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## Synthesis and Biological Activity of Some Ethers of Testosterone. Implications Concerning the Biological Activity of Esters of Testosterone

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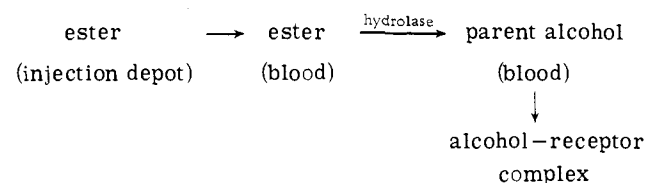
Received May 28, 1974

The benzyl (2), allyl (4), propyl (10), 3-hydroxypropyl (12), 2,3-dihydroxypropyl (11), 4-pentenyl (7), and pentyl (8) ethers of testosterone were synthesized. Compounds 2, 4, 7, 8, 10, and 12 were found to be almost devoid of anabolic or androgenic activity in a modified Hershberger Assay, but 2, 4, 10, and 12 were found to be effective inhibitors of testosterone  $5\alpha$ -reductase from human skin. These findings suggest that esters of testosterone and of 19-nortestosterone must hydrolyze before interacting with the hormonal receptors, but that the esters may competitively compete with the parent alcohols for interaction with enzymes. The latter effect may shift the distribution of metabolites of the esters relative to the alcohols and thus influence the pharmacological effect of these compounds.

Esterification of testosterone with short-chain fatty acids gives compounds which, on intramuscular injection, show prolonged and enhanced biological activity.<sup>1,2</sup> Intramuscular injection of low doses of such agents also was found to produce an enhanced ratio of anabolic to androgenic activity when compared to the effect of brief intravenous infusion of higher doses of testosterone.<sup>3</sup>

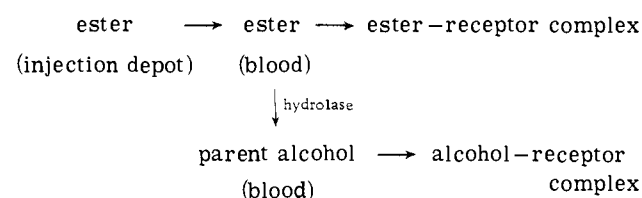
A further enhancement of the anabolic-androgenic ratio has been reported for 19-nortestosterone<sup>4</sup> and its esters.<sup>5,6</sup> Van der Vies<sup>7</sup> claims to have demonstrated that, in the rat, both the duration of action and the degree of enhancement of the anabolic-androgenic ratio of various 19-nortestosterone esters can be closely approximated by subcutaneous injection of 19-nortestosterone essentially according to the schedule at which the particular ester was found to be released from the oily intramuscular injection depot. Van der Vies<sup>7</sup> also found that rat plasma contains an enzyme which rapidly hydrolyzes esters of 19-nortestosterone. Therefore, he hypothesized that the sole function of the acyl portion of the 19-nortestosterone esters is to control the rate of release of the ester from its injection depot and that the ester was immediately hydrolyzed in blood to afford 19-nortestosterone which interacted with the various biological receptors (Scheme I). Van der Vies acknowledged that his results did not rule out di-

### Scheme I



rect interaction between the ester and the hormonal receptor. His results also seem compatible with both the ester and the alcohol interacting (probably with different affinities) with the receptor, as shown in Scheme II.

### Scheme II

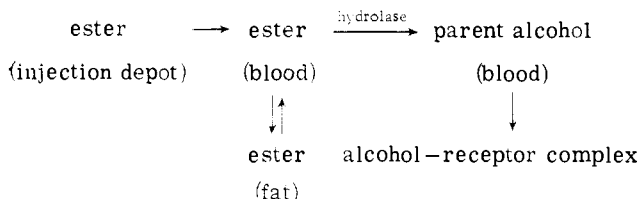


While van der Vies' preferred hypothesis (Scheme I) has been widely accepted, considerable evidence supports the alternative hypothesis (Scheme II). Thus, van der Vies reported that 19-nortestosterone esters showed much less tendency to hydrolyze in the plasma of the dog or of man than in the rat, in spite of showing comparable biological effects in all of these species.<sup>7</sup> Moreover, he found that administration of esterase inhibitors to the rat failed to reduce the effect of 19-nortestosterone esters.<sup>7</sup> A number of very hindered esters of 19-nortestosterone have been reported<sup>8,9</sup> to show more prolonged activity and more favorable anabolic-androgenic ratios than the compounds studied by van der Vies. Because the bulk of such esters makes their facile hydrolysis seem improbable, the need for such a hydrolysis has been questioned.<sup>8</sup>

