Carbocyclic Prostaglandin Analogs. 1. Steroid Carboxylic Acids

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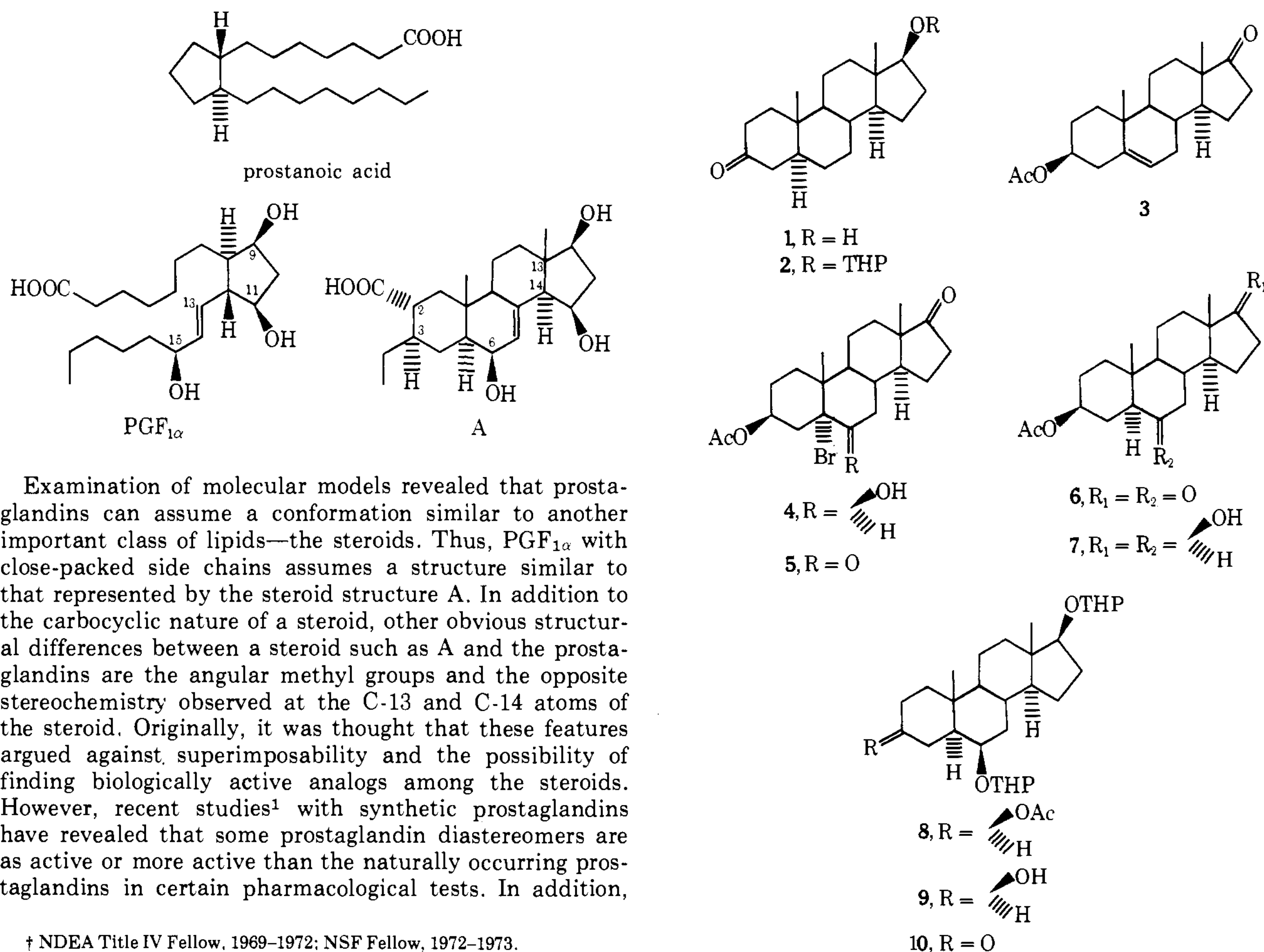
Certain structural similarities between prostaglandins with close-packed side chains and the perhydrocyclopentanophenanthrene nucleus of steroids prompted the synthesis and biological evaluation of 6β,17β-dihydroxy-5α-androstane-2α-carboxylic acid (**30**), its 6-deoxy derivative **28**, and the corresponding 6-deoxy-2β derivative **29** in an attempt to evaluate carbocyclic acids as potential prostaglandin analogs. Preliminary *in vitro* studies on isolated guinea pig ileum have shown weakly specific, prostaglandin-stimulated smooth muscle antagonism for **28** when compared with antagonism of bradykinin- and acetylcholine-induced contractions. Complete dose-response curves for **28** on prostaglandin-stimulated guinea pig ileum have shown a reduction in the maxium response and a decrease in the slope of the curve, indicating a noncompetitive type of inhibition for this type of derivative.

Recent interest in prostaglandin research is well attested by the 400-fold increase in research publications in this field during the last 10 years. Much of this literature has been concerned with isolation, structure elucidation, total synthesis, and biological actions of the prostaglandins, but little work has been published on structural analogs and their pharmacology.

Chemically, the prostaglandins are all C-20 fatty acids having the same basic carbon skeleton, prostanoic acid. At present, 16 primary prostaglandins are known which differ from each other in the number and position of double bonds, hydroxyl, or ketone groups. The diverse pharmacological actions observed for prostaglandins may be due to these subtle differences in chemical structure as well as conformational arrangements of their side chains.



Examination of molecular models revealed that prostaglandins can assume a conformation similar to another important class of lipids—the steroids. Thus, $PGF_{1\alpha}$ with close-packed side chains assumes a structure similar to that represented by the steroid structure A. In addition to the carbocyclic nature of a steroid, other obvious structural differences between a steroid such as A and the prostaglandins are the angular methyl groups and the opposite stereochemistry observed at the C-13 and C-14 atoms of the steroid. Originally, it was thought that these features argued against superimposability and the possibility of finding biologically active analogs among the steroids. However, recent studies[1] with synthetic prostaglandins have revealed that some prostaglandin diastereomers are as active or more active than the naturally occurring prostaglandins in certain pharmacological tests. In addition, prostaglandins having alkyl substituents on both side chains have shown biological activity.[2]

This paper describes the synthesis and preliminary biological activity of two model steroid acids, 17β-hydroxy-5α-androstane-2α-carboxylic acid (**28**) and 6β,17β-dihydroxy-5α-androstane-2α-carboxylic acid (**30**), which possess prostaglandin-like functionality. Compound **30** was chosen as an initial model based, in part, on the observed pharmacological activity for 13,14-[3] and 11-deoxy-13,14-dihydroprostaglandin[4] derivatives. The 6β-hydroxy group in compound **30** was retained to simulate the 15(*S*)-hydroxy group in the prostaglandin. The presence of this group appears to be essential for prostaglandin agonist activity.[5]

