obtained which solidified. A $CHCl_3$ solution, upon standing for a few hours, afforded 300 mg of a crystalline product, mp 151–154°. Chromatography of the mother liquors (400 mg) on 12 g of alumina with eluents ranging from 30% Et_2O in C_6H_6 to pure Et_2O furnished an additional 230 mg of the same material, heavily solvated with $CHCl_3$; yield 60%, mp 154°, $[\alpha]D^{24}$ +9° (*c* 1.5). *Anal.* ($C_{22}H_{34}O_2$) C, H.

17,17-Dimethyl-18-nor-A-nor-5α-androst-13-en-2-one (XVIII).—A solution of 5 g of VIa[5] in 50 ml of HCO_2H was allowed to stand overnight at room temperature. After addition of a little H_2O, the solution was heated for 15 min on the steam bath. Addition of more H_2O precipitated 3.43 g of product which was recrystallized from hexane, giving a first crop of 1.4 g, mp 115°. The mother liquors were filtered through a short alumina column and the crystalline material obtained was recrystallized from hexane; mp 115°, $[\alpha]^{22}_{578}$ +127.6°, $[\alpha]^{22}_{364}$ +955° (*c* 1.03). *Anal.* ($C_{19}H_{28}O$) C, H.

2α-Ethynyl-17,17-dimethyl-18-nor-A-norandrost-13-en-2β-ol (XIX).—To a solution of 1.4 g of lithium acetylide–ethylenediamine complex in 10 ml of dry DMSO was added dropwise a solution of 0.8 g of 17,17-dimethyl-18-nor-A-nor-5α-androst-13-en-2-one in 20 ml of dry THF, with stirring under N_2. Stirring was maintained for 3.5 hr after addition was complete, and the reaction was then worked up in the usual manner (*vide supra*) to give 0.86 g of resin which still possessed ketone. Treatment with Girard's T reagent removed the starting material and gave 400 mg of ethynylcarbinol which was recrystallized twice from aqueous MeOH to give 290 mg of XIX. Drying under reduced pressure removed solvent of crystallization to give an analytical sample, mp 85°, $[\alpha]^{22}D$ +1.4°, $[\alpha]^{22}_{364}$ +17° (*c* 0.72). *Anal.* ($C_{21}H_{30}O$) C, H.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. A. Patchett (Rahway) for his continued interest and many helpful discussions.

Antiandrogenic and Progestational Activity of Some 17-Oxygenated 15-Dehydro Steroids

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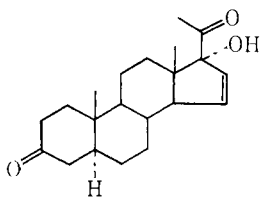
The synthesis of a group of steroids related to 17α-hydroxy-15-dehydroprogesterone is described. Several of these compounds exhibited moderate antiandrogenic activity by subcutaneous administration in castrate rats. A few 17α-acetoxy-15-dehydroprogesterones showed slight progestational activity when injected intramuscularly in rabbits.

Although the great interest in enhancement of progestational activity has led to numerous modifications of the steroid molecule,[2] relatively little is known about the effect of such structural modifications on the antiandrogenic activity. Introduction of a methyl or chloro substituent and/or unsaturation at C-6,[3] as well as a 1,2α-cyclomethylene moiety[4] in the 17-oxygenated progesterone molecule have been among the major structural changes leading to compounds with increased antiandrogenic activity.

The preparation of 16-unsubstituted 17α-hydroxy-15-pregnen-20-ones from the corresponding 16-pregnen-20-ones was recently reported from these laboratories.[5] Biological evaluation of several of the 17α-hydroxy-15-pregnen-20-ones revealed antiandrogenic activity in castrate rats treated with testosterone. The two most active compounds among the 16-unsubstituted 15-dehydropregnanes were found to be **1** and **2a**. In an attempt



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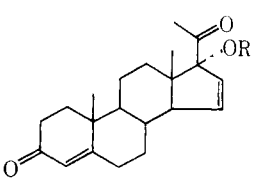
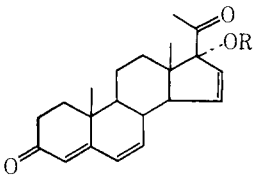


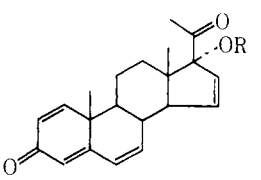
2a, R = H
b, R = $COCH_3$

to prepare 15-dehydro steroids with increased antiandrogenic activity, we set out to synthesize dehydrogenated derivatives of **2** as well as simple modified structures related to the 5α,15-dehydro steroid **1**.