In a recent series of papers, James has demonstrated that the prolongation of the biological response to testosterone and to 19-nortestosterone esters can be correlated with their lipid-water partition coefficients.<sup>10-12</sup> The ana-

bolic effect of nortestosterone esters shows a similar correlation.<sup>12</sup> James' data required him to postulate that, for both series of esters, the esters were rapidly absorbed from the injection depot, then distributed into the body fat, and slowly released back to the blood where they hydrolyzed (Scheme III).<sup>12</sup> James' experimental results seem to us to require that the hydrolysis of the esters in the blood *not be rapid* (as rapid hydrolysis would prevent the esters from being distributed into the body fat and then being slowly released from it). James appears to accept the postulate<sup>7</sup> that only the parent alcohol is the active species although his data are equally compatible with the hypothesis that the ester itself interacts with the biological receptor(s).

Scheme III



Graves and Ringold demonstrated that testosterone acetate and testosterone benzoate respectively are 27.5 and 13.9% as effective as testosterone or 5 $\alpha$ -dihydrotestosterone at blocking binding of labeled 5 $\alpha$ -dihydrotestosterone by tissue slices from rat ventral prostate.<sup>13,14</sup> If these esters are metabolically more inert than testosterone, a substantial part of their reported activities could be caused by the esters themselves rather than by the parent alcohol. It should be noted that Wolff recently demonstrated that various structurally dissimilar androgens may each have a unique binding site within rabbit ventral prostate and that compounds which bind to one site do not necessarily inhibit binding to other such sites.<sup>15</sup> Hence, the competitive binding of the testosterone esters, as reported by Graves and Ringold, must be regarded as lower limits for the binding affinity of these compounds since higher affinity binding to alternate sites remains a possibility.

To determine whether the esters of testosterone and its analogs must be hydrolyzed prior to interacting with their biological receptors, we proposed to synthesize a series of testosterone esters and to determine their biological activities. It was already known that various acid-labile ethers of testosterone<sup>16-20</sup> and 19-nortestosterone<sup>21</sup> have good oral activity, but these compounds are believed to decompose to the parent alcohol while in the gastrointestinal tract. Testosterone trimethylsilyl ether is reported to be effective when injected,<sup>21-23</sup> but such substances are known to hydrolyze rapidly in aqueous media. To our knowledge the only ether of testosterone which might be stable under the conditions of its assay, and for which biological data has been reported, is testosterone methyl ether. On subcutaneous injection into rats that ether is reported to have 34% the activity of testosterone on the ventral prostate.<sup>24</sup> In Graves and Ringold's *in vitro* assay this ether was found to be less than 6.5% as effective as testosterone. Whether the higher *in vivo* activity of the ether indicates inefficient, but substantial, cleavage to testosterone which then interacts with the receptor, or whether it represents a direct interaction with a second receptor, or whether it is caused by a low intrinsic activity which is offset by an abnormally long half-life for the ether has not been established.

We hoped that by synthesizing and assaying a variety of other testosterone ethers we could resolve these questions since if an ether at 17 $\beta$  will suffice for such activity, the

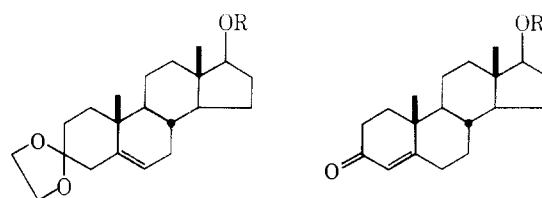
compounds should be reasonably active and their activity should correlate with their lipid-water partition coefficients in a manner similar to that which has been demonstrated for the esters. While such a finding would strongly support the contention that such species need not hydrolyze prior to interacting with their hormonal receptors, more rigorous proof would require that alkylating functions be built into the distal end of the ethers and that such substances be found to irreversibly bind to the receptor site. Conversely, lack of substantial activity by the ethers of testosterone would indicate that a free 17 $\beta$ -hydroxy group is required for high hormonal activity.