Chemistry. A general synthetic scheme was envisioned

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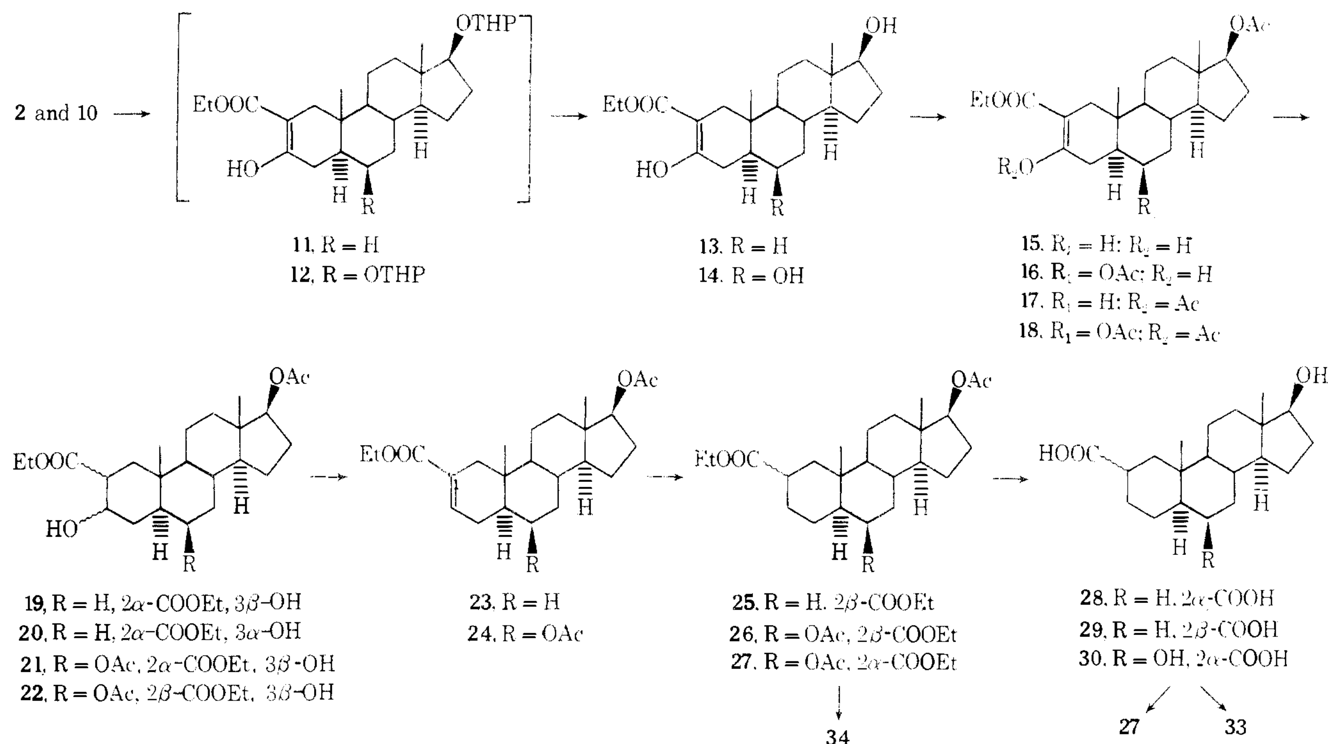
Scheme I



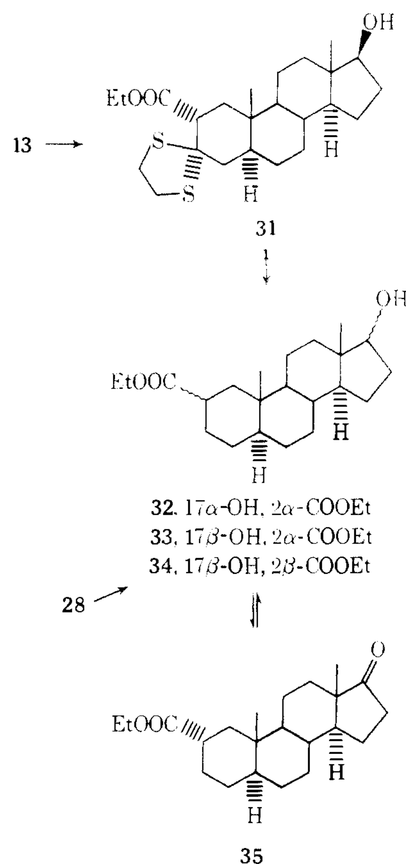
for the synthesis of 30 starting from the readily available dehydroepiandrosterone acetate (3). The intended scheme was to use the unsaturation in 3 to introduce the 6β-hydroxy group and, after appropriate modification, the 3β-acetoxy group for introduction of the 2α-carboxylic acid moiety. As such, the chemistry took a natural division between steroid A- and B-ring modification.

Dihydrotestosterone (1) was used as a model for studying reactions appropriate for A-ring modification, eventually leading to 28 (Scheme I).‡ The 17β-hydroxy group of 1 was first protected as the tetrahydropyranyl (THP) ether 2.[8] Protection of the THP ether was deemed necessary to avoid the previously reported 17-cathylation reaction observed to occur with the unprotected steroid[6] and because of its anticipated use in chemical differentiation of the alcohol groups of 8 discussed below. Treatment of the THP ether 2 with diethyl carbonate and sodium hydride gave the intermediate 11 which resisted crystallization and was converted directly to 13 by treatment with ethanolic HCl. Carboethoxylation was assumed to occur in the 2 position based on the well-precedented involvement of this position in enolization of 3-keto 5α steroids[9] and this was later confirmed by spectral investigation of 31. The almost exclusive existence of 13 in the enol form in solution was indicated by integration of the enol proton at 12.4 ppm. This possibly explains the poor reactivity of 13 to subsequent ketalization.

The most direct route to 28 was originally thought to be ethylene thioketal formation to give 31 (Scheme II), Raney nickel desulfurization to 33, and hydrolysis to give the desired acid 28. Treatment of 13 with 1,2-ethanedithiol and boron trifluoride etherate ($BF_3 \cdot Et_2O$) gave 31 in moderate yield along with unreacted starting material which could be recycled. However, in contrast to previously reported results for 3-keto steroids,[10] ketalization of 13 was sluggish. The stereochemistry of the 2-carboethoxy group was assigned on the basis of dihedral splitting ($J_{H(2\beta),H(1\beta)}$ = 4, $J_{H(2\beta),H(1\alpha)}$ = 12 Hz) observed for the proton at the 2 position and was in good agreement with a 2α orientation for the carboethoxy group.[11] In addition, such a doublet of doublets is consistent only with the anticipated carboethoxylation in the 2 position.

Raney nickel desulfurization of 31 gave the desired ester

Scheme II



‡ Several methods for introduction of a 2-carboxylate moiety have been investigated.[6,7]

33 and, unexpectedly, a considerable amount of its 17α epimer 32. The 17α epimer could be partially separated from 33 by fractional crystallization. Attempts to completely separate 32 and 33 by this method failed and it was found necessary to oxidize the mixture to 35 and then reduce with $(t\text{-BuO})_3LiAlH$ to get the pure β epimer 33. Metal hydride reduction of 6- and 17-oxosteroids is known to give predominately products having the β orientation due to steric factors.[9] Choice of the stereoselective $(t\text{-BuO})_3LiAlH$ gave exclusively the β-alcohols for both the reduction of 35 and 6 discussed below.

Stereochemical assignment of alcohol and acetoxy groups was based on the well-precedented difference in half-bandwidths for axial and equatorial protons attached to the same carbon atom as these groups and is a reflection mainly of differences in dihedral splitting.[11] In many cases, where appropriate models were available, Zurcher's additivity constants§ lent supportive evidence to the assignments.

Although the above method was effective in producing the desired 33, it was anticipated that lengthy exposure to $BF_3 \cdot Et_2O$ would be unacceptable for the 6β-hydroxy analog 14 because of the susceptibility of such alcohols to dehydration. As such, an alternate route to 33 was sought which involved the intermediate 23 and which had the additional advantage of offering future potential for introduction of alkyl groups in the 2 position by conjugate addition to the α,β-unsaturated ester.

