$$\log k_{Ac} + \log\left(\frac{K_A + [H^+]}{[H^+]}\right)$$

	n	s	r	
$= -1.255 + 0.876\pi$ (±0.432) (±0.299)	6	0.222	0.971	(111)

by Nelson[27] with the use of rats.[12] Here, with the correction term, the log k_{Ac} values are well correlated only with the hydrophobicity of the N^1 substituent. Although the test objects are different from each other, the slope in eq 96 for the value of $1/K_m$ with the pigeon liver enzyme is very similar to that in eq 111 for the k_{Ac} with rats. This would suggest that a step of hydrophobic bonding equilibrium of the neutral form of drugs with liver components is critical for *in vivo* acetylation mechanism.

The present work underlines the importance of hydrophobic bonding instead of the electrostatic interaction for the binding of sulfonamide drugs with serum protein as well as enzyme preparations. A critical assumption that the drug is bound in the neutral form seems to be justified by correlations which are statistically as well as physicochemically significant. Unless the effect of ionization is separated from other physicochemical effects, a true correlation of physicochemical significance is not obtained. The results also show that the extrathermodynamic approach, considering the free energy related hydrophobic parameter of drugs, is capable of improving earlier points of view of structure-activity relationship in certain series of drugs.

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References

(1) G. Zbinden, "Molecular Modification in Drug Design," F. W. Schuler, Ed., American Chemical Society, Washington, D. C., 1964, p 25.
(2) A. H. Anton, *J. Pharmacol. Exp. Ther.*, 129, 282 (1960).
(3) B. B. Newbould and R. Kilpatrik, *Lancet*, i, 887 (1960).
(4) K. Beyer, *Pharmacol. Rev.*, 2, 227 (1950).
(5) I. M. Klotz and F. M. Walker, *J. Amer. Chem. Soc.*, 70, 943 (1948).
(6) W. Scholtan, *Arzneim.-Forsch.*, 14, 348 (1964).
(7) J. Rieder, *ibid.*, 13, 81 (1963).
(8) M. Nakagaki, N. Koga, and H. Terada, *Yakugaku Zasshi*, 84, 516 (1964).
(9) W. Scholtan, *Arzneim.-Forsch.*, 18, 505 (1968).
(10) J. Clausen, *J. Pharmacol. Exp. Ther.*, 153, 167 (1966).
(11) T. Fujita and C. Hansch, *J. Med. Chem.*, 10, 991 (1967).
(12) T. Fujita, "Biological Correlations, The Hansch Approach," W. von Valkenberg, Ed., American Chemical Society, Washington, D. C., 1972, in press.
(13) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, 86, 5175 (1964).
(14) C. Tanford, S. A. Swanson, and W. S. Shore, *ibid.*, 77, 6414 (1955).
(15) M. Yamazaki, M. Aoki, A. Kamada, and N. Yata, *Yakuzaigaku*, 27, 40 (1967).
(16) K. Kakemi, T. Arita, R. Hori, R. Konishi, and K. Nishimura, *Chem. Pharm. Bull.*, 17, 248 (1969).
(17) L. G. Goldbaum and P. K. Smith, *J. Pharmacol. Exp. Ther.*, 111, 197 (1954).
(18) I. Moriguchi, S. Wada, and T. Nishizawa, *Chem. Pharm. Bull.*, 16, 601 (1968).
(19) H. Nogami, T. Nagai, and S. Wada, *ibid.*, 18, 342 (1970).
(20) S. Wada and I. Moriguchi, *ibid.*, 16, 1440 (1968).
(21) H. Nogami, T. Nagai, and S. Wada, *ibid.*, 18, 348 (1970).
(22) F. Helmer, K. Kiehs, and C. Hansch, *Biochemistry*, 7, 2858 (1968).
(23) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).
(24) K. Kakemi, R. Arita, and T. Koizumi, *Yakuzaigaku*, 25, 22 (1965).
(25) Y. Martin and C. Hansch, *J. Med. Chem.*, 14, 777 (1971).
(26) K. B. Jacobson, *J. Biol. Chem.*, 236, 343 (1961).
(27) E. Nelson, *J. Pharm. Sci.*, 50, 181 (1961).
(28) M. Yamazaki, M. Aoki, A. Kamada, and N. Yata, *Yakuzaigaku*, 27, 37 (1967).
(29) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, 12, 413 (1964).
(30) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *ibid.*, 15, 1534 (1967).
(31) (a) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *ibid.*, 15, 1705 (1967); (b) C. Hansch, R. Steward, S. Anderson, and D. Bentley, *J. Med. Chem.*, 11, 1 (1968).
(32) A. V. Willi, *Helv. Chim. Acta*, 39, 46 (1956).

