; H, 11.84. Found: C, 88.14; H, 11.62.

20-Spirocyclopropylpregn-4-en-3-one (XII) was obtained from the general Simmons–Smith procedure using 2.5 g (0.02 mole) of Zn–Cu couple, 5.4 g (0.02 mole) of CH_2I_2, a few crystals of iodine, 50 ml of anhydrous ether, and 0.70 g (0.0022 mole) of XI. Chromatography on 30 g of neutral alumina gave 0.30 g of product, mp 150–157°. Recrystallization gave the analytical sample: mp 157–158°, $[\alpha]^{25}D$ +92° (c 1, $CHCl_3$); nmr, 0.77 (C-18 H) (3 H), 1.05 (C-21 H) (3 H), 1.18 (C-19 H) (3 H), 5.68 (C-4 H) (1 H).

Anal. Calcd for $C_{24}H_{36}O$: C, 84.60; H, 10.50. Found: C, 84.36; H, 10.26.

21-Hydroxy-2α,3α-methano-5α-pregnan-20-one Acetate (III).—A solution of 0.20 g (0.0004 mole) of II in 5 ml of redistilled THF and 5 ml of methanol was treated with 0.34 g of powdered CaO and 12 mg of recrystallized azobisisobutyronitrile. To the stirred mixture, immersed in a 25° water bath, there was added 0.22 g of iodine dissolved in a mixture of 1.1 ml of THF and 0.7 ml of methanol. The iodine solution was added dropwise but fast enough to slightly exceed the rapid decolorization rate. The mixture was stirred for 2–4 hr until only a pale yellowish color remained. It was diluted with ether and filtered. The filter cake was washed with ether and discarded. The combined ether filtrates were washed free of excess iodine with 15% aqueous NaI solution, dried (Na_2SO_4), and evaporated under reduced pressure. Without purification, the 21-iodo residue was dissolved in 10 ml of acetone and treated with a mixture of 1.7 ml of acetic

(22) T. Miyake, *Methods Hormone Res.*, **2**, 135 (1962).

(23) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 or a Perkin-Elmer 337 instrument. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Nmr spectra were obtained at a field strength of 60 Mc/sec on samples in $CDCl_3$ solution on a Varian A-60 instrument using $Si(CH_3)_4$ as internal standard and are reported in parts per million. Gas chromatography was carried out using a Barber-Colenian Model 5000 system employing 1.83-m U-tube columns of 2% SE-30 on Gas Chrom Q or Z, He carrier, hydrogen flame detection, column temperatures of 220–240°, "on column" injection at 290°, and detector temperatures of 250°.

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°, $[\alpha]^{26}D$ +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]

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