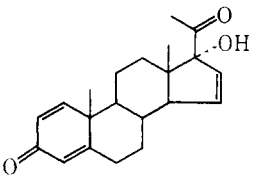
Dehydrogenation of **2a** with chloranil gave **3a**, which



3a, R = H
b, R = $COCH_3$



4a, R = H
b, R = $COCH_3$



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was then converted with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) into **4a**. When **2** was treated with DDQ directly, the 1,4,15-triene **5** was obtained. Similarly the 17-acetate **2b** was converted into **3b**, which then afforded **4b**. When **4a** was allowed to react with a large excess of diazomethane, the pyrazoline **6** was isolated in low yield. The conversion of the 1α,2α-(4′,3′,1′-pyrazolino)-4,6-dien-3-one system to the corresponding 1,2α-cyclomethylene-4,6-dien-3-one has been effected by pyrolysis[6] or by treatment with acid.[7] When **6** was subjected to either of these procedures none of the desired **7** was obtained. Treatment of **4a** with dimethylsulfoxonium

(1) Physiology and Biochemistry Department, Biological Research Division.
(2) For a recent review see T. Miyake and W. H. Rooks II, *Methods Hormone Res.*, **5**, 59 (1966).
(3) R. I. Dorfman, *ibid.*, **4**, 91 (1965).
(4) (a) K. Junkmann and F. Neumann, *Acta Endocrinol., Suppl.*, **90**, 139 (1964); (b) F. Neumann and M. Kramer, *Endocrinology*, **75**, 428 (1964).
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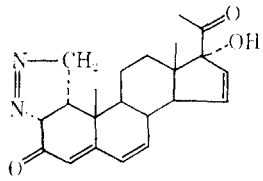
(7) G. W. Krakower and H. Ann Van Dine, *J. Org. Chem.*, **31**, 3467 (1966).



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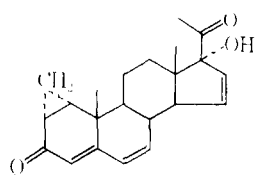

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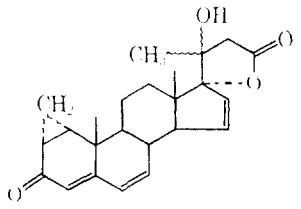

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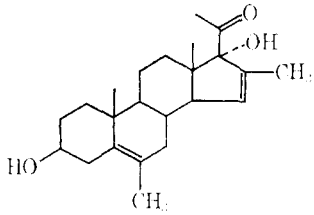
methylide reagent in DMSO,[8] generated from trimethylsulfoxonium iodide with sodium hydride, gave the desired 1,2α-cyclomethylene **7**. When the acetate **4b** was treated with the Corey reagent, the hydroxylactone **8** was formed in good yield.[9]

Several 16-methyl-15-dehydro steroids related to **1** and **2a** were also prepared. Dehydrogenation of **9**[10] with *Flavobacterium dehydrogenans*[11] afforded the 6α,16-dimethyl compound **10**. Catalytic hydrogenation of **11**[12] under the conditions described by Spring and coworkers[13] gave the 5β-steroid **12**, which on treatment with HI in THF afforded **13** in 60% yield, free of the 16-methylene isomer **14** as determined by nmr and ir spectroscopy. When other conditions, such as HCl in dioxane[14] or in acetone,[15] were used for the opening of the epoxide **12** the Δ^{15}-16-methyl compound **13** was accompanied by **14**, and occasionally the $\Delta^{14,16}$-diene **15** was also isolated.