Cycloprop[16α,17α]androstanes

Kenneth E. Fahrenholtz,* Kenneth P. Meyers, and R. W. Kierstead

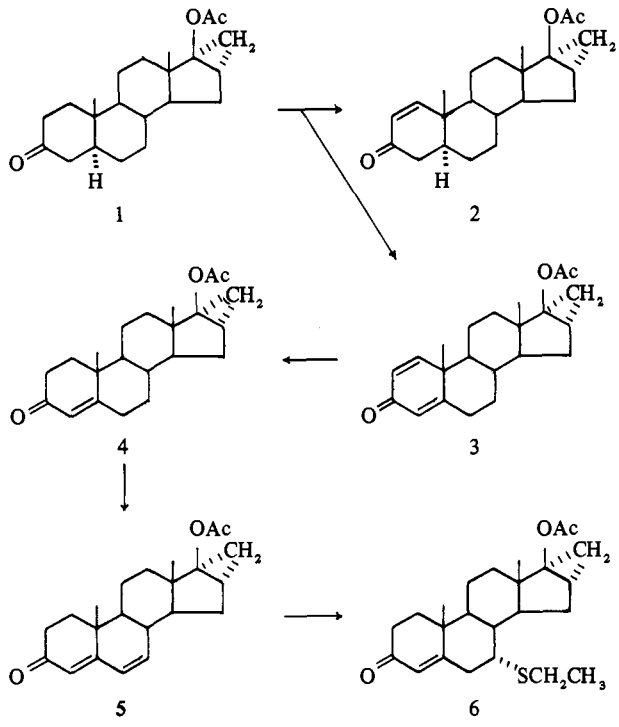
Chemical Research and Pharmacology Departments, Hoffmann-La Roche Inc., Nutley, New Jersey. *Received January 10, 1972*

A number of 17β-acyloxycycloprop[16α,17α]androstanes were prepared, some of which had substantial levels of oral androgenic activity. The corresponding 17β-alkoxy-3-keto derivatives were also prepared and converted to androstano[2,3-*d*]isoxazoles **23a-d** by standard procedures. These latter compounds combine significant levels of oral anabolic activity with diminished androgenicity.

The preparation of orally active anabolic agents has been pursued by chemists for many years.[1,2] This goal is complicated by the observation that, with a few exceptions, useful levels of oral anabolic activity are found only in steroids containing a 17α-alkyl substituent. Unfortunately this group also causes the steroid to exert undesirable side effects, including reversible hepatotoxicity.[3]

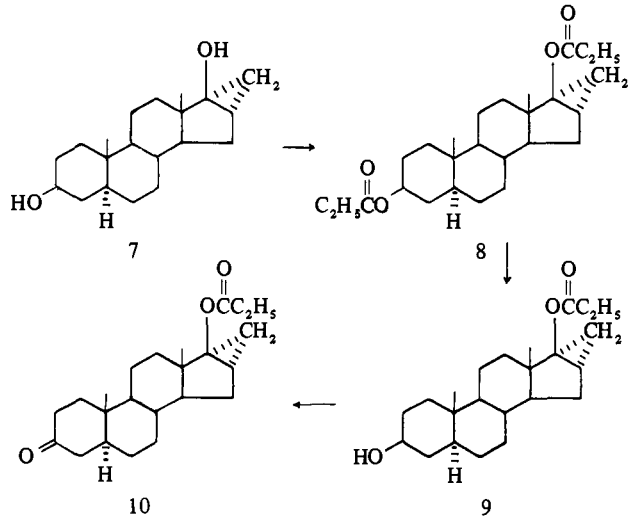
In the search for types of compounds which might circumvent the problems of liver toxicity, it occurred to us that the steric and electronic effects of a 17α-methyl group would not be altered greatly by its incorporation into a cycloprop[16α,17α] steroid. At the beginning of this work, numerous examples of this type of substitution in pregnanes and corticoids had been reported, but no reports of cycloprop[16α,17α]androstanes had appeared. After the conclusion of our synthetic work, Johns and Salamon[4] described the preparation of some of the intermediates used in our work. Therefore, we are prompted to report our results of chemical and biological interest.

When 3′*H*-cycloprop[16α,17α]-5α-androstan-17β-ol-3-one acetate (1)[4] was found to have a high level of oral androgenic activity, several ring A analogs were prepared in an effort to increase the anabolic activity. Dehydrogenation of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

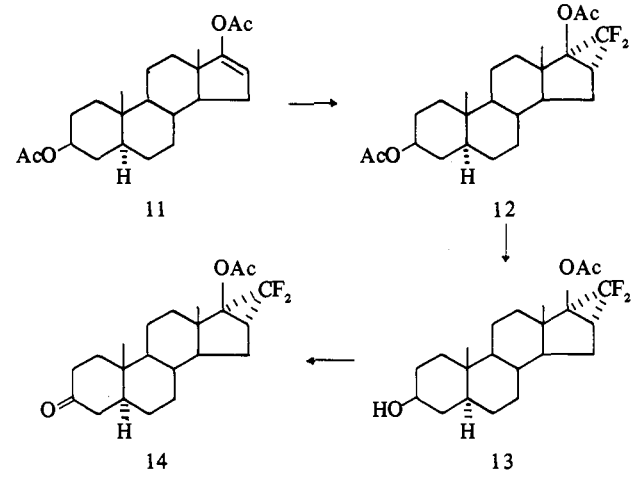


gave a mixture of **2** and **3** which was separated by chromatography over silica gel. Selective hydrogenation[5,6] of the Δ^1 double bond of **3** was then accomplished by using as a catalyst tris(triphenylphosphine)rhodium chloride. The resulting **4** (prepared in a different manner by Johns and Salamon[4]) was dehydrogenated with DDQ in the presence of hydrogen chloride[7] to give the dienone **5**. This dienone, upon treatment with ethyl mercaptan and sodium methoxide[8] in dioxane, gave the thioether **6**. Several of the above compounds were found to have high levels of oral androgenic activity but exhibited only low levels of oral anabolic activity. We then turned to the preparation of ring D analogs of **1**.