The second method of A-ring modification (Scheme I) consisted of acetylation of the 17β-hydroxy group of 13 to give 15 and subsequent catalytic hydrogenation over Pt to afford a mixture of epimers 19 and 20. Care must be taken in the acetylation of 13 in order to avoid formation of the enol acetate 17. The hydrogenation step gave two products in a 1:1 ratio as determined by nmr analysis and isolation by chromatography. It was evident from an nmr analysis of the C-3 proton that these compounds were epimeric at this position and the hydroxyl orientations were assigned on the basis of half-bandwidths. Assignment of the equatorial orientation for the carboethoxy group in 19 and 20 was based on a comparison of calculated Zurcher additivity constants and observed values for the C_{19}-angular methyl group in these compounds. The Zurcher constants were calculated from compounds 33 and 34 and from the previously mentioned tables.§ Observed values for the C_{19}-angular methyl group in 19 and 20 were within 0.01 ppm of the values calculated for the equatorial orientation of the carboethoxy group while this difference was an order of magnitude larger when calculated for the axial orientation.

Dehydration of epimers 19 and 20 with $POCl_3$ in pyridine gave a single compound 23 in good yield. Examination of the crude reaction mixture indicated that if any β,γ elimination was occurring, such a product was being isomerized to the α,β-unsaturated ester under the reaction conditions. Catalytic hydrogenation of 23 gave a single product which upon base-catalyzed ethanolysis of the 17β-acetoxy group furnished a compound different from 33. Based on the demonstrated epimerization, discussed below, and the observed spectral evidence, the products of hydrogenation and subsequent ethanolysis were assigned the structures 25 and 34, respectively. This result is also consistent with catalytic hydrogenation occurring from the less-hindered α face of the steroid molecule.

Complete hydrolysis of 25 with aqueous KOH and subsequent neutralization gave a mixture of the epimeric acids 28 and 29. This mixture of acids was easily separated by selective esterification of the equatorial 2α epimer 28. Thus, overnight treatment with EtOH containing a catalytic amount of HCl completely esterified the 2α epimer which after removal of the solvent could be extracted from the unesterified 29. The ester thus obtained was identical with 33 derived from the thioketal route (Scheme II). On the other hand, the 2β-acid 29 resisted esterification under these conditions for up to 1 week. When 25 was first epimerized with sodium ethoxide and hydrolyzed without isolation, 28 could be obtained free from its corresponding epimer 29.

Unlike the previous method of A-ring modification (Scheme II), the reactions in Scheme I appeared to be compatible with steroid structures having a 6β-hydroxy function. The desired intermediate needed for this series of reactions, 10, was prepared from dehydroepiandrosterone acetate (3). Introduction of a 6-keto function was carried out by a previously reported sequence[12] involving the bromohydrin 4, oxidation to the 5α-bromo-6-keto derivative 5, and subsequent dehalogenation to give 6 in good overall yield. Reduction of 6 with $(t\text{-BuO})_3LiAlH$ gave the previously reported 7 prepared by a different route.& Conversion of 7 to the bis(THP) ether 8 could be effected in high yield with dihydropyran and p-toluenesulfonic acid. For identification purposes, 8 was purified by preparative thin-layer chromatography. The nmr of 8 clearly showed the presence of two THP ethers and a single acetate group as indicated by integration of the 2′ protons of the THP ethers and the methyl protons of the acetate. The ir gave no indication of unreacted hydroxyl groups.

The product 8 actually represents a trihydroxyandrostane derivative in which the 6β- and 17β-hydroxy groups are protected with acid-labile functionality and the 3β-hydroxy group with a base-labile acetate. The latter was easily removed by alkaline methanolysis at reflux temperature to give 9. Chromatography of 9 gave a colorless, noncrystalline glass in high yield whose spectral properties were consistent with the assigned structure. Oxidation of 9 using the Sarett[15] procedure gave the desired derivative 10, needed for the preparation of 30 as shown in Scheme I. At this stage, rigorous thin-layer chromatography suggested a homogeneous material whose spectral properties were consistent with structure 10. The purified 10, not unexpectedly, resisted crystallization as did the previous THP ethers and was converted directly to 12.

Carboethoxylation of 10 in a manner similar to that described for 2, removal of the protecting groups, and chromatography gave 14 as a white crystalline solid in a reproducible 45–55% overall yield from the dihydroxy derivative 7. In a series of reactions analogous to the 6-deoxy derivative 13, 14 was converted to the 6β-hydroxy acid 30. In general, the reaction techniques and products were analogous to the model compounds with two notable exceptions. With the model compounds, care had to be taken in the acetylation of 13 in order to avoid unwanted formation of the 3-enol acetate 17. All attempts to prepare 16 free from its 3-enol acetate 18 by direct acetylation were unsuccessful. Under the best of the observed reaction conditions, a ratio of 2:1 (16:18) was found to prevail. Apparently, under conditions sufficiently vigorous to acetylate the hindered 6β-hydroxy group, enol acetate formation could not be avoided. Analysis of this mixture was readily carried out by integration of the free enol H in 16 and the acetate protons in 18. Since the enol acetate group in 18 is a vinyl analog of an anhydride, it was readily cleaved by

§ See, for example, Bhacca[11] and tables therein.

&For reversal of the configuration at C-7 originally assigned,[13] see Gallagher.[14]

Table I. Response of PGE_2, Bradykinin, and Acetylcholine Stimulated Guinea Pig Ileum to 17β-Hydroxy-5α-androstane-2α-carboxylic Acid Derivatives

Compound	Dose of indicated compd, μg/ml	Mean % change from submaximal control: Bdkn	PGE_2	Ach	No. of determinations
17β-Hydroxy-5α-androstane-2β-carboxylic acid (**29**)	30	−36	−50	−26	2
	10	−33	−43	−25	2
	3	11	−5	11	1
17β-Hydroxy-5α-androstane-2α-carboxylic acid (**28**)	30	−46 ± 8	−75 ± 8	−34 ± 12[a]	4
	10	−17 ± 6	−46 ± 4	−15 ± 3[a]	3
	3	−8 ± 13	−4 ± 25	−4 ± 6[a]	3
6β, 17β-Dihydroxy-5α-androstane-2α-carboxylic acid (**30**)	30	6	−3	4	2
	10	2	−11	0	2

[a]Mean % change from submaximal control ± standard error.

treatment of the mixture of **16** and **18** with EtOH and Na_2CO_3. After ethanolysis and chromatography, **16** was obtained in good yield.

The other major difference observed between the model compounds and their 6β-hydroxy derivatives was in the catalytic hydrogenation of **16**. The β-keto ester system of **16** appeared to be somewhat more resistant to catalytic hydrogenation and gave a different distribution of isomers. The major hydrogenation product was the β-hydroxy ester **21** isolated by fractional crystallization (42%). Chromatography of the mother liquors gave another 9% of **21**, 19% starting material, and a small amount (24%) of a material whose structure was assigned as **22** based on a spectral analysis similar to that described for **19** and **20** above.

Dehydration of **21** and **22**, either as a mixture or separately, gave **24** as the sole product. Catalytic hydrogenation, epimerization, and hydrolysis of **24** as described for the model compounds gave **30**. Reesterification and reacetylation of **30** to give **27**, indicated that catalytic hydrogenation of **24** had given the 2β epimer **26** and that epimerization had occurred in the conversion of **26** to **30**. Stereochemistry was again assigned on the basis of Zurcher additivity constants, half-bandwidths, and the demonstrated epimerization.