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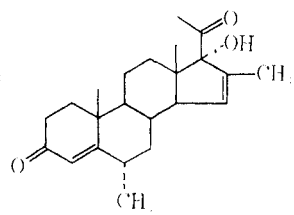

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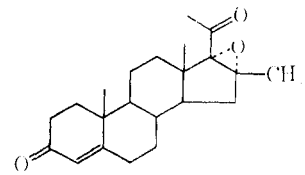

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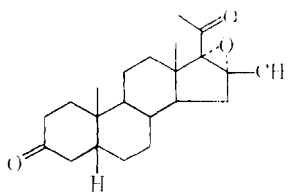

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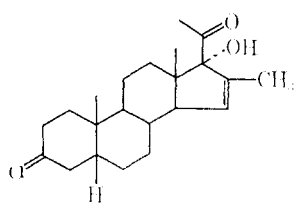

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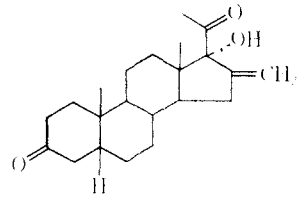

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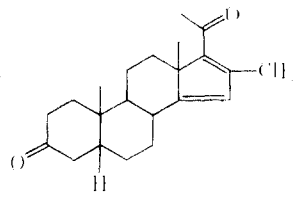

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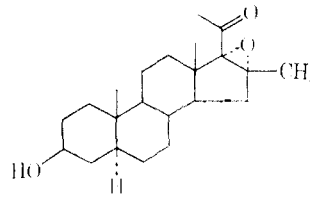
The epimeric 5α derivative **18** was prepared in the following manner. Oxidation of **16**[16] with 8 *N* chromic acid in acetone[17] gave the 3-ketone **17**. The assignment of the configuration for the hydrogen at C-5 in **12** as 5β *vs.* **17** as 5α was also supported by CD measurements. By considering the contribution of the C-20 carbonyl group as calculated from the CD spectrum of **12**, the contribution of the C-3 carbonyl group in **17** is in complete agreement with the 5α configuration in the latter compound.[18] When **17** was allowed to react with concentrated HCl in acetone,[15] the desired **18** was isolated



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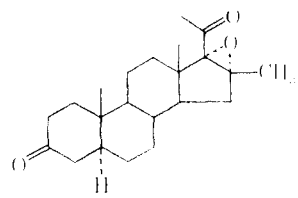

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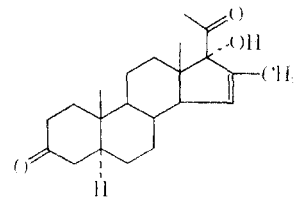

18

in 67% yield, free of the isomeric 16-methylene compound.

Biological Testing.—The antiandrogenic activities of some of the 15-dehydro steroids and precursors are reported in Table I. The progestational activities are reported in Table II.

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(9) This cyclization of 17α-acetoxy-20-ketopregnanes to β-hydroxylactones or butenolides under strongly basic conditions was reported recently: (a) H. G. Lehmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 783 (1965); (b) N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 1841 (1966); (c) G. W. Moersch, D. E. Evans, and G. S. Lewis, *J. Med. Chem.*, **10**, 254 (1967).

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(11) We are indebted to Dr. W. Charney and Miss C. Federbush for carrying out this experiment.

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(15) G. Nomine, D. Bertin, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960); *cf.* D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Amer. Chem. Soc.*, **82**, 4012 (1960), who found that under these conditions both the Δ^{15}-16-methyl and the 16-methylene isomers are formed.

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TABLE I

Compd	Daily dose, mg/kg	Testosterone daily dose, μg	% inhib[a,b] Seminal vesicles	% inhib[a,b] Ventral prostate
1	15	100	43	32
2a	50	100	59	35
2b	20	100	35	27
3a	20	100	15	10
4a	20	50	0	11
5	18	100	17	9
7	25	10[c]	0	0
8	20	50	40	27
12	20	100	31	41
13	20	100	30	28
17	20	100	28	32
18	20	100	18	37

[a] Antiandrogenic activity was determined in orchiectomized androgen-stimulated rats by the procedure of R. I. Dorfman and D. F. Stevens, *Endocrinology*, **67**, 394 (1960). The androgen, dissolved in sesame oil, was injected subcutaneously concomitantly with the test compound. The latter was suspended in a 5% aqueous carboxymethylcellulose solution and injected subcutaneously in a site different from the androgen. [b] % inhib = [1.0 − (compound + androgen − controls)/(androgen − controls)]100. [c] Testosterone propionate.