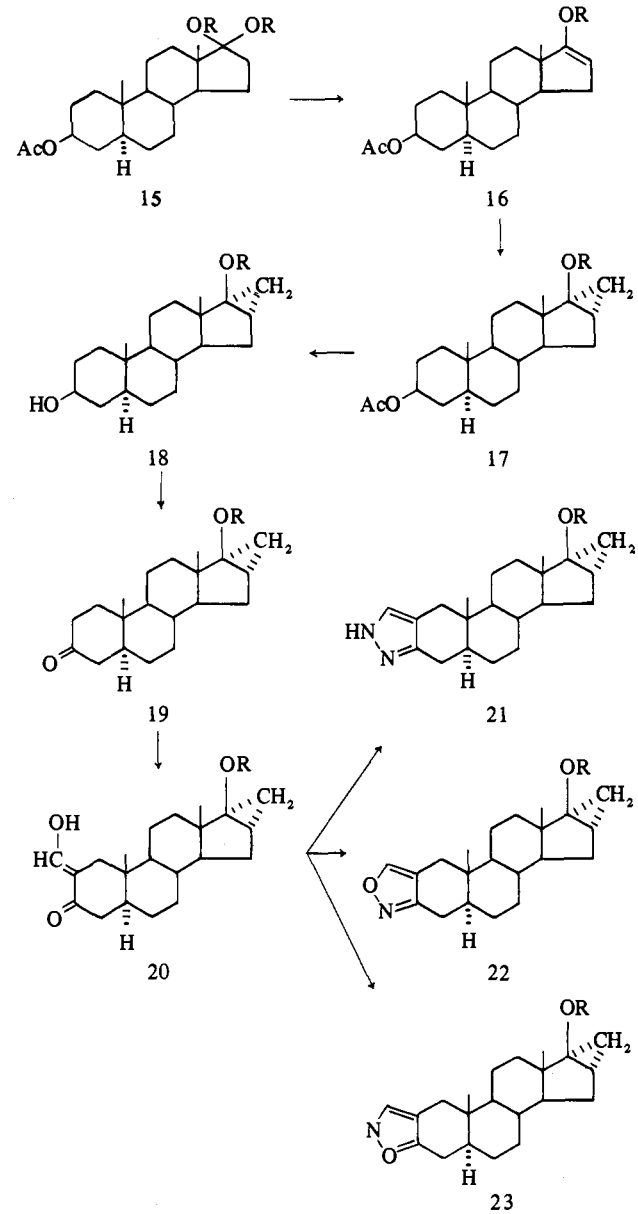
Treatment of the diol **7**[4] with propionic anhydride and pyridine gave the diester **8** which on selective hydrolysis with hydrochloric acid gave the 3-alcohol **9**, which on Jones' oxidation gave **10**.



In order to prepare the difluorocyclopropa analogs of **1**, the reaction of the enol acetate **11**[9] with difluorocarbene gave the cyclopropane **12**. Selective acid hydrolysis of **12** followed by Jones' oxidation then gave **14**.



None of these compounds incorporating ring D variations of **1** exhibit high oral levels of anabolic activity. However, more success was achieved with the series of compounds containing a 17β-alkoxy substituent.



a, R = CH_3
b, R = CH_2CH_3
c, R = $CH_2CH_2CH_3$
d, R = $CH_2CH_2CH_2CH_3$

Table I

Compound	Per cent difference from controls of organ weights: Seminal vesicles	Ventral prostate	Levator ani
Stanazolol (Winstrol)	+80[a]	+60[a]	+52[a]
Methandrostenolone (Dianabol)	+32[a]	+43[a]	+34[a]
1	+150[a]	+167[a]	+33[b]
2	+163[a]	+166[a]	+38[c]
3	+19[b]	+14	−9
4	+197[a]	+283[a]	+35[b]
5	+13	+45[a]	+6
6	+9	+8	+7
7	+74[c]	+121[a]	+30[b]
8	+132[a]	+171[a]	+10
10	+226[a]	+389[a]	+5
12	−21[b]	+36[c]	+20
14	+11	+82[c]	+8
19a	+173[a]	+289[a]	+14
19b	+147[a]	+387[a]	+34[a]
19c	+122[a]	+183[a]	+43[a]
19d	+103[a]	+212[a]	+5
20a	+18	+37[c]	−22
21a	+37[a]	+45[c]	+12
22a	+32[a]	+34[a]	+7
23a	+15	+21[b]	+35[a]
23b	+73[a]	+164[a]	+64[a]
23c	+22[b]	+11	+49[a]
23d	+24[c]	0	+11

[a] $p < 0.001$ when compared to vehicle-treated controls. [b] $p < 0.05$. [c] $p < 0.01$.

The reaction of **19a**[4] with ethyl formate and sodium methoxide in pyridine[10] readily gave the hydroxymethylene derivative **20a**. This was converted into the androstano[3,2-*c*]pyrazole **21a** with hydrazine in hot ethanol;[10] with hydroxylamine in hot pyridine[11] the androstano[3,2-*c*]isoxazole **22a** was formed, and treatment of **20a** with hydroxylamine in hot acetic acid[12] gave the isomeric androstano[2,3-*d*]isoxazole **23a**. When **23a** was found to have an interesting level of oral anabolic activity with diminished androgenic activity, the corresponding ethyl, propyl, and butyl ethers, **23b**, **23c**, and **23d**, respectively, were prepared.

Biological Activity. The compounds prepared in this paper were given orally to castrated immature rats[13,†] at a dose of 1 mg/rat per day for 7 days. On the eighth day, the animals were sacrificed and the target organs were removed and weighed with the results shown in Table I.

As can be seen from Table I only three compounds, the androstano[2,3-*d*]isoxazoles, **23a**, **23b**, and **23c**, show a significant ratio of anabolic to androgenic activity.‡ Therefore, these three compounds were retested at several dose levels. The results of this test showed that the propyl ether **23c** exhibits the widest separation of anabolic from androgenic activity. Compound **23c** was then compared to two standard compounds (stanazolol and methandrostenolone) with the results as outlined in Table II.