Biological. The two epimeric hydroxy steroid acids **28** and **29** and the corresponding 6β-hydroxy analog **30** were examined for prostaglandin-like activity in several prostaglandin assays. When examined in standard platelet aggregation,[16] rat blood pressure,[17] and 15-hydroxyprostaglandin dehydrogenase assays,[18] compounds **28**, **29**, and **30** showed no significant prostaglandin-like activity at concentrations corresponding to maximal response from the prostaglandin controls. These same steroid acids were also evaluated for prostaglandin-like activity on isolated gerbil colon[19] and found to have less than 5×10^{-4} the activity of PGE_2 in this assay. The two epimeric hydroxy steroid acids **28** and **29** and the corresponding 6β-hydroxy analog **30** were also evaluated for *in vitro* antagonist activity on PGE_2-stimulated guinea pig ileum, the results of which are shown in Table I. In this test the excised ileum was mounted in a tissue bath containing modified Tyrode solution. Bradykinin triacetate, PGE_2 as the sodium salt, and acetylcholine chloride solutions are injected into the bath to cause contractions of the tissue. The doses of these agonists were adjusted to obtain approximately equal submaximal control contractions to each. Then a solution or suspension of the test compound in modified Tyrode solution was substituted for the plain modified Tyrode solution and the agonist additions were continued at regular intervals. A series of treated responses was compared with a series of control responses to obtain per cent change caused by the compound.[20]

As may be seen from the data in Table I, the 6β-hydroxy analog **30** did not suppress guinea pig ileum contractions elicited by bradykinin, PGE_2, or acetylcholine at either the 10- or 30-μg levels. On the other hand, the steroid acid **28** appeared to produce some specific prostaglandin inhibition at the 30 μg/ml level. Statistical evaluations, pairing results in each experiment, showed that PGE_2-induced contractions were reduced significantly more than were acetylcholine-induced contractions by a 30 μg/ml dose of **28**. There was no significant difference, however, between effects on PGE_2- and bradykinin-induced contractions at this dose level. At a concentration of 10 μg/ml, the prostaglandin-induced contractions were reduced more than both bradykinin- and acetylcholine-induced contractions. At 3 μg/ml the steroid acid **28** produced no significant reductions in the bradykinin-, PGE_2-, or acetylcholine-induced contractions. In addition, the corresponding 2β-acid **29** appeared to be less specific than its 2α epimer **28** for reduction of PGE_2-induced contractions.

These data indicate that the steroid acid **28** had a slightly specific inhibitory effect on PGE_2-induced contractions when compared with the bradykinin- and acetylcholine-induced contractions. In order to determine if this inhibition was a receptor-oriented type of activity, complete dose–response curves were determined by the method of Van Rossum.[21] Control dose–response curves were elicited on segments of isolated proximal ileum of guinea pigs suspended in modified Tyrode solution in a 2-ml tissue bath maintained at 37° and bubbled with 95% oxygen–5% carbon dioxide. Doses of PGE_2 were added to achieve cumulative concentrations increasing in half log increments. Then the control bathing solution was replaced by one containing concentrations of 3, 10, or 30 μg/ml of the steroid acid **28** and another cumulative dose–response curve was determined after a 15-min equilibration period.

The mean responses of three experiments for each concentration of **28** are shown in Figure 1. The per cent of the maximum control responses is plotted against the negative log of the PGE_2 concentration in μg/ml. It is seen that 3 μg/ml of **28** had a negligible effect on PGE_2 dose–response curves. At concentrations of 10 and 30 μg/ml, **28** caused a reduction in the maximum response and a decrease in the slope of the curve, indicating noncompetitive inhibition. The mean pD_2', calculated from inhibition produced by 10 and 30 μg/ml of **28**, was 3.62 (pD_2' is defined as the negative log of the molar concentration of antagonist that will reduce the maximum contractions 50%). This finding of noncompetitive inhibition suggests that

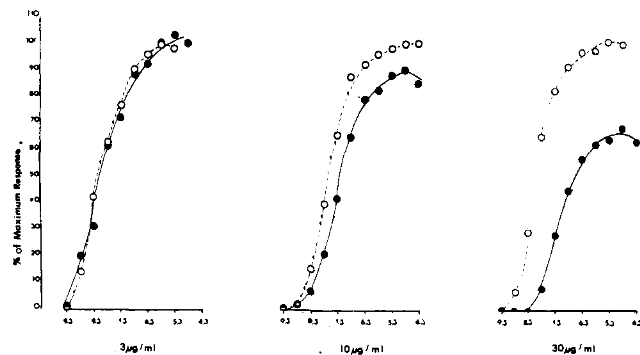


Figure 1. ○ - - - ○, control; ●—●, treated.

the previously observed inhibition of prostaglandin-induced contractions of the guinea pig ileum is mediated through a mechanism that does not involve prostaglandin receptors or that the compound binds prostaglandin receptors in an irreversible manner. Studies with these and related compounds on prostaglandin receptor protein preparations are now in progress.

Experimental Section**

Ethyl **3,17β-Dihydroxy-5α-androst-2-ene-2-carboxylate (13).** To dry NaH [prepared by washing three times with dry hexane a 52% white oil dispersion of NaH (5.5 g) and drying under N_2] were added diethyl carbonate (200 ml) and 17β-hydroxy-5α-androstane 17-tetrahydropyranyl ether (2, 6 g).[8] The reaction mixture was allowed to stir 9–12 hr at room temperature under N_2 before excess NaH was treated with EtOH and the reaction mixture poured into an ice–Et_2O mixture. The organic layer was washed with 10% HCl and 5% $NaHCO_3$ and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave 11 as an amorphous solid which produced one spot on tlc examination. This material was dissolved in EtOH (50 ml) and EtOH (25 ml) containing concentrated HCl (3%, v/v) was added dropwise. The reaction mixture was stirred for 2.5 hr and poured into ice covered with 10% Na_2CO_3, and the organic layer was extracted with Et_2O, washed with H_2O, and dried (Na_2SO_4). The material remaining after removal of solvents was chromatographed on silica gel (80 g) using hexane–EtOAc (9:1) as an eluent to give crystalline 13 (4.2 g, 72%). Recrystallization from hexane–Et_2O gave an analytical sample: mp 141.5–143.5° dec; uv λ_{max} 256 (9600); mass spectrum *m/e* 362 (M^+); nmr δ 12.4 (s, 1, enol H); $[\alpha]_D$ +60.8°. *Anal.* ($C_{22}H_{34}O_4$) C, H.

Ethyl **3,3-Ethylenedithio-17β-hydroxy-5α-androstane-2α-carboxylate (31).** To a suspension of 13 (4.2 g) in 1,2-ethanedithiol (12 ml) was added dropwise $BF_3 \cdot Et_2O$ (8 ml) in 1,2-ethanedithiol (8 ml) and the reaction mixture allowed to stir for 4 hr. The reaction mixture was rinsed with Et_2O into ice covered with 10% NaOH and extracted with Et_2O. The organic layer was washed with 10% NaOH, H_2O, and saturated NaCl solution and dried (Na_2SO_4). Concentration of the Et_2O solution caused 31 to crystallize (2.6 g, 51%, mp 179–180°). Examination of the mother liquor indicated only the presence of starting material and 31. Recrystallization from Et_2O gave an analytical sample: mp 180.0–180.5°; nmr δ 3.00 (dd, $J_{H(2\beta)H(1\beta)}$ = 4 Hz and $J_{H(2\beta)H(1\alpha)}$ = 12 Hz, 1, $C_{2\beta}$-H); $[\alpha]_D$ +7.6°. *Anal.* ($C_{24}H_{38}O_3S_2$) C, H.

Ethyl **17α-Hydroxy-5α-androstane-2α-carboxylate (32).** Raney nickel W-2 (8 teaspoonsful, *ca.* 24 g) was washed with EtOH into a 500-ml flask and the volume brought to 400 ml with EtOH.[22] To this mixture was added 31 (2.4 g) and the reaction mixture refluxed 24 hr. The reaction mixture was allowed to cool and filtered through Celite. Removal of the solvent *in vacuo* afforded an amorphous solid (1.9 g) which was chromatographed on silica gel (70 g) using hexane–EtOAc (9:1) as the eluent. A nonpolar component (240 mg; ir, no –OH stretch) was eluted first and discarded. The remaining fractions (1.5 g, 79%) contained a 1:2.9 (nmr analysis) mixture of **32** and **33**, respectively.