TABLE II

Compd	Progestational act.[a]
Progesterone	1.0
2b	2.0
3b	1.25
4b	0.39

[a] Progestational activity was determined by the method of M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934). The test substances were dissolved in sesame oil and injected intramuscularly into immature rabbits for 5 days.

Experimental Section[19]

17α-Hydroxy-4,6,15-pregnatriene-3,20-dione (3a).—A solution of **2a**[5] (917 mg) in *t*-BuOH (70 ml) was heated at reflux with chloranil (4.12 g) for 3 hr. The solids were removed by filtration, and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, washed (10% NaOH), and dried. After evaporation of the solvent, the residue was crystallized (Me_2CO–(C_6H_{14}), yielding 523 mg (58%) of **3a**: mp 259–264° dec; $[\alpha]_D$ −68°; λ_{max} 284 mμ (ε 25,300); nmr, δ 0.85 (13-CH_3), 1.12 (10-CH_3), 2.25 (20-CH_3), 5.67 (4-H), 6.03 (15-H, m), 6.19 (6-H, 7-H), and 6.40 (16-H, d, $J_{15,16}$ = 6 Hz) ppm. *Anal.* ($C_{21}H_{26}O_3$) C, H.

17α-Hydroxy-4,6,15-pregnatriene-3,20-dione 17-Acetate (3b).—A solution of **2b**[5] (7.30 g) in *t*-BuOH (300 ml) was heated at reflux with chloranil (9.70 g) for 5 hr. After cooling, the supernatant was separated by filtration and evaporated to dryness *in vacuo* and the residue was chromatographed over alumina (Merck, act. grade I, 37 × 5.2 cm). Elution with Et_2O–CH_2Cl_2 (4:1), followed by crystallization (*i*-Pr_2O), yielded 2.98 g (41%) of **3b**: mp 195–198°; $[\alpha]_D$ −268° (dioxane); λ_{max} 283 mμ (ε 27,100); nmr, δ 0.89 (13-CH_3), 1.16 (10-CH_3), 2.05 (17-OCOCH_3), 2.19 (20-CH_3), 5.70 (4-H), 6.22 (6-H, 7-H), and 6.38 (15-H, 16-H) ppm. *Anal.* ($C_{23}H_{28}O_4$) C, H.

17α-Hydroxy-1,4,6,15-pregnatetraene-3,20-dione (4a).—A solution of **3a** (316 mg) and DDQ (1.54 g) in C_6H_6 (80 ml) was heated at reflux for 24 hr. After cooling, the supernatant was separated by filtration, and the filtrate was washed (10% NaOH, H_2O). The solution was dried, concentrated to small volume, and crystallized from C_6H_6–*i*-Pr_2O yielding 147 mg (47%) of **4a**. Several recrystallizations (Me_2CO) gave the analytical sample: mp 237–244° dec; $[\alpha]_D$ −88°; λ_{max} 222 mμ (ε 11,620), 257 (9000), 298 (12,000); nmr, δ (CDCl$_3$–DMSO-d_6, 4:1) 0.82 (13-CH_3), 1.24 (10-CH_3), 2.22 (20-CH_3), 2.94 (17-OH), 6.03 (15-H, m), 6.10–6.36 (2-H, q, 4-H, 6 + 7-H and 16-H), and 7.13 (1-H, d, J = 10 Hz) ppm. *Anal.* ($C_{21}H_{24}O_3 \cdot 0.5C_3H_6O$) C, H.

17α-Hydroxy-1,4,6,15-pregnatetraene-3,20-dione 17-Acetate (4b).—A solution of **3b** (608 mg) and DDQ (1.88 g) in C_6H_6 (50 ml) was heated at reflux for 24 hr. After cooling, the supernatant was separated by filtration and evaporated to dryness *in vacuo*, and the residue was chromatographed over alumina (Merck, act. grade **I**, 80 g). Elution with Et_2O–CH_2Cl_2 (6:1), followed by crystallization (*i*-Pr_2O), gave 239 mg (39%) of **4b**: mp 192–194°; $[\alpha]_D$ −266°; λ_{max} 220 mμ (ε 10,500), 256 (8250), 297 (11,000). *Anal.* ($C_{23}H_{26}O_4$) C, H.