The results in Table II indicate that although 17β-propoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[2,3-*d*]isoxazole (**23c**) has oral anabolic activity somewhat weaker than stanazolol but equal to that of methandrostenolone, it is significantly less androgenic than either of these two standard compounds. It is not yet known whether the level of hepatotoxicity[3] of **23c** is lower than that shown by compounds possessing a 17α-methyl group.

†In the present work, drug treatment was initiated 7 days after castration.

‡The anabolic activity was determined by the increase in the levator ani weight and the androgenic activity by the increase in the weight of the seminal vesicles and the ventral prostate.

Table II

Compound	Dose, mg	% increase from controls of organ weights: Seminal vesicles	Ventral prostate	Levator ani
Stanazolol	0.5	6.6	7.4	37.3[a]
	1	52.9[a]	33.3[b]	54.4[a]
	2	97.3[a]	64.4[a]	69.4[a]
	4	264.1[a]	137.6[a]	90.6[a]
Methandrostenolone	0.5	33.4[a]	16.4	0.5
	1	32.4[a]	43.3[a]	34.8[a]
	2	62.3[a]	54.9[a]	37.2[a]
	4	163.2[a]	189.7[a]	70.6[a]
23c	0.5	13.9	2.6	10.1
	1	17.7[b]	6.7	14.2
	2	49.3[b]	51.4[a]	35.1[b]
	4	83.1[a]	53.9[a]	68.8[a]

[a] $p < 0.0001$ when compared to vehicle-treated controls. [b] $p < 0.01$.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus and are corrected. Nuclear magnetic resonance spectra were recorded with a Varian A-60 or Varian HA-100 instrument using Me_4Si as internal standard. All compounds reported in this paper had ir, uv, and nmr spectra compatible with the assigned structure and only significant values are reported. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within 0.4% of the theoretical values.

17β-Hydroxy-3′*H*-cycloprop[16α,17α]-5α-androst-1-en-3-one Acetate (2) and 17β-Hydroxy-3′*H*-cycloprop[16α,17α]androsta-1,4-dien-3-one Acetate (3). A mixt of 3.00 g (0.0087 mole) of 3′*H*-cycloprop[16α,17α]-5α-androstan-17β-ol-3-one acetate (1) (prepared by a procedure analogous to that reported)[4] and 4.08 g (0.018 mole) of DDQ in 90 ml of dioxane was heated under reflux for 2.75 hr. The cooled mixt was filtered, the solid (2,3-dichloro-5,6-dicyanohydroquinone) was washed with dioxane, and the combined filtrates were concd under vacuum. The gummy residue was dissolved in CH_2Cl_2 and adsorbed onto 200 g of silica gel. The steroidal material was removed by elution with Et_2O and 20% EtOAc in Et_2O and was again adsorbed onto 100 g of silica gel from CH_2Cl_2 solution. After first washing with less polar solvents, elution with 250 ml of 7% Et_2O in CH_2Cl_2 gave crude crystalline 2. Recrystn first from CH_2Cl_2–Et_2O–hexane and then from Et_2O gave 0.702 g (24%) of 2 as colorless crystals: mp 187–188°. The analytical sample had mp 187–188.5°, $[\alpha]^{25}D$ +57.1° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{22}H_{30}O_3$) C, H.

Further elution of the column with from 10 to 17% Et_2O in CH_2Cl_2 gave crude crystalline 3. Recrystn from CH_2Cl_2–Et_2O gave 0.867 g (29%) of 3 as colorless crystals: mp 218.5–220.5°. Further recrystn gave the analytical sample: mp 219–220.5°; $[\alpha]^{25}D$ + 54.8° (*c* 0.977, $CHCl_3$). *Anal.* ($C_{22}H_{28}O_3$) C, H.

17β-Hydroxy-3′*H*-cycloprop[16α,17α]androst-4-en-3-one Acetate (4). A mixt of 3.43 g (0.0101 mole) of 3, 3.43 g of tris(triphenylphosphine)rhodium chloride, 540 ml of C_6H_6, and 60 ml of EtOH was shaken under H_2 at room temp and pressure. After 3.75 hr, the rate of uptake had slowed considerably and the shaking was stopped. The total uptake was 225 ml (theoretical uptake was 243 ml). The soln was concd under vacuum, and the residue was dissolved in CH_2Cl_2 and passed over a column of alumina. Concentration followed by recrystn from CH_2Cl_2–Et_2O gave a mixt of pale yellow crystals and red solid. Trituration with CH_2Cl_2 dissolved the yellow crystals, and the red solid was discarded. The CH_2Cl_2 was evapd, and the residue was recrystd from CH_2Cl_2–Et_2O to give 2.89 g (84%) of 4 as colorless crystals: mp 207–210°. Further recrystn gave the analytical sample: mp 211–214°; $[\alpha]^{25}D$ +112.8° (*c* 1.032, $CHCl_3$). *Anal.* ($C_{22}H_{30}O_3$) C, H.