When the mixture of 32 and 33 was dissolved in hexane–Et_2O and concentrated, 32 crystallized as fine needles (300 mg, mp 118.0–118.5°) and further recrystallization did not alter the melting point: nmr δ 3.75 (pseudo-d, half-bandwidth = 9 Hz, 1, $C_{17\beta}$-H); $[\alpha]_D$ −9.1°. *Anal.* ($C_{22}H_{36}O_3$) C, H.

Ethyl **17-Oxo-5α-androstane-2α-carboxylate (35). A. By Oxidation of a Mixture of 32 and 33.** To an acetone solution of 32 and 33 (1.1 g) isolated above was added Jones reagent[23] until a red color persisted. The reaction was then back titrated with excess isopropyl alcohol, poured into H_2O, and extracted with Et_2O. The organic layer was washed successively with H_2O and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents gave 35 as an amorphous solid (1 g, 90%) whose spectral and chromatographic properties were identical with an analytical sample prepared by crystallization from hexane: mp 94–95°; $[\alpha]_D$ +74.0°. *Anal.* ($C_{22}H_{34}O_3$) C, H.

B. By Oxidation of 32. When 32 (0.09 g) was subjected to a procedure similar to the above, an amorphous solid (0.08 g, 90%) was obtained which had spectral and chromatographic properties identical with 35.

Ethyl **17β-Hydroxy-5α-androstane-2α-carboxylate (33). A. By Metal Hydride Reduction of 35.** To a solution of crude 35 (0.67 g, as prepared above without chromatographic isolation) in THF (50 ml) was added $(t\text{-BuO})_3LiAlH$ (0.49 g). The reaction mixture was stirred 5 hr, poured into ice covered with 10% HCl, and extracted with Et_2O. The organic layer was washed successively with H_2O and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave a yellow amorphous solid which was chromatographed on silica gel (80 g) using hexane–EtOAc (9:1) as the eluent. The first few fractions contained a yellow oil which was discarded. The subsequent solid-containing fractions were 33 (0.56 g, 84%) which slowly crystallized from hexane: mp 108.5–109.5°; nmr δ 0.83 (s, 3, C_{19}-H), 3.65 (pseudo-t, half-bandwidth = 17 Hz, 1, $C_{17\alpha}$-H); $[\alpha]_D$ +10.0°. *Anal.* ($C_{22}H_{36}O_3$) C, H.

B. By Esterification of 28. A small sample of 28 (100 mg) was dissolved in EtOH (5 ml) containing a catalytic amount of concentrated HCl and allowed to set overnight. The reaction was then poured into H_2O and extracted with Et_2O. The organic layer was washed and dried in the usual manner. Removal of the solvents *in vacuo* gave a residue which when examined by tlc appeared a single spot that cochromatographed with the ester 33 (98 mg, 90%). Recrystallization of the residue gave a compound identical in all respects with **33**.

Ethyl **17β-Acetoxy-3-hydroxy-5α-androst-2-ene-2-carboxylate (15).** Crude 13 (4 g), pyridine (16 ml), and Ac_2O (8 ml) were heated on a steam bath 18 min and the reaction flask quenched immediately in ice. The reaction mixture was poured into an ice–Et_2O mixture and the organic layer washed successively with 10% HCl, 10% $NaHCO_3$ (until neutral), and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents *in vacuo* and crystallization of the residue from EtOH gave 15 solvated with 1 equiv of EtOH (3.3 g, 67%, mp 107.5° dec). Repeated recrystallization did not alter the decomposition point: uv λ_{max} 256 (9800); nmr δ 2.05 (s, 3, $-OOCCH_3$); $[\alpha]_D$ +41.3°. *Anal.* ($C_{24}H_{36}O_5 \cdot$ EtOH) C, H.

Ethyl **17β-Acetoxy-3α-hydroxy-5α-androstane-2α-carboxylate (20).** A solution of 15 (2.5 g) in glacial AcOH (50 ml) containing PtO_2 (300 mg) was hydrogenated at 60 psi and 60° for 36 hr in a Parr hydrogenation apparatus. The reaction mixture was filtered through Celite followed by AcOH washing of the filter bed. Concentration of the filtrate to 10% its original volume and addition of H_2O precipitated a 1:1 mixture (nmr analysis) of **19** and **20** (2.2 g, 98%). The products were collected by filtration, washed well with H_2O, and air-dried. Chromatography of the mixture (2 g) on silica gel (70 g) using hexane–EtOAc (9:1) as the eluent gave the α epimer **20** (0.78 g, 31%, mp 149–150°) as the least polar

** Satisfactory ir and nmr spectra were obtained for all compounds reported. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer as KBr pellets unless otherwise indicated. Nmr spectra were recorded in parts per million relative to standard TMS on a Varian A-60A spectrometer in $CDCl_3$ unless otherwise indicated. Uv spectra were recorded in nanometers (ε) on a Cary Model 14 spectrophotometer using EtOH as the solvent. The melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical value. Analyses were performed by Spang Microanalytical Lab., Ann Arbor, Mich., and Midwest Microlab, Ltd., Indianapolis, Ind. Optical rotations were measured in $CHCl_3$, unless indicated otherwise, on a Perkin-Elmer 141 polarimeter at ambient temperature. Mass spectra were recorded on a Du Pont 21-490 mass spectrometer. Neutral alumina (Woelm) and silica gel (200 mesh, Mallinckrodt) were used as absorbents for column chromatography. Silica gel G according to Sthal (Brinkmann) was used as the absorbent for preparative thin-layer chromatography. The analytical thin-layer chromatography (tlc) was performed on prepared thin-layer, silica gel sheets with 254 fluorescent indicator (Eastman), developed with hexane–acetone (7:3) and visualized with uv or I_2 vapor.

band. Recrystallization from hexane–Et_2O did not alter the melting point: nmr δ 0.84 (s, 3, C_{19}-H), 4.27 (m, –, $C_{3\beta}$-H). The ethyl quartet and the 3β-H resonances were superimposed and integrated for 3 protons. The half-bandwidth for this latter resonance could not be accurately measured but was clearly much less than 17 Hz: $[\alpha]$D +6.29°. *Anal.* ($C_{24}H_{38}O_5$) C, H.

Ethyl 17β-Acetoxy-3β-hydroxy-5α-androstane-2α-carboxylate (19). Further elution of the column prepared for **20** above gave the β epimer **19** (0.95 g, 38%, mp 140–141°) with several of the intermediate fractions containing both **20** and **19**. Recrystallization of **19** increased the mp to 141–142°; nmr δ 0.87 (s, 3, C_{19}-H), 3.82 (pseudo-t, half-bandwidth = 19 Hz, 1, $C_{3\alpha}$-H); $[\alpha]$D −88.0°. *Anal.* ($C_{24}H_{38}O_5$) C, H.

Ethyl 17β-Acetoxy-5α-androst-2-ene-2-carboxylate (23). A solution of **19** and **20** (6.7 g) in pyridine (50 ml) containing $POCl_3$ (2.5 ml) was heated (standard vacuum oven) in a sealed tube to 150° for 3 hr and allowed to cool to room temperature in the oven. The tube was then broken and the dark contents were poured over ice covered with Et_2O. The organic layer was washed successively with 10% HCl, 5% $NaHCO_3$, and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents gave an amorphous solid **23** (6.2 g, 96%), whose spectral and chromatographic properties were identical with those of the analytical sample. The nmr of the crude reaction mixture showed no indication of β,γ-elimination products. The analytical sample was prepared by recrystallization from EtOH: mp 114–115°; uv λ_{max} 218 (9400); mass spectrum m/e 388 (M^+); nmr δ 7.00 (m, half-bandwidth = 8 Hz, 1, C_3-H); $[\alpha]$D +51.3°. *Anal.* ($C_{24}H_{36}O_4$) C, H.