17α-Hydroxy-1,4,15-pregnatriene-3,20-dione (5).—A solution of **2a** (324 mg) and DDQ (1.218 g) in C_6H_6 (60 ml) was heated at reflux for 40 hr. The reaction mixture was filtered, and the filtrate was washed with 10% NaOH, then H_2O. After drying the solvent was evaporated *in vacuo*, and the residue crystallized from CH_2Cl_2–Et_2O yielding 153 mg (48.5%) of **5**: mp 250–257°; $[\alpha]_D$ −47°; λ_{max} 243 mμ (ε 16,120). *Anal.* ($C_{21}H_{26}O_3$) C, H.

1α,2α-(4′,3′,1′-Pyrazolino)-17α-hydroxy-4,6,15-pregnatriene-3,20-dione (6).—Into a solution of **4a** (1.203 g) in CH_2Cl_2 (100 ml), maintained at approximately 5°, was distilled 300 ml of an Et_2O–CH_2N_2 solution [from *bis*(*N*-methyl-*N*-nitroso)terephthalamide by adding to ENR-101[20] (40 g) suspended in Et_2O (1 l.) and H_2O (80 ml), a solution of KOH (20 g) in EtOH (80 ml) and H_2O (40 ml)]. The closed reaction flask was then allowed to remain at room temperature for 5 days. Excess CH_2N_2 was removed by air entrainment. The solvents were evaporated *in vacuo*, and the residue was chromatographed over Florisil (24 × 3.4 cm). Elution with Et_2O–CH_2Cl_2 (3:1), followed by crystallization from EtOAc–*i*-Pr_2O yielded 251 mg (18.5%) of **6**: mp 222–223° dec; λ_{max} 244 mμ (ε 6840), 290 mμ (ε 22,600); ν_{max} 3508, 1721, 1658, 1615, and 1587 cm^{-1}. *Anal.* ($C_{22}H_{26}O_3N_2$) *m/e* (366).

1,2α-Methylene-17α-hydroxy-4,6,15-pregnatriene-3,20-dione (7).[21]—NaH (53 mg, 50% in mineral oil) was added to a solution of trimethylsulfoxonium iodide (482 mg) in DMSO (15 ml) under N_2. After 1 hr **4a** (356 mg) was added, and the resulting dark solution was stirred under N_2 for 3 hr. After addition to H_2O, the precipitate was collected by filtration, dried, and crystallized from CH_2Cl_2–C_6H_{14}, yielding 125 mg (34%) of **7**: mp 238–242° dec; $[\alpha]_D$ +9° (pyridine); λ_{max} 283 mμ (ε 19,800); ν_{max} 3460, 1715, 1655, 1618, and 1589 cm^{-1}; nmr, δ 0.90 (13-CH_3), 1.25 (10-CH_3), 2.27 (20-CH_3), 5.54 (4-H), 5.98 (15-H, d, $J_{15,16}$ = 6 Hz), 6.12 (6-H, 7-H), and 6.31 (16-H, d, $J_{15,16}$ = 6 Hz) ppm. *Anal.* ($C_{23}H_{26}O_3$) C, H.

1,2α-Methylene-3-keto-20-hydroxy-Δ^{4,6,15}-norcholatrienic Acid 23→17-Lactone (8).—NaH (120 mg, 50% in mineral oil) was added to a solution of Me_3SO^+ I^- (975 mg) in DMSO (7 ml) under N_2. After 2 hr a 2-ml aliquot of the above-prepared dimethylsulfoxonium methylide was added to a solution of **4b** (200 mg) in DMSO (2 ml), and the reaction mixture was stirred under N_2 for 17 hr. After addition to H_2O (100 ml), containing AcOH (0.5 ml), the precipitate was collected by filtration, dried, and crystallized from MeOH–*i*-Pr_2O, affording 133.5 mg (64%) of **8**: mp 283–286° dec; λ_{max} 282 mμ (ε 20,800); ν_{max} 3436, 1795, 1669, 1636, 1605, and 1228 cm^{-1}; nmr, δ (DMSO-d_6) 0.70 (cyclopropyl), 1.12, 1.18 (13-CH_3, 10-CH_3), 1.40 (20-CH_3), 1.80 (20-OH), 5.50 (4-H), 6.26 (6-H, 7-H), 6.34 (15-H, d, $J_{15,16}$ = 5.5 Hz), 6.58 (16-H) ppm. *Anal.* ($C_{24}H_{28}O_4 \cdot 0.5CH_3OH$) C, H.