**Chemistry.** The procedure of Woroch<sup>25</sup> was used to convert 3,3-ethylenedioxyandrost-5-en-17 $\beta$ -ol (1) to 17 $\beta$ -benzyloxyandrost-4-en-3-one (2). Similarly, the potassium alcoholate derived from 1 was alkylated by allyl bromide, in benzene, to form the allyl ether 3 in a yield of 95%. The ethylene ketal moiety of 3 was hydrolyzed to give 17 $\beta$ -allyloxyandrost-4-en-3-one (4).<sup>26</sup>

The potassium alcoholate also could be alkylated by 5-bromo-1-pentene, in benzene or glyme, to form the pentenyl ether 5 but only in yields of 20-25%. However, 1-bromopentane reacted with the same alcoholate, in benzene, to give the pentyl ether 6 in yields of 59%. Hydrolysis of the ketal moiety of 5 and 6 was effected in approximately 75% yield to afford respectively the pentenyl (7) and pentyl (8) ethers of testosterone.

The allyl ether 3 was hydrogenated over palladium to form the propyl ether 9 in 85% yield. Hydrolysis of the ketal moiety of 9 afforded 17 $\beta$ -propyloxyandrost-4-en-3-one (10). Similarly catalytic reduction of the pentenyl ether 5 gave the pentyl ether 6.

The allyl ether of testosterone, 4, reacted with osmium tetroxide, in pyridine, to form 17 $\beta$ -(2',3'-dihydroxypropoxy)androst-4-en-3-one (11) in 46% yield. An attempt to react 4 with 9-borabicyclo[3.3.1]nonane, in order to form the hydroxypropyl ether 12, appeared, judging by the ir and nmr spectra, to have resulted mainly in reduction of the carbonyl group. Therefore, the 3-hydroxypropyl ether 12 was prepared by hydroboration of 3 with 9-borabicyclo[3.3.1]nonane, followed by oxidation to 13 and then by hydrolytic removal of the ketal group.



- |  |  |
|--|--|
| 1, R = H   | 2, R = CH <sub>2</sub> Ph  |
| 3, R = CH <sub>2</sub> CH=CH <sub>2</sub>  | 4, R = CH <sub>2</sub> CH=CH <sub>2</sub>  |
| 5, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH=CH <sub>2</sub>              | 7, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH=CH <sub>2</sub>              |
| 6, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> | 8, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> |
| 9, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>                                 | 10, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>                                |
| 13, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH                             | 11, R = CH <sub>2</sub> CH <sub>2</sub> (OH)CH <sub>2</sub> OH                         |
|  | 12, R = CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH                             |

**Biological Results.** As shown in Table I, preliminary assay of compounds 2, 4, 7, 8, 10, and 12, by a modification<sup>27</sup> of the Hershberger<sup>4</sup> assay, showed that they were all much less active than testosterone or even than testosterone methyl ether. The low activity of these compounds contrasts sharply with the high activity reported for testosterone esters of similar bulk and polarity and strongly supports the hypothesis that esters of testosterone hydrolyze prior to interacting with the hormonal receptors.

Compounds 2, 4, 10, and 12 were assayed by Voigt<sup>29,30</sup> as inhibitors of the testosterone 5 $\alpha$ -reductase from human skin. The finding that testosterone ethers are effective in-

**Table I.** Relative Androgenic and Anabolic Activity of Testosterone Ethers<sup>a</sup>

Compound	Ven- pro- state <sup>b</sup>	Sem- inal vesi- cles <sup>b</sup>	Le- va- tor ani <sup>c</sup>
Testosterone	100	100	100
Testosterone methyl ether	34 <sup>d</sup>	23 <sup>d</sup>	23 <sup>d</sup>
Testosterone benzyl ether (2)	10	14	5
Testosterone allyl ether (4)	9	17	5
Testosterone propyl ether (10)	4	15	20
Testosterone 3'-hydroxypropyl ether (12)	3	<1	<1
Testosterone 4'-pentenyl ether (7)	4	<1	
Testosterone pentyl ether (8)	<1	<1	

<sup>a</sup>Compounds administered by subcutaneous injection. See ref 27 for detailed conditions of assay. <sup>b</sup>Activity relative to testosterone based on graphic estimate using data from preliminary assay only. Estimate made at dose required to double<sup>28</sup> organ weight. <sup>c</sup>Approximate activity as judged by comparison to the effects of testosterone administered at 10- and 50- $\mu$ g daily dose levels. <sup>d</sup>See ref 24.