Ethyl 17β-Acetoxy-5α-androstane-2β-carboxylate (25). A solution of **23** (1 g) in glacial AcOH (50 ml) was hydrogenated in a Parr hydrogenation apparatus at room temperature for 12 hr at 60 psi. The mixture was filtered through Celite and followed by several washings with AcOH. The filtrate was concentrated to a fraction of its original volume, poured over ice, and extracted with Et_2O. The organic layer was washed with 5% $NaHCO_3$ until neutral and saturated NaCl solution and dried (Na_2SO_4). The residue obtained after removal of the solvents was recrystallized from hexane to give **25** (0.7 g, 70%, mp 116–118°). The analytical sample was prepared by recrystallization from hexane: mp 117–118°; nmr δ 0.72 (s, 3, C_{19}-H); $[\alpha]$D −22.6°. *Anal.* ($C_{24}H_{38}O_4$) C, H.

Ethyl 17β-Hydroxy-5α-androstane-2β-carboxylate (34). To a solution of **25** (3 g) in EtOH (100 ml) was added Na_2CO_3 (3 g) and the reaction mixture refluxed for 24 hr. The mixture was poured into H_2O and extracted with Et_2O, washed with H_2O and saturated NaCl, and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave **34** (2.4 g, 90%) as a semisolid whose spectral and chromatographic properties were identical with those of the analytical sample prepared by repeated recrystallization from Et_2O-hexane: mp 158–160°; mass spectrum m/e 348 (M^+); nmr δ 0.71 (s, 6, C_{18}- and C_{19}-H); $[\alpha]$D −9.7°. *Anal.* ($C_{22}H_{36}O_3$) C, H.

17β-Hydroxy-5α-androstane-2β-carboxylic Acid (29). Aqueous 10% NaOH was added to a solution of **25** (1.7 g) in EtOH (100 ml) until it became cloudy and then the mixture was refluxed overnight. The reaction mixture was extracted with Et_2O; the organic layer was washed with H_2O and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave the neutral fraction which appeared to be mainly **34** (100 mg). The aqueous layer remaining was neutralized with concentrated HCl. The precipitate which formed was filtered, washed several times with distilled H_2O, and air-dried. This material (1 g, 72%) was found to consist of a 3:2 mixture (nmr analysis, C_{19}-H) of **29** and **28**, respectively. The air-dried mixture of acids (670 mg) was dissolved in EtOH (20 ml) containing a catalytic amount of concentrated HCl and allowed to stir overnight. Removal of the solvents and trituration of the residue with hexane gave a crystalline solid which was collected by filtration. The solid material was washed several times with hexane. Removal of the solvents from the combined filtrate and hexane washings gave a material which upon recrystallization was found to be identical in all respects with the ester **33**.

The hexane-insoluble solids were recrystallized from acetone giving the pure β epimer **29** solvated with 1 equiv of acetone (400 mg, 51%, mp 236.5–238°). The analytical sample was prepared by repeated recrystallization from acetone: mp 236.5–237°; mass spectrum m/e 320 (M^+); nmr (pyridine) δ 0.94 and 1.05 (s, 2 × 3, C_{18}- and C_{19}-H); $[\alpha]$D (MeOH) −9.5°. *Anal.* [($C_{20}H_{32}O_3$·$(CH_3)_2CO$] C, H.

17β-Hydroxy-5α-androstane-2α-carboxylic Acid (28). To a solution of Na (50 mg) in absolute EtOH (10 ml) was added **25** (100 mg) and the reaction mixture refluxed overnight. The epimerized ester was then hydrolyzed without isolation by adding H_2O (5 ml) and allowing the reaction mixture to reflux another 5 hr with the condenser and an additional 6 hr without. As needed, H_2O was added to maintain a volume of about 15 ml. After cooling, the cloudy mixture was extracted with Et_2O and the organic layer discarded. Neutralization of the aqueous layer with concentrated HCl precipitated the desired acid **28** (72 mg, 88%). The analytical sample was prepared by recrystallization from Et_2O: mp 275° dec; mass spectrum m/e 320 (M^+); nmr (pyridine) δ 0.94 and 0.81 (s, 2 × 3, C_{18}- and C_{19}-H); $[\alpha]$D (MeOH) +14.8°. *Anal.* ($C_{20}H_{32}O_3$) C, H.

3β-Acetoxy-5α-androstane-6β,17β-diol (7). To a solution of 3β-acetoxy-5α-androstane-6,17-dione[12] (6, 2 g) in THF (100 ml) was added $(t\text{-BuO})_3LiAlH$ (5.84 g) in portions and the reaction mixture allowed to stir 12 hr at room temperature. After addition of saturated NH_4Cl (50 ml), the reaction mixture was allowed to stir for an additional 0.5 hr before extracting with $CHCl_3$. The $CHCl_3$ extracts (1000 ml) were combined, washed with H_2O and saturated NaCl solution, and dried (Na_2SO_4). Removal of the solvents and trituration with hexane-ether gave 7 (1.8 g, 90%), collected by filtration: mp 203–207° (lit.[8] mp 204–207°).

Ethyl 3,6β,17β-Trihydroxy-5α-androst-2-ene-2-carboxylate (14). To a slurry of 7 (13 g) in Et_2O (700 ml) was added dihydropyran (100 ml) and TsOH (1 g) and the reaction mixture allowed to stir for 6 hr. At this time, 5% $NaHCO_3$ was added and the organic layer washed with H_2O and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave a noncrystalline material (26.3 g) which was used without further purification. A small sample (250 mg) was chromatographed on preparative tlc plates using hexane–acetone (7:3) as the eluent. The edges of the plates were briefly exposed to I_2 vapor and marked and the I_2 was allowed to sublime. The next-to-least polar band was removed from each plate and extracted with Et_2O on a Büchner funnel. Removal of the solvents *in vacuo* gave **3β-acetoxy-5α-androstane-6β,17β-diol 6,17-bis(tetrahydropyranyl) ether** (8, 96%) as a colorless glass: ir ν_{max} ($CDCl_3$) no absorbance in the region 3000-4000 cm^{-1}; nmr δ 4.66 (m, –, 2′-THP-H), 4.85 (m, –, $C_{3\alpha}$-H). The resonance peaks at 4.66 and 4.88 partially overlap and could not be cleanly integrated. Their sum, however, integrated for 3 protons.

The unpurified residue 8 (26 g) was dissolved in MeOH (500 ml), solid K_2CO_3 (5 g) added, and the reaction mixture refluxed 5 hr, poured into H_2O, and extracted with Et_2O. The organic layer was washed with H_2O and saturated NaCl solution and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave a residue which was chromatographed on neutral AlO_3 (activity III, 600 g) using $CHCl_3$ as the eluent. The first material to be eluted appeared to be polymers of dihydropyran corresponding to the least polar band observed in the above isolation of **8**. Further elution gave the desired **5α-androstane-3β,6β,17β-triol 6,17-bis(tetrahydropyranyl) ether** (**9**, 83% from **7**) which was used without further purification: ir ν_{max} ($CDCl_3$) 3410 and 3580 (-OH), no absorbance in the region 1500–2000 cm^{-1}; nmr δ 4.55–4.83 (m, 2, 2′-THP-H).