6α,16-Dimethyl-17α-hydroxy-4,15-pregnadiene-3,20-dione (10).—6,16-Dimethyl-5,15-pregnadiene-3β,17α-diol-20-one (960 mg) was incubated with *Flavobacterium dehydrogenans* for 234 hr at 137 mg/l. of medium, and the product was chromatographed over Florisil (32 × 3.2 cm). Elution with Et_2O–C_6H_{14} (4:1) resulted in 172 mg (18%) of **10** which was recrystallized several times from EtOAc–Et_2O; mp 194–198°; λ_{max} 241 mμ (ε 16,100); nmr, δ 0.86 (13-CH_3), 1.09 (6-CH_3, d, J = 6 Hz), 1.21 (10-CH_3), 1.76 (16-CH_3, m), 2.23 (20-CH_3), and 5.79 (4-H, 15-H) ppm. *Anal.* ($C_{23}H_{32}O_3$) C, H.

16β-Methyl-16,17α-oxido-5β-pregnane-3,20-dione (12).—A solution of KOH (4 g) in absolute EtOH (130 ml) and 5% Pd-C catalyst (1 g) was prehydrogenated at 23°. Then a solution of

(19) All melting points were determined on a Kofler hot stage microscope and are uncorrected. Rotations were determined in $CHCl_3$ at 25° at about 1% concentration, uv spectra are of MeOH solutions, and ir spectra are in Nujol unless otherwise stated. Ir absorption bands were consistent with all structures described and therefore have not been included unless deemed instructive. The nmr spectra were measured on a Varian A 60-A spectrometer in $CDCl_3$ (Me_4Si) unless otherwise stated. Mass spectra were determined on a CEC 21-103 spectrometer using a heated inlet system at a temperature of 200–230°. Solutions were dried over anhydrous Na_2SO_4. Analyses were determined by the Physical Organic Chemistry Department of Schering Corp.

(20) A mixture of the amide with 30% mineral oil, E. I. duPont de Nemours and Co., Explosives Department, Wilmington, Del.

(21) We are indebted to Mrs. O. Gnoj for carrying out this experiment.

11 (5 g) in absolute EtOH (140 ml) was added. The theoretical amount of H_2 (332 ml) was taken up in 15 min. After the catalyst was removed by filtration, the solvent was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2, washed (H_2O), and dried. Crystallization from CH_2Cl_2–C_6H_{14} yielded 3.39 g (67%) of **12**: mp 178.5–181°; $[\alpha]D$ +74°; nmr, δ 1.05 (13-CH_3, 10-CH_3), 1.44 (16-CH_3), and 2.20 (20-CH_3) ppm. *Anal.* ($C_{22}H_{32}O_4$) C, H.

Preparation of 14 from 12.—A solution of **12** (1.022 g) in dioxane (15 ml) was stirred with concentrated HCl (5 ml) at 5° for 65 min. The reaction mixture was added to H_2O (500 ml), and the precipitate was filtered, dried, and chromatographed over Florisil (22 × 3 cm). Elution with C_6H_6–Et_2O (9:1) gave 410 mg of somewhat impure **15** (λ_{max} 309 mμ). Further elution with C_6H_6–Et_2O (2:1) gave a mixture of **13** and **14**. Several crystallizations from Me_2CO–C_6H_{14} yielded 252 mg (24.7%) of pure **14**: mp 181–184°; $[\alpha]D$ −72°; nmr, δ 0.79 (13-CH_3), 1.01 (10-CH_3), 2.21 (20-CH_3), 5.08, and 5.27 (16 =CH_2) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

16-Methyl-17α-hydroxy-5β,15-pregnene-3,20-dione (13).—A solution of **12** (301 mg) in THF (13 ml) was cooled to 5°, and 48% HI (2.4 ml) was added dropwise over 5 min. The dark solution was stirred at room temperature for 25 min. After dilution (H_2O, 15 ml) the solution was decolorized with 5% $NaHSO_3$ and poured into H_2O (200 ml). The precipitate was filtered and dried. Crystallization from Me_2CO–C_6H_{14} gave 181 mg (60%) of **13**: mp 188° (softening), 193–196°; $[\alpha]D$ −73°; nmr, δ 0.82 (13-CH_3), 1.06 (10-CH_3), 1.76 (16-CH_3, m), 2.22 (21-CH_3), and 5.82 (15-H, m) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H. The nmr spectrum of the mother liquor indicated the presence of **14**.