17β-Hydroxy-3′*H*-cycloprop[16α,17α]androsta-4,6-dien-3-one Acetate (5). Hydrogen chloride was passed over the surface of a soln of 1.470 g (0.0043 mole) of 4 in 60 ml of dioxane and over a soln of 0.976 g (0.0043 mole) of DDQ in 60 ml of dioxane for a

few seconds. The two solns were mixed and stirred while HCl gas was passed over the surface for 2 min. A ppt formed, and the mixt was stirred for an additional 5 min. The ppt (2,3-dichloro-5,6-dicyanohydroquinone) was removed by filtration, and the filtrate was poured into 1 l. of H_2O. The resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was passed over a short column of alumina and concd. The resulting oil was crystd from Et_2O–hexane and recrystd from CH_2Cl_2–Et_2O–hexane. On one occasion, the solution deposited two different types of colorless crystals which were separated manually. The minor type melted at 152–154° with no prior change. The major type of crystal melted completely at 141.5–143.5°, then resolidified in the oil bath and remelted at 147.5–149.5°. A mmp showed a change at 142° and then melted at 149–152.5°. A total of 0.818 g (56%) of pure product was obtained, and the analytical sample was obtained from CH_2Cl_2–hexane: mp 149–152° after a change at ~142°; $[\alpha]^{25}D$ +56.9° (*c* 1.07, $CHCl_3$). *Anal.* ($C_{22}H_{28}O_3$) C, H.

7α-Ethylthio-17β-hydroxy-3′*H*-cycloprop[16α,17α]androst-4-en-3-one Acetate (6). To a soln of 594 mg (1.74 mmoles) of 5 in 6 ml of dioxane was added 1.5 ml of EtSH and 180 mg of NaOMe. The heterogeneous reaction was stirred at room temp for 7 days and then filtered. The filtrate was concd under a stream of air, and the resulting oil was dissolved in CH_2Cl_2. The soln was filtered through a filter aid and concd. The residue was crystd from Et_2O and recrystd from CH_2Cl_2–Et_2O to give 304 mg (43%) of 6 as colorless crystals: mp 199–202.5°. Further recrystn gave the analytical sample: mp 200–204°; $[\alpha]^{25}D$ −3.2° (*c* 0.69, $CHCl_3$). *Anal.* ($C_{24}H_{34}O_3S$) C, H, S.

3′*H*-Cycloprop[16α,17α]-5α-androstane-3β,17β-diol Dipropionate (8). To a solution of 29.60 g (0.097 mole) of 3′*H*-cycloprop[16α,17α]-5α-androstane-3β,17β-diol (7) in 225 ml of pyridine was added 225 ml of propionic anhydride, and the reaction was stirred at room temp for 3 days. The reaction was then poured into 5 l. of ice and H_2O, and the resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was washed 3 times with H_2O, dried, and passed over a column of 45 g of silica gel. The eluate was concd to give a colorless cryst residue which on recrystn from CH_2Cl_2–Et_2O–pentane gave 29.10 g (72%) of 8: mp 154.5–157.5°. Further recrystn gave the analytical sample: mp 155.5–157.5°; $[\alpha]^{25}D$ +4.79° (*c* 1.02, $CHCl_3$). *Anal.* ($C_{26}H_{40}O_4$) C, H.

3′*H*-Cycloprop[16α,17α]-5α-androstane-3β,17β-diol 17-Propionate (9). A soln of 29.1 g (0.070 mole) of 8 in 291 ml of THF, 291 ml of MeOH, and 5.82 ml of HCl was allowed to stand at room temp for 6 hr and then in the refrigerator for 5 days. The reaction was made essentially neutral with 6.2 ml of pyridine, concd to 100 ml under vacuum, dild with 1 l. of H_2O, and filtered. The solid was air-dried, dissolved in C_6H_6, and adsorbed onto a column of Florisil. Elution with benzene gave some 8 and other materials. Later C_6H_6 fractions, increasing amounts of CH_2Cl_2 in C_6H_6 and 2% Et_2O in CH_2Cl_2 gave fractions rich in product which were combined and recrystd from CH_2Cl_2–hexane to give 5.68 g (23%) of 9 as colorless crystals: mp 180–182°. Further recrystn gave the analytical sample of identical mp: $[\alpha]^{25}D$ +14.2° (*c* 0.964, $CHCl_3$). *Anal.* ($C_{23}H_{36}O_3$) C, H.

3′*H*-Cycloprop[16α,17α]-5α-androstan-17β-ol-3-one Propionate (10). A soln of 5.30 g (0.0147 mole) of 9 in 265 ml of Me_2CO and 35 ml of THF was cooled to 2° and treated dropwise with 5.9 ml of Jones' reagent. *i*-PrOH (3 ml) was added, the inorganic ppt was removed by filtration, and the soln was treated with a little $NaHCO_3$ and dried over Na_2SO_4. The soln was concd, and the residue was crystd from Et_2O to give 2.88 g (55%) of 10 as colorless crystals: mp 130.5–133.5°. Further recrystn from Et_2O–pentane gave the analytical sample: mp 131.5–133.5°; $[\alpha]^{25}D$ +36.0° (*c* 0.934, $CHCl_3$). *Anal.* ($C_{23}H_{34}O_3$) C, H.

3′,3′-Difluoro-3′*H*-cycloprop[16α,17α]-5α-androstane-3β,17β-diol Diacetate (12). A soln of 20.0 g (0.053 mole) of 5α-androst-16-ene-3β,17β-diol diacetate (11) in 340 ml of diglyme (dried over 4A molecular sieves) in a 2-l. round-bottom flask was heated under reflux with vigorous stirring while a soln of 65 g (0.423 mole) of $CClF_2CO_2Na$ in 320 ml of diglyme was added over 30 min. The soln was heated under reflux for an additional 5 min, and then 200 ml of solvent was distd out under vacuum over 15 min. The reaction was cooled with an ice bath and poured into 3 l. of ice H_2O. The resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was dried, filtered through a short column of silica gel, and concd to an oil which soon crystd. Recrystn from CH_2Cl_2–Et_2O–hexane gave 18.8 g (83%) of 12 as colorless crystals (17.1 g, mp 155.5–158.5°, and 1.7 g, mp 151.5–157.5°). Further recrystn from Et_2O–hexane gave the analytical sample: mp 157.5–159°; $[\alpha]^{25}D$ −10.4° (*c* 1.27, $CHCl_3$). *Anal.* ($C_{24}H_{34}F_2O_4$) C, H, F.