inhibitors of testosterone 5 $\alpha$ -reductase implies that testosterone esters also should inhibit this and possibly other steroid metabolizing enzymes. Since James' studies<sup>12</sup> imply that at least during the time that a testosterone ester is equilibrating between the injection depot and body fat (see Scheme III) the blood level of the testosterone ester must approximate and may exceed the level of the testosterone, the esters temporarily may modify the metabolism of testosterone. If different tissues differ in their metabolism of testosterone and in their physiological response to these metabolites,<sup>32</sup> the change in relative concentration of the testosterone metabolites provides an alternate explanation for the difference in pharmacological effects between testosterone or 19-nortestosterone and their esters. In particular, if it is true that testosterone is a true hormone for levator ani but only 5 $\alpha$ -dihydrotestosterone can function as a hormone in the ventral prostate, then our findings offer an alternate explanation for the enhanced ratio of anabolic to androgenic activity reported for these esters (Table II).

### Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Ir spectra were determined on a Beckman IR-8 spectrophotometer. Nmr spectra were determined in CDCl<sub>3</sub> on a Varian A-60 spectrometer and are reported in parts per million downfield from a TMS internal standard. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, results obtained for those elements were within  $\pm 0.4\%$  of theory.

**17 $\beta$ -Benzyloxyandrost-4-en-3-one (2).** The procedure of Woroch<sup>25</sup> was employed to convert 1 g of 3,3-ethylenedioxyandrost-5-en-17 $\beta$ -ol (1) to 2 in a yield of 83%. The compound crystallized from MeOH: mp 124–125° (lit.<sup>25</sup> mp 126–128.5°); nmr  $\delta$  0.88 (s, C-18 H's), 1.20 (s, C-19 H's), 4.53 (s, benzyl H's), 5.72 (s, C-4 H), and 7.31 (s, aromatic H's). *Anal.* (C<sub>26</sub>H<sub>34</sub>O<sub>2</sub>) C, H.

**17 $\beta$ -Allyloxyandrost-5-ene-3,2'-(1',3'-dioxolane) (3).** To a dispersion of K (0.82 g, 0.021 mol) in 5 ml of dry C<sub>6</sub>H<sub>6</sub> was added 1 (1 g, 0.31 mmol) in 50 ml of dry C<sub>6</sub>H<sub>6</sub>. The reaction was refluxed for 3 hr and then allyl bromide (2.6 ml, 0.030 mol) was added dropwise. Reflux was continued for 17 hr. After 10 ml of *t*-BuOH was added to the mixture, it was washed (H<sub>2</sub>O), dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue crystallized from MeOH to afford 3 in a yield of 95%: mp 151–152°; nmr  $\delta$  0.80 (s, C-18 H's), 1.04 (s, C-19's H's), and 3.95 (ketal). *Anal.* (C<sub>24</sub>H<sub>36</sub>O<sub>3</sub>) C, H.

**17 $\beta$ -Allyloxyandrost-4-en-3-one (4).** A solution of 3 in acetone

**Table II.** Inhibitors of Testosterone 5 $\alpha$ -Reductase of Human Skin<sup>a</sup>

Compound	% inhibition
Progesterone <sup>b</sup>	93.3
Testosterone 3'-hydroxypropyl ether (12)	75.2
Testosterone benzyl ether (2)	67.8
Testosterone allyl ether (4)	62.5
Testosterone propyl ether (10)	53.0

<sup>a</sup>See ref 30 for conditions of assay. Duplicate analyses agree within a few per cent. <sup>b</sup>Progesterone has  $K_1 \approx 0.7 \times 10^{-6}$  M and testosterone has  $K_m \sim 1.1 \times 10^{-6}$  M for this enzyme. See ref 31.

containing aqueous HCl was refluxed for 3 hr. After standard work-up 4 was obtained in a yield of 95%. The compound crystallized from EtOH: mp 89–90° (lit.<sup>26</sup> mp 89–91°); nmr  $\delta$  0.83 (s, C-18 H's), 1.20 (s, C-19 H's), and 5.74 (s, C-4 H). *Anal.* (C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>) C, H.

**17 $\beta$ -(4'-Pentenoxy)androst-5-ene-3,2'-(1',3'-dioxolane) (5).** A. To a dispersion of K (4.095 g, 0.103 mol) in 25 ml of dry C<sub>6</sub>H<sub>6</sub> was added, under N<sub>2</sub> and with stirring, 1 (5 g, 1.5 mmol) in 150 ml of dry glyme. The mixture was refluxed 4 hr. Then 5-bromo-1-pentene (33.5 g, 0.223 mol) in 25 ml of glyme was added dropwise. The mixture was refluxed 17 hr. After usual work-up the residue was chromatographed over 280 g of neutral Al<sub>2</sub>O<sub>3</sub>. The C<sub>6</sub>H<sub>6</sub> eluent afforded 5 as crystals from MeOH in a yield of 20%: mp 101–102°; nmr  $\delta$  0.77 (s, C-18 H's), 1.03 (s, C-19 H's), and 3.98 (t, CH<sub>2</sub>O). *Anal.* (C<sub>28</sub>H<sub>40</sub>O<sub>3</sub>) C, H.