16β-Methyl-16,17α-oxido-5α-pregnane-3,20-dione (17).—A solution of **16** (1.05 g) in Me_2CO (75 ml) under N_2 was titrated with 8 *N* H_2CrO_4 to permanent yellow color. The color change was observed after the addition of 1.17 ml of the reagent. The reaction mixture was added to H_2O (300 ml), and the precipitate was collected by filtration and dried. Crystallization from CH_2Cl_2–C_6H_{14} gave 811 mg (78%) of **17**: mp 209–211.5°; $[\alpha]D$ +73°; nmr, δ 1.02 (13-CH_3, 10-CH_3), 1.42 (16-CH_3), and 2.20 (20-CH_3) ppm. *Anal.* ($C_{22}H_{32}O_3$) C, H.

16-Methyl-17α-hydroxy-5α-15-pregnene-3,20-dione (18).—A solution of **17** (1.72 g) in Me_2CO (160 ml) was stirred with concentrated HCl (6 ml) for 30 min. H_2O (80 ml) was added dropwise, and on concentration to 100 ml *in vacuo* crystallization occurred. The crude solid was filtered, dried, and recrystallized (Me_2CO), yielding 1.149 g (67%) of **18**: mp 236–239°; $[\alpha]D$ −64°; nmr, δ 0.87 (13-CH_3), 1.08 (10-CH_3), 1.78 (16-CH_3, m), 2.23 (20-CH_3), and 5.82 (15-H, m) ppm. *Anal.* ($C_{22}H_{32}O_4$) C, H.

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Preparation and Antiinflammatory Properties of Some 1-Substituted 3-(5-Tetrazolylmethyl)indoles[1] and Homologs

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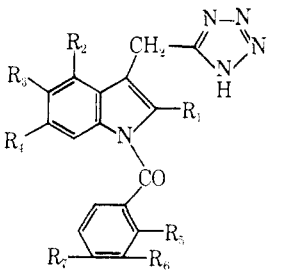
A series of 1-substituted 3-(5-tetrazolylmethyl)indoles and homologs were prepared as tetrazole analogs of indomethacin and other indole-3-acetic acid antiinflammatory agents. Some of the products show significant antiinflammatory activity when tested orally in rats. Structure–activity relationships in this series do not correspond to those for the carboxylic acid compounds. The most active compound is 1-(4-chlorobenzoyl)-3-(5-tetrazolylmethyl)indole.

The replacement of the carboxyl group in biologically active compounds with the comparably acidic 5-tetrazolyl group (CN_4H) has not always resulted in the retention of activity.[2,3] The discovery,[2] however, that tetrazole analogs of a series of known N-phenylanthranilic acids showed antiinflammatory activity comparable to that of the corresponding acids has encouraged us to prepare tetrazole analogs of other carboxylic acid antiinflammatory agents. We now report the preparation, properties, and preliminary pharmacology of a series of 1-substituted 3-(5-tetrazolylmethyl)indoles and homologs suggested by indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] and related compounds.[4]

Chemistry.—The first aim was to prepare close analogs (I) of indomethacin (II). Two synthetic approaches



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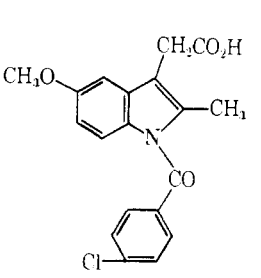

II

were made and these are outlined in Scheme I. Route A failed at the first step, probably because of the ability of III to react with NaH to form a carbanion at the CH_2 carbon which could react with the acylating agent.

An example of the first step of route B has already been reported by McManus and Herbst.[5] Using the general conditions of Finnegan, *et al.*,[6] we were able to convert the nitriles III to the tetrazoles V with NaN_3 and NH_4Cl in DMF in yields of 46–85%. The acidic 3-(5-tetrazolylmethyl)indoles (V) were converted to their disodium salts with NaH in DMF. Treatment of each salt with 1 molar equiv of a benzoyl chloride gave

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