3′3′-Difluoro-3′*H*-cycloprop[16α,17α]-5α-androstan-17β-ol-3-one Acetate (14). To a soln of 1.56 g (0.0037 mole) of 12 in 75 ml of MeOH and 10 ml of THF was added 1.5 ml of HCl. The reaction was stirred at room temp and followed by tlc on silica gel plates with 15% EtOAc in C_6H_6. After 3.3 hr, when ~90% of the starting material had been consumed, the reaction was poured into 1 l. of ice and H_2O. The resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was dried and evapd to give crude 13 which could be recrystd from Et_2O to give almost pure (by analysis) 13 (mp 146–152°; *Anal.* ($C_{22}H_{32}F_2O_3$) calcd: C, 69.09; H, 8.43; F, 9.93; found: C, 69.70, 69.46; H, 8.40, 8.39; F, 10.02) but which in this example was directly oxidized with 1.7 ml of Jones' reagent in 75 ml of Me_2CO. After addn of some *i*-PrOH, the reaction mixt was filtered through a filter aid and dild with H_2O. The organic solvents were removed under vacuum, and the aqueous suspension was filtered. The solid was dissolved in CH_2Cl_2, and the soln was dried and evapd. The resulting solid was recrystd from CH_2Cl_2–Et_2O to give 0.60 g (43%) of 14 as colorless crystals: mp 196–198°. Further recrystn gave the analytical sample: mp 197–199°; $[\alpha]^{25}D$ +15.1° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{22}H_{30}F_2O_3$) C, H, F.

2-Hydroxymethylene-17β-methoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3-one (20a). To a rapidly stirred soln of 3.00 g (0.0095 mole) of 17β-methoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3-one (19a) in 60 ml of pyridine and 10 ml of ethyl formate was added a soln of NaOMe prepared from 0.84 g (0.04 g-atom) of Na and 7.8 ml of MeOH. Within 1 min the reaction mixt set solid and was allowed to stand for 45 min. It was then dild with H_2O, neutralized with AcOH, and extd with CH_2Cl_2. The CH_2Cl_2 ext was dried, passed over a little silica gel, and concd to an almost colorless oil. Crystn and recrystn from CH_2Cl_2–Et_2O gave 2.83 g (87%) of 20a as colorless crystals: mp 174–176°. Further recrystn gave the analytical sample: mp 175–176°; $[\alpha]^{25}D$ +75.4° (*c* 0.471, $CHCl_3$). *Anal.* ($C_{22}H_{32}O_3$) C, H.

17β-Methoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[3,2-*c*]-pyrazole (21a). A mixt of 1.065 g (0.0031 mole) of 20a, 25 ml of EtOH, and 0.4 ml of 85% hydrazine hydrate was heated under reflux for 30 min, and the solvent was removed under vacuum to leave a colorless cryst residue. Recrystn from CH_2Cl_2–Et_2O gave 917 mg (87%) of 21a as colorless crystals: mp 243–245°. Further recrystn gave the analytical sample: mp 244–246°; $[\alpha]^{25}D$ +78.0° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{22}H_{32}N_2O$) C, H, N.

17β-Methoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[3,2-*c*]-isoxazole (22a). A hot soln of 1.00 g of $NH_2OH \cdot HCl$ in 6 ml of water was added to a hot soln of 2.00 g (0.058 mole) of 20a in 30 ml of pyridine. The soln was heated under reflux for 3 hr and allowed to cool to room temp overnight. The solvents were removed under vacuum, and the residue was dild with CH_2Cl_2 and washed twice with H_2O. The soln was dried and concd, and the residue was stirred at room temp for 30 min with 30 ml of THF and 0.76 g of NaOMe. The solvent was evapd, and the residue was mixed with H_2O and extd with CH_2Cl_2. The exts were dried and concd. The residue was dissolved in C_6H_6 and adsorbed onto a column of silica gel. Elution with solvents from 5% CH_2Cl_2 in C_6H_6 through 10% Et_2O in CH_2Cl_2 gave cryst fractions which were combined and recrystd from CH_2Cl_2–Et_2O to give 1.55 g (78%) of 22a as colorless crystals: mp 166.5–168°. Further recrystn gave the analytical sample: mp 167.5–168.5°; nmr ($CDCl_3$) δ 8.12 (s, isoxazole CH); $[\alpha]^{25}D$ +71.4° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{22}H_{31}NO_2$) C, H, N.

17β-Methoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[2,3-*d*]-isoxazole (23a). To a flask contg 8.27 g (0.024 mole) of 20a was added 250 ml of hot AcOH, and the flask was immediately placed in an oil bath preheated to 170°. Four minutes later a soln of 3.68 g (0.053 mole) of $NH_2OH \cdot HCl$ and 4.14 g (0.0505 mole) of NaOAc in 47 ml of H_2O was added. The soln began to boil 4 min later and was allowed to reflux for 5 min. It was then immediately removed from the oil bath, cooled in an ice bath, and poured into 3.5 l. of H_2O. The resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was dried and concd under vacuum. The residue was dissolved in C_6H_6 and adsorbed on a silica gel column. Elution with solvents from C_6H_6 through 5% Et_2O in CH_2Cl_2 gave cryst fractions which were combined and recrystd from CH_2Cl_2–Et_2O to give 4.79 g (58%) of 23a as colorless crystals: mp 144–145.5°. Further recrystn gave the analytical sample: mp 142.5–143.5°; nmr ($CDCl_3$) δ 8.03 (s, isoxazole CH); $[\alpha]^{25}D$ +76.2° (*c* 1.02, $CHCl_3$). *Anal.* ($C_{22}H_{31}NO_2$) C, H, N.