B. By essentially the same procedure as had been used to prepare 3, 1 was converted to 5. After chromatography 5 was obtained in a yield of 16.6%. The compound crystallized from MeOH: mp 97–98°. Spectra were identical with those obtained from 5 prepared by method A.

**17 $\beta$ -Pentoxoandrost-5-ene-3,2'-(1',3'-dioxolane) (6).** A. By using conditions similar to those used to prepare 3, 1 was converted to 6 in a yield of 59% after chromatography: mp 96–97°; nmr  $\delta$  0.77 (s, C-18 H's), 1.04 (s, C-19 H's), and 5.38 (m, C-6 H). *Anal.* (C<sub>26</sub>H<sub>42</sub>O<sub>3</sub>) C, H.

B. A solution of 0.15 g of 5 in 25 ml of MeOH was hydrogenated over 15 mg of 5% Pd/C at an initial pressure of 3.5 kg/cm<sup>2</sup> for 1 hr. The product was obtained in a yield of 90% and was identical in melting point and spectroscopic properties with 6 prepared as in method A.

**17 $\beta$ -(4'-Pentenoxy)androst-4-en-3-one (7).** A mixture of 5 (0.156 g, 3.8 mmol), 5 ml of 10% aqueous HCl, and 25 ml of acetone was refluxed for 5 hr. The solvent was distilled under reduced pressure. The residue was partitioned between water and ether. The ether layer was washed with water, dried (MgSO<sub>4</sub>), and distilled to yield 0.147 g of crude product which was purified by preparative tlc using silica gel plates and developing with 20% ethyl acetate in benzene. The product, 7, was isolated in 75% yield as an oil: nmr  $\delta$  0.80 (s, C-18 H's), 1.20 (s, C-19 H's), 5.73 (s, C-4 H), and 4.88 and 5.77 (m, vinyl hydrogens). *Anal.* (C<sub>24</sub>H<sub>36</sub>O<sub>2</sub>) C, H.

**17 $\beta$ -Pentoxoandrost-4-en-3-one (8).** By a procedure similar to that used to obtain 7, 6 was transformed to 8. The compound was isolated as an oil: nmr  $\delta$  0.80 (s, C-18 H's), 1.20 (s, C-19 H's), 5.73 (s, C-4 H), and 3.34 (t, CH<sub>2</sub>O). *Anal.* (C<sub>24</sub>H<sub>38</sub>O<sub>2</sub>) C, H.

**17 $\beta$ -Propoxyandrost-5-ene-3,2'-(1',3'-dioxolane) (9).** Conditions similar to those used to form 6 by method B were used to synthesize 9 from 3. The product crystallized from MeOH in a yield of 85%: mp 157–158°; nmr  $\delta$  0.78 (s, C-18 H's), 1.05 (s, C-19 H's), 5.38 (m, C-6 H), and 3.43 (t, CH<sub>2</sub>O). *Anal.* (C<sub>24</sub>H<sub>38</sub>O<sub>3</sub>) H; C: calcd, 76.96; found, 76.23.

**17 $\beta$ -Propoxyandrost-4-en-3-one (10).** Conditions similar to those used to form 7 were used to synthesize 10 from 9. The product crystallized from aqueous EtOH in a yield of 75%: mp 73–74°; nmr  $\delta$  0.81 (s, C-18 H's), 1.20 (s, C-19 H's), 5.75 (s, C-4 H), and 3.43 (t, CH<sub>2</sub>O). *Anal.* (C<sub>22</sub>H<sub>34</sub>O<sub>2</sub>) C, H.