To a solution of **9** (14.4 g) in pyridine (144 ml) was added a solution of CrO_3 (14.4 g) in pyridine (144 ml) and the mixture allowed to stir overnight. Isopropyl alcohol (200 ml) was added and the mixture allowed to stir an additional 1 hr before filtering through a bed of Celite. The Celite bed was washed several times with hot *p*-dioxane and the combined washings and filtrate were concentrated *in vacuo*. The concentrated mixture was poured into H_2O and extracted with Et_2O which was again filtered through a bed of Celite, washed successively with H_2O, 10% HCl, 5% $NaHCO_3$, and saturated NaCl solution, and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave **6β,17β-dihydroxy-5α-androstan-3-one 6,17-bis(tetrahydropyranyl) ether** (**10**, 86%) as a colorless glass which was a single spot by tlc and was used without further purification: mass spectrum m/e 474 (M^+); ir ν_{max} ($CDCl_3$) 1700 cm^{-1} (C_3=O).

To solid NaH (6 g), dried as previously described for **13**, was added a solution of **10** (12 g) in diethyl carbonate (500 ml). The usual treatment and work-up afforded a yellow glass (**12**, 13 g). Examination of this material by tlc indicated one major spot (R_f 0.7) and several insignificant more polar spots. Removal of the THP ethers was carried out without further purification by dissolving in EtOH (300 ml) containing concentrated HCl (3%, v/v). Tlc analysis of the reaction mixture showed that over a period of 3–4 hr the faster moving product (R_f 0.7) was converted to the desired product **14** (R_f 0.3) along with several minor products. At the end of this time, the reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed with H_2O, 5% $NaHCO_3$, and saturated NaCl solution and dried

(Na_2SO_4). Removal of the solvents, adsorption on silica gel (600 g), and elution with hexane containing increasing amounts of EtOAc gave crystalline **14** solvated with 1 equiv of EtOAc (9.4 g, 54% from **7**). The analytical sample was prepared by several recrystallizations from hexane containing a small amount of EtOAc and was air-dried overnight: mp 143° dec; mass spectrum *m/e* 378 (M^+); uvλ_{max} 256 (10,000); nmr δ 12.5 (s, 1, enol H); $[\alpha]_D$ +33.6°. *Anal.* ($C_{22}H_{34}O_5 \cdot$EtOAc) C, H.

Ethyl 6β,17β-Diacetoxy-3-hydroxy-5α-androst-2-ene-2-carboxylate (16). To a solution of **14** (5 g) in pyridine (5 ml) was added Ac_2O (5 ml) and the reaction allowed to set 48 hr before pouring into H_2O and extracting with Et_2O. The organic layer was washed with H_2O, 10% HCl, 5% $NaHCO_3$, and saturated NaCl solutions and dried (Na_2SO_4). Removal of the solvents *in vacuo* left a residue which when examined by nmr analysis (integration of the enol proton and individual acetate protons) and tlc indicated it to be a mixture of the two compounds **16** and its 3-enol acetate derivative **18** in the approximate ratio of 2 to 1.

A small sample of the residue (604 mg) was chromatographed on preparative thin-layer plates using hexane-acetone (7:2) as the eluent. The two uv-absorbing bands were removed and extracted with Et_2O. Removal of the solvents gave ethyl **3,6β,17β-triacetoxy-5α-androst-2-ene-2-carboxylate (18,** 117 mg) as the most polar band: nmr δ 2.18 (s, 3, enol $OOCCH_3$). The least polar band was **16** (336 mg).

The residue obtained from the acetylation (4.5 g) was dissolved in EtOH (100 ml), solid Na_2CO_3 (3 g) added, and the reaction allowed to stir for 24 hr. After the usual work-up, the residue was again examined and the ratio of **16** to **18** found to be 15 to 1. The solvolyzed material was chromatographed on silica gel (80 g) and eluted with hexane containing increasing amounts of EtOAc as a gradient. The first product to be eluted was the desired **16** (4.5 g, 90%) followed by a mixture of **16** and **18**. The analytical sample was prepared by recrystallization from hexane: mp 116–124°; mass spectrum *m/e* 462 (M^+); uv λ_{max} 256 (11,000); nmr δ 2.05 and 2.09 (s, 2 × 3, $-OOCCH_3$), 12.5 (s, 1, enol H); $[\alpha]_D$ +8.3°. *Anal.* ($C_{26}H_{38}O_7$) C, H.

Ethyl 6β,17β-Diacetoxy-3β-hydroxy-5α-androstane-2α-carboxylate (21). To a solution of **16** (3.3 g) in glacial AcOH (250 ml) was added PtO_2 (1 g) and the mixture hydrogenated for 48 hr as previously described for **20**. The usual work-up and addition of H_2O gave an amorphous solid which was extracted with Et_2O. The organic layer was washed and dried in the usual manner and the solvents were removed. The residue was dissolved in hexane, concentrated, and placed in the refrigerator. Pure **21** (1.4 g, 42%) crystallized and was recrystallized several times from hexane-acetone for the analytical sample: mp 179–180°; nmr δ 1.07 (s, 3, C_{19}-H), 3.84 (m, half-bandwidth = 22 Hz, 1, $C_{3\alpha}$-H); $[\alpha]_D$ −46.2°. *Anal.* ($C_{26}H_{40}O_7$) C, H.

Ethyl 6β,17β-Diacetoxy-3β-hydroxy-5α-androstane-2β-carboxylate (22). Removal of the solvents from the mother liquor of **21** gave a material (1.67 g) which when examined by tlc was found to contain at least four different compounds. This residue was chromatographed on silica gel (200 g) using $CHCl_3$ as the eluent. The first band to be eluted was an unidentified material (40 mg) which was discarded. The second band was starting material (0.6 g, 19%). The third compound to be eluted was **22** (0.8 g, 24%) contaminated with a trace of **21**. Further elution gave pure **21** (0.3 g, 9%).

The partially purified **22** (700 mg) was chromatographed on neutral AlO_3 (80 g, activity III) using CH_2Cl_2-EtOAc (1:1) as the eluent. The column was followed by tlc as well as nmr analysis of the C_{19} protons and the fractions containing pure **22** (500 mg) were combined. Further elution gave a mixture of **21** and **22** (150 mg). The purified **22** resisted crystallization from common solvents. The analytical sample was prepared by several precipitations from acetone-H_2O: mp 65–75°; mass spectrum *m/e* 464 (M^+); nmr δ 0.93 (s, 3, C_{19}-H), 3.51–3.93 (2, overlapping $C_{3\alpha}$-H and -OH): nmr δ ($CDCl_3$-D_2O) 3.68 (m, half-bandwidth = 18 Hz, 1, $C_{3\alpha}$-H); $[\alpha]_D$ −23.2°. *Anal.* ($C_{26}H_{40}O_7$) C; H: calcd, 67.22; found, 66.79.

Ethyl 6β,17β-Diacetoxy-5α-androst-2-ene-2-carboxylate (24). A. By Dehydration of 21. A solution of **21** (1.5 g) in pyridine (30 ml) containing $POCl_3$ (2 ml) was treated and worked up as for **23**. The spectral and chromatographic properties of the residue (1.2 g, 83%) were identical with those of the analytical sample prepared by chromatography on silica gel (80 g), elution with hexane-EtOAc (9:1), and subsequent recrystallization from hexane: mp 89–93°; uv λ_{max} 215 (9400); mass spectrum *m/e* 446 (M^+); nmr δ 7.02 (m, half-bandwidth = 7 Hz, 1, C_3-H); $[\alpha]_D$ +19.1°. *Anal.* ($C_{26}H_{38}O_6$) C, H.