17β-Ethoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[2,3-*d*]-isoxazole (23b). A soln of NaOMe prepared from 1.56 g (0.068 g-atom) of Na and 14.5 ml of MeOH was added all at once to a stirred solution of 5.573 g (0.0169 mole) of 17β-ethoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3-one (19b)[4] in 110 ml of pyridine and 18.5

ml of ethyl formate. The reaction set solid almost immediately and was allowed to stand for 45 min. It was then dild with H_2O, neutralized with AcOH, and extd with CH_2Cl_2. The ext was dried and concd to give a pale yellow solid. This was dissolved in C_6H_6 and passed over a column of silica gel. The first C_6H_6 fraction contained 3.75 g of a white solid of 20b which gelled out of all the solvents tried for recrystn, and was therefore used directly for the preparation of 23b. To a flask containing the 3.75 g of 20b was added 115 ml of hot AcOH, and the flask was immediately immersed in an oil bath heated to 160°. Three minutes later a soln of 1.67 g of $NH_2OH \cdot HCl$ and 1.88 g of NaOAc in 21 ml of H_2O was added. In 2 min the reaction began to boil and heating was continued under reflux for an additional 5 min. The soln was immediately cooled in an ice bath and then poured into 2 l. of ice and H_2O. The resulting ppt was collected by filtration and dissolved in CH_2Cl_2. The soln was dried and concd, and the residue was dissolved in C_6H_6 and adsorbed onto a column of 38 g of silica gel. Elution with C_6H_6, with mixtures of CH_2Cl_2 and C_6H_6, and with CH_2Cl_2 gave colorless cryst fractions which were recrystd from CH_2Cl_2–Et_2O to give 789 mg (13% overall) of 23b: mp 160.5–162°. Further recrystn gave the analytical sample: mp 160.5–162.5°; nmr ($CDCl_3$) δ 8.06 (s, isoxazole CH); $[\alpha]^{25}D$ +68.3° (*c* 0.956, $CHCl_3$). *Anal.* ($C_{25}H_{33}NO_2$) C, H, N.

17β-Propoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3β-ol Acetate (17c). A mixt of 600 g (1.81 moles) of isoandrosterone acetate, 2.5 l. of *n*-PrOH, and 920 ml of tripropyl orthoformate[14] was heated with an oil bath until soln took place (soln temp was 53°), and then 14 ml of H_2SO_4 was added. Heating was continued for 10 min (soln was 62°), the reaction was stirred at ambient temp for 20 min, 90 ml of pyridine was added, and the volatile materials were removed under aspirator vacuum to give a residue of crude 17,17-dipropoxy-5α-androstan-3β-ol acetate (15c).

A mixt of 3.8 l. of toluene, 1.21 ml of pyridine, and 2.85 g of $TsOH \cdot H_2O$ was heated and distilled until no more H_2O was seen in the upper portions of the apparatus. This soln and an additional 4.4 l. of toluene was added to the flask containing the crude 15c. The mixt was gradually heated with an oil bath over 1.75 hr to 100° Volatile materials were then removed under aspirator vacuum to give a residue of crude 17-propoxy-5α-androst-16-en-3β-ol acetate (16c), which was dissolved in 900 ml of CH_2I_2 and 900 ml of CH_2Cl_2.

In another flask fitted with a mechanical stirrer and under an argon blanket was added 14.4 g of $Cu(OAc)_2 \cdot H_2O$ and 2 l. of AcOH. The soln was heated on the steam bath, 960 g of 20-mesh Zn was added, and the mixt was stirred vigorously until the copper color had faded. The AcOH was removed; the resulting zinc–copper couple[15] was washed twice with 2 l. of hot AcOH, cooled with a cooling bath, and washed three times with 2 l. of Et_2O. The solid was covered with 400 ml of Et_2O, and this slurry was washed into the flask containing the crude 16c with 900 ml of CH_2Cl_2. The mixt was stirred, and, after about 15 min, a vigorous exothermic reaction ensued which was controlled by external cooling of the flask with Dry Ice. When the exotherm had subsided, the reaction was stirred and heated under reflux overnight to generate a tan slurry. This was mixed with 2 l. of ice, and the organic layer was washed repeatedly with 500 ml of H_2O each time until the aqueous layer was less dense than the organic layer. The organic layer was then dried and concd to give ~900 g of an orange oil. This was mixed with hexane and passed over a column of 1.6 kg of silica gel. Elution with 5% C_6H_6 in hexane to 10% Et_2O in C_6H_6 gave fractions containing product as shown by tlc in C_6H_6. The cryst fractions were recrystd from CH_2Cl_2–hexane to give 66.8 g of 17c as colorless crystals: mp 141–145°. The noncryst product-containing fractions and mother liquors were combined and rechromatographed over silica gel (6 g of silica gel/g of material) to give further material: mp 141–145°; a total yield of 17c of 23% overall from isoandrosterone acetate. Further recrystn from CH_2Cl_2–hexane gave the analytical sample of 17c: mp 144–146°; $[\alpha]^{25}D$ +18.1° (*c* 0.980, $CHCl_3$). *Anal.* ($C_{25}H_{40}O_3$) C, H.