**17 $\beta$ -(2',3'-Dihydroxypropoxy)androst-4-en-3-one (11).** A solution of OsO<sub>4</sub> (0.5 g, 1.97 mmol) in 25 ml of pyridine was added to 4 (0.5 g, 1.53 mmol). The flask was covered with aluminum foil and stirred at room temperature for 21 hr. A solution of NaHSO<sub>4</sub> (0.87 g) in 14 ml of H<sub>2</sub>O and 7 ml of pyridine was then added and the mixture stirred for 30 min. After standard work-up, the product was purified by thick-layer chromatography over SiO<sub>2</sub> using

30% acetone in  $\text{CHCl}_3$  as solvent. The product recrystallized from aqueous MeOH to afford 11 in a yield of 46%: mp 98–99°; nmr  $\delta$  0.81 (s, C-18 H's), 1.21 (s, C-19 H's), and 5.76 (s, C-4 H). *Anal.* ( $\text{C}_{22}\text{H}_{34}\text{O}_4$ ) C, H.

**17 $\beta$ -(3'-Hydroxypropyl)androst-4-en-3-one** (12). Conditions similar to those used to prepare 7 were used to convert 13 to 12 in a yield of 91%. The product was recrystallized from aqueous acetone: mp 85–86°. *Anal.* ( $\text{C}_{22}\text{H}_{34}\text{O}_3$ ) C, H.

**17 $\beta$ -(3'-Hydroxypropoxy)androst-5-ene-3,2'-(1',3'-dioxolane)** (13). To a flask which contained 9-borabicyclo[3.3.1]nonane (0.219 g, 1.79 mmol) and which was cooled in an ice bath was added, under  $\text{N}_2$ , a solution of 3 (0.5 g, 1.34 mmol) in 10 ml of THF. The mixture was stirred at room temperature for 3 hr and under reflux for 1 hr. The solution was cooled to room temperature and a solution of 2 ml of  $\text{H}_2\text{O}$ , 2 ml of 3 N aqueous NaOH, and 2 ml of 30%  $\text{H}_2\text{O}_2$  was added. The mixture was stirred until gas evolution ceased. The product was chromatographed over 17 g of neutral  $\text{Al}_2\text{O}_3$  using benzene as solvent. Crystallization from aqueous EtOH or acetone gave 13 in a yield of 49%: mp 168–169°; nmr  $\delta$  0.80 (s, C-18 H's), 1.05 (s, C-19 H's), and 5.40 (m, C-6 H). *Anal.* ( $\text{C}_{24}\text{H}_{38}\text{O}$ ) C, H.

**Acknowledgments.** This work was supported, in part, by Grant CA-10116 from the National Cancer Institute of NIH and, in part, by Grant 5 SO1-RR 05454 from NIH. We are also grateful to Carole Hayden for technical services, to Dr. Voigt for assaying our compounds as inhibitors of testosterone 5 $\alpha$ -reductase, and to Dr. Ringold for sending us his assay data.

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## Substituted Pyrazolo Corticoids as Topical Antiinflammatory Agents

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The synthesis of a series of substituted pyrazolo corticoids is described. Of these 11 $\beta$ ,17 $\alpha$ ,21-trihydroxy-6,16 $\alpha$ -dimethyl-4,6-pregnadieno[3,2-c]-2'-(4-pyridyl)pyrazole (21) shows an excellent separation of systemic to local activity in the model animal test. Compound 21 exhibits high vasoconstriction activity in human volunteers and is clinically effective in the treatment of psoriasis.

The discovery that certain heterocycles, especially pyrazoles containing 2'-aryl substituents, imparted enhanced antiinflammatory activity when fused to the corticoid nucleus at the 2,3 positions was reported some years ago by Hirschmann, *et al.*,<sup>1a</sup> and has been further explored by the Merck group<sup>1,2</sup> and by others.<sup>3</sup> The Merck findings have been reviewed.<sup>1c</sup>

To date, there have been no reports that such derivatization raises steroidal androgenic, progestational, or aldosterone antagonist potency. This implies potentially increased selectivity with respect to the antiinflammatory process. Furthermore, preliminary studies indicated that pyrazolo corticoids could be active antiinflammatory

agents without requiring all of the typical corticoid functionality and that they could show a high local to systemic ratio relative to hydrocortisone. An early example was 17 $\alpha$ ,21-dihydroxy-20-oxopregn-4-eno[3,2-c]-2'-(4-fluorophenyl)pyrazole (1) which was 30 times as potent in the local granuloma test as hydrocortisone and which unexpectedly displayed 12 times greater local than systemic inhibition of granuloma formation in the same test system.

With this encouraging data, we initiated a search for an optimal topical antiinflammatory steroid among the pyrazolo corticoids using as criteria high local activity, low systemic activity, and good skin penetration.