B. By Dehydration of 22. A solution of **22** (256 mg) in pyridine (3 ml) containing $POCl_3$ (0.5 ml) was treated and worked up as above. The residue (198 mg, 80%) obtained was identical in all respects with that from the dehydration of **21**.

Ethyl 6β,17β-Diacetoxy-5α-androstane-2β-carboxylate (26). A solution of **24** (900 mg) in AcOH (30 ml) containing PtO_2 (100 mg) was hydrogenated and worked up as described for **25**. Chromatography on silica gel (80 g), using hexane-EtOAc (9:1) as the eluent, gave **26** (837 mg, 93%) which resisted crystallization from common solvents. The analytical sample was prepared by precipitation from acetone-H_2O: nmr δ 0.92 (s, 3, C_{19}-H); $[\alpha]_D$ −38.4°. Anal. ($C_{26}H_{40}O_6$) C, H.

6β,17β-Dihydroxy-5α-androstane-2α-carboxylic Acid (30). To a solution of $NaOCH_3$ (1.35 g) in absolute MeOH (50 ml) was added **26** (1.35 g) and the reaction mixture refluxed overnight. The epimerized ester was then hydrolyzed and worked up as described for **28**. Neutralization of the aqueous layer precipitated the desired acid **30** (800 mg, 79%). The analytical sample was prepared by recrystallization from acetone: mp 268–270°; mass spectrum *m/e* 336 (M^+); $[\alpha]_D$ (MeOH) −0.7°. *Anal.* ($C_{20}H_{32}O_4$) C, H.

Ethyl 6β,17β-Diacetoxy-5α-androstane-2α-carboxylate (27). A small sample of **30** (200 mg) was esterified by treatment with EtOH (5 ml) and a catalytic amount of concentrated HCl (1-2 drops) overnight. The usual work-up gave an amorphous solid (200 mg) whose nmr was consistent with the desired ester.

Acetylation of this residue (200 mg) overnight with pyridine (2 ml) and Ac_2O (1 ml) and the usual work-up gave **27** (200 mg, 75%) as a white crystalline solid. The analytical sample was prepared by recrystallization from hexane: mp 168–169°; nmr δ 1.02 (s, 3, C_{19}-H), 4.64 (pseudo-t, half-bandwidth = 17 Hz, 1, $C_{17\alpha}$-H), 5.03 (m, half-bandwidth = 7 Hz, 1, $C_{6\alpha}$-H); $[\alpha]_D$ −26.4°. *Anal.* ($C_{26}H_{40}O_6$) C, H.

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Aromatic Amino Acid Hydroxylase Inhibitors. 4.[1] 3-Substituted α-Methyltyrosines

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In the present study a series of 3-alkenyl-α-methyltyrosines and their corresponding 3-alkyl- and dihydrobenzofuran analogs was synthesized for potential tyrosine hydroxylase (TH) inhibitory activity. The appropriately substituted hydantoins IIIa and IIIb, which were prepared from the corresponding allyloxybenzylhydantoins IIa and IIb through Claisen rearrangement, served as intermediates for the synthesis of these amino acids. TH inhibition was reduced upon either saturation of the double bond in the side chain or cyclization to form the dihydrobenzofuran analogs. Formation of the epoxide had a similar effect. The inhibitory activity of these compounds against aromatic amino acid decarboxylase (AADC) and dopamine β-hydroxylase (DBH) was also investigated. Unsaturation, in both cases, decreases the inhibitory activity; however, the presence of a free phenolic group appears to be essential for AADC inhibitory activity.

In recent years, numerous agents have been synthesized for the explicit purpose of modulating the central and peripheral biosynthesis of catecholamines. Since tyrosine hydroxylase (TH) is involved in the rate-limiting enzymatic step,[2] it is understandable that many of the investigations have been concerned with regulation of this enzyme.[3]

The α-methylated analogs of phenylalanine and tyrosine (α-MT) are competitive inhibitors of TH[4] and the *in vitro* activity of these compounds was enhanced by introduction of iodine at the 3 position. The relative activity for the halogen derivatives was I > Br > Cl > F.

This order of activity for halogenated analogs has been also noted for thyroxine hormones.[5] In this instance, replacement of the 3′-iodine with alkyl groups led to more potent thyromimetic agents.[6] Unfortunately, this change was not as rewarding when introduced into the TH inhibitors. In this case, the 3-alkylated derivatives showed much less enzyme inhibitory activity than their 3-iodo counterparts.[7]

The 3-alkylated analogs, however, do have an advantage over the 3-iodo derivatives in that they are also active inhibitors of TH *in vivo*. The 3-iodo derivatives lack significant *in vivo* activity because they are rapidly destroyed by tissue dehalogenases and transaminases.[3]

Among the 3-alkylated α-MT derivatives, the 3-methyl, ethyl, and isopropyl were as effective as α-MT as inhibitors of TH. The 3-*tert*-butyl derivative, on the other hand, was completely devoid of inhibitory activity at similar concentrations. While a certain degree of bulk at the 3 position does not interfere with interaction with the enzyme, apparently there is some limitation imposed as to the size of this substituent.

In an effort to derive additional information regarding the steric and structural prerequisites for TH inhibition, this paper describes the synthesis and evaluation of several 3-alkenyl derivatives of α-MT and their corresponding cyclization products.

Since the most widely used synthesis of α-methylamino acids involves hydrolysis of the appropriate hydantoin, the initial goal was the synthesis of hydantoins typified by III. Treatment of *p*-hydroxyphenyl-2-propanone with allyl bromide or methallyl chloride under basic conditions gave the desired ethers Ia and Ib. Treatment of these ketones with ammonium carbonate and KCN in aqueous alcohol afforded the desired hydantoins IIa and IIb in good yield.

On the basis of the extensive study of the Claisen rearrangement by White and Wolfarth,[8] ethylene glycol was initially selected as the most appropriate solvent for converting IIa to IIIa. Unfortunately, isolation of the product from this solvent proved difficult. When octanoic acid was used for the thermal rearrangement, IIIa was isolated in 72% yield. The best yields, however, were achieved when diphenyl ether was used as the solvent (Scheme I).

Catalytic reduction of IIIa and IIIb over Pd/C gave the hydantoins IVa and IVb which were readily hydrolyzed with aqueous $Ba(OH)_2$ to 3-*n*-propyl-α-methyltyrosine (VIIa) and 3-isobutyl-α-methyltyrosine (VIIb). Treatment of IIIa and IIIb with 48% HBr in glacial acetic acid[9] cyclized the o-allylphenols to the corresponding dihydrobenzofurans Va and Vb. Hydrolysis of these hydantoins furnished the amino acids VIIIa and VIIIb.

Barium hydroxide hydrolysis of the allyl derivatives was not as straightforward and the nature of the product was found to vary with the reaction temperature. For example, when IIIa was hydrolyzed in a sealed tube at 160°, only the amino acid IX was isolated. When the temperature was lowered to 130°, on the other hand, VIa was obtained in good yield. At temperatures between 130 and 160°, both amino acids were formed. At the reflux temperature, 26 hr was required to effect complete hydrolysis of IIIa, and, in this instance, only VIa was isolated. Isomerization of the allyl double bond[10] of VIa to give IX was achieved by treatment with base at high temperature. The hydantoin IIIb was hydrolyzed similarly, at 130°, and the amino acid VIb was obtained. Treatment of VIa with H_2O_2 in formic acid at 8° afforded the epoxide X in 23% yield.

Nmr and other spectral properties of all the compounds in this study were consistent with the assigned structures except for one case. In this instance, amino acid VIIIb gave a molecular ion peak at m/e 231 (P − 18) instead of

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