3β-Acetoxy-23-hydroxy-24-nor-5β-chol-14-en-21-oic Acid γ-Lactone (6). After 22 hr at room temp, a mixt of alcohol **5a** (1.9 g, 5.1 mmoles), pyridine (9 ml), and Ac_2O (4.5 ml) was poured into crushed ice. The ppt was collected and dried (vacuum) to yield acetate **5b** (1.96 g). The crude acetate **5b** was heated (steam bath, 2 hr) with AcOH–H_2O (2:1), poured into H_2O (250 ml), and extd with $CHCl_3$ (3 × 100 ml). The combined ext was washed with H_2O (100 ml), satd $NaHCO_3$ soln (100 ml), H_2O (100 ml), and dried and solvent removed *in vacuo* to yield 1.7 g of a brown solid. Chromatography in ligroin–EtOAc (17:3) on silica gel (50 g) and elution with the same solvent gave purified hemiacetal **5c** (0.84 g, 46%). To a soln of the hemiacetal (**5c**, 0.165 g) in Me_2CO (15 ml) was added dropwise with stirring 8 *N* Jones' reagent[6] until an orange color persisted. After 5 min, a few drops of *i*-PrOH was added and the ppt collected and washed with Me_2CO. The combined Me_2CO soln was poured into H_2O (20 ml) and the Me_2CO removed *in vacuo*. The resultant solid and aqueous soln was extd with $CHCl_3$ (2 × 10 ml) and the combined ext dried. Removal of solvent *in vacuo* yielded isocardanolide **6** (0.16 g, 96% from **5c**). Three recrystn from Me_2CO–hexane afforded large needles, mp 203–206°. *Anal.* ($C_{25}H_{36}O_4$) C, H.

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New Compounds

Synthesis and Antiinflammatory Activity of Betamethasone 17-Benzoate

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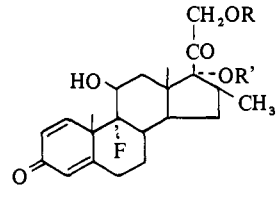
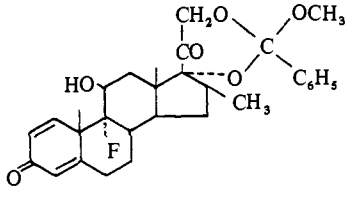
Corticosteroid 17-esters were first prepared some years ago in our laboratory by acid hydrolysis of the corresponding cyclic 17,21-alkyl ortho esters.[1,2]

Many 17-alkanoates of various corticosteroids have been found to display enhanced antiinflammatory activity after local application.[3] Here, we wish to report the synthesis and some biological properties of betamethasone 17-benzoate (III).†

The compound was prepared from betamethasone (I) through epimeric cyclic 17,21-methyl orthobenzoates II (for the stereoisomery of corticosteroid 17,21-alkyl ortho esters see ref 4) and subsequent hydrolysis of the latter in buffered medium.[5,6] Base-catalyzed rearrangement[2] of III gave betamethasone 21-benzoate (IV), identical with the product obtained by conventional benzoylation of I. A





II

I, R = R' = H
III, R = H; R' = C_6H_5CO
IV, R = C_6H_5CO; R' = H
V, R = H; R' = *n*-C_4H_9CO

benzoyl group cannot be introduced at 17α-O by direct acid-catalyzed acylation.[7]

Betamethasone 17-benzoate (III) was compared with I and betamethasone 17-valerate (V)[8,‡] in five assays for the antiinflammatory, thymolytic, and vasoconstrictive activity after different administration routes.§ The relative potencies are given in Table I. Compound III displayed the highest ratio between topical and systemic activities.

Table I. Topical (T) and Systemic (S) Activities of III and V

Assay	Route	Activity	Potency[a] III	Potency[a] V
1[b]	Oral	Antigranulomatous (S)	<1	<1
2[c]	Oral	Antiexudative (S)	<1	<1
3[c]	Intracavitary	Antiexudative (T)	100	1
	Intracavitary	Thymolytic (S)	3	1
4[d]	Percutaneous	Antiedematous (T)	1	<1
	Percutaneous	Thymolytic (S)	1	1
5[e]	Percutaneous	Vasoconstrictive (T)	500	450[f]

[a] Betamethasone (I) = 1. [b] On rat.[10] [c] On rat.[11] [d] On rat.[12] [e] On man.[13] [f] Data from ref 8.

Experimental Section#

Betamethasone 17-Benzoate (III). To a boiling solution of I (10 g) in dioxane (400 ml) and C_6H_6 (1,000 ml) under anhyd conditions, trimethyl orthobenzoate (10 ml) was added, followed by Py·TsOH (1 g). Heating was pursued for 1 hr, about two-thirds of the solvent being removed by distn. After addn of a few drops of Py and complete removal of the solvent under reduced pressure, the residue was triturated with petr ether to give II, cryst isomeric mixt (12 g). Recrystallization from CH_2Cl_2–Et_2O gave the analytical sample; mp 169–172°; tlc, R_f 0.56; [α]D +91°. *Anal.* ($C_{30}H_{35}O_6F$) H, C.

To a solution of crude II in MeOH (2,000 ml), sodium acetate

†Beben.

‡The compound prepared in our laboratory showed mp 195–198°; [α] +77°. *Anal.* ($C_{27}H_{37}O_6F$) C, H.

§For other biological assays on compound III see ref 9.

#Melting points were taken in a capillary apparatus and are uncorrected. Optical rotations were detd in dioxane at 24°, $c \sim 1$. Uv were detd in 95% EtOH and ir in Nujol mull. Absorption bands of these spectra were as expected. Tlc were done using 250-μ thick layers (Fluorosil G) and 8:2 C_6H_6–Me_2CO. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

buffer of pH 3.9 (80 ml), prepared by mixing 0.1 *N* AcOH (90 ml) and 0.1 *N* NaOAc (10 ml), was added. The reaction mixt was refluxed for 1 hr, cooled at room temp, and allowed to crystallize overnight. The pptd crystals were collected, washed (H_2O), and dried *in vacuo* to give III (7.8 g); mp 224–227°. Trituration with Me_2CO–Et_2O of the material recovered after concn of the mother liquor gave a second crop (3 g) of comparable product. Crystn of the combined yields from Me_2CO–Et_2O gave pure III (8.9 g); mp 225–228°; tlc, R_f 0.3; [α]D +63.5°. *Anal.* ($C_{29}H_{33}O_6F$) C, H.

Betamethasone 21-Benzoate (IV). To a solution of III (0.5 g) in MeOH (10 ml), kept stirring under an atmosphere of N_2, MeOH–0.1 *N* KOH (0.5 ml) was added. After 25 min, crystals began