17β-Propoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3β-ol (18c). A mixt of 116.6 g (0.30 mole) of 17c, 120 g of $NaHCO_3$, 3 l. of MeOH, and 750 ml of H_2O was heated under reflux overnight. The MeOH was removed under vacuum, and the residue was dild with H_2O and filtered. The solid was dissolved in CH_2Cl_2, and the soln was dried and concd to a small volume. The resulting crystals were filtered and washed with Et_2O to give (in two crops) 93.08 g (89%) of 18c as colorless crystals: mp 198–199.5°. Further recrystn gave the analytical sample: mp 199.5–200.5°; $[\alpha]^{25}D$ +28.5° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{23}H_{38}O_2$) C, H.

17β-Propoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3-one (19c). To a soln of 256 ml of pyridine in 7.1 l. of CH_2Cl_2 was added gradually 105.8 g of CrO_3, followed by a soln of 51.4 g (0.148 mole) of 18c in 2.5 l. of CH_2Cl_2. The mixt was stirred for 30 min, and the soln and a CH_2Cl_2 wash of the residue of chromium salts were washed with H_2O, dried, passed over a short column of Florisil, and concd to give a colorless cryst residue. Recrystn from CH_2Cl_2–MeOH gave 43.7 g (85%) of 19c: mp 113–115°. The analytical sample had mp 112.5–115°, $[\alpha]^{25}D$ +48.6° (*c* 0.916, $CHCl_3$). *Anal.* ($C_{23}H_{36}O_2$) C, H.

17β-Propoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[2,3-*d*]-isoxazole (23c). Treatment of 19c with ethyl formate and reaction of the crude 20c with $NH_2OH \cdot HCl$ in AcOH as in the prepn of 23b gave a 20% yield overall of the analytical sample of 23c as colorless crystals: mp 111–112°; nmr ($CDCl_3$) δ 8.00 (s, isoxazole CH); $[\alpha]^{25}D$ +70.3° (*c* 0.788, $CHCl_3$). *Anal.* ($C_{24}H_{35}NO_2$) C, H, N.

17β-Butoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3β-ol Acetate (17d). Following the procedure used for the prepn of 17c, except that the intermediate 15d was converted into 16d in hot xylene rather than toluene, gave, after recrystn from Et_2O–MeOH, a 6% yield of 17d: mp 105–109°. The analytical sample had mp 103–107°, $[\alpha]^{25}D$ +17.6° (*c* 1.01, $CHCl_3$). *Anal.* ($C_{26}H_{42}O_3$) C, H.

17β-Butoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3β-ol (18d). Hydrolysis of 17d as for the prepn of 18c gave after concn, filtration, and air-drying a colorless solid of 18d, mp 190–194°, used directly for analysis, spectra, and the next step: $[\alpha]^{25}D$ +19.9° (*c* 1.08, $CHCl_3$). *Anal.* ($C_{24}H_{40}O_2$) C, H.

17β-Butoxy-3′*H*-cycloprop[16α,17α]-5α-androstan-3-one (19d). Oxidation of the crude 18d as for the prepn of 19c gave after recrystn from Et_2O–MeOH a 72% yield (overall from 17d) of 19d: mp 102–104°. Further recrystn gave the analytical sample of the same mp: $[\alpha]^{25}D$ +49.5° (*c* 0.998, $CHCl_3$). *Anal.* ($C_{24}H_{38}O_2$) C, H.

17β-Butoxy-3′*H*-cycloprop[16α,17α]-5α-androstano[2,3-*d*]isoxazole (23d). Treatment of 19d with ethyl formate and treatment of the crude 20d with $NH_2OH \cdot HCl$ in AcOH as in the prepn of 23b gave, after recrystn from MeCN, a 46% overall yield of 23d: mp 105–108°. The analytical sample had the same mp: nmr ($CDCl_3$) δ 8.01 (s, isoxazole CH); $[\alpha]^{25}D$ +68.2° (*c* 1.05, $CHCl_3$). *Anal.* ($C_{25}H_{37}NO_2$) C, H, N.

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References

(1) J. A. Vida, "Androgens and Anabolic Agents," Academic Press, New York, N. Y., 1969.
(2) P. D. Klimstra in "The Chemistry and Biochemistry of Steroids," N. Kharasch, Ed., Geron-X, Los Altos, Calif., 1969, Chapter VIII.
(3) H. D. Lennon, *J. Pharmacol. Exp. Ther.*, 151, 143 (1966). See also ref 1, p 19.
(4) W. F. Johns and K. W. Salamon, *J. Org. Chem.*, 36, 1952 (1971).
(5) A. J. Birch and K. A. M. Walker, *J. Chem. Soc. C*, 1894 (1966).
(6) C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, 88, 4537 (1966).
(7) A. B. Turner and H. J. Ringold, *J. Chem. Soc. C*, 1720 (1967).
(8) H. Kaneko, K. Nakamura, Y. Yamato, and M. Kurokawa, *Chem. Pharm. Bull.*, 17, 11 (1969).
(9) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, 76, 2943 (1954).
(10) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *ibid.*, 83, 1478 (1961).
(11) E. Marchetti and P. Donini, *Gazz. Chim. Ital.*, 91, 1133 (1961).
(12) A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, 6, 1 (1963).
(13) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exp. Biol. Med.*, 83, 175 (1953).
(14) R. Ohme and E. Schmitz, *Justus Liebigs Ann. Chem.*, 716, 207 (1968).
(15) E. LeGoff, *J. Org. Chem.*, 29, 2048 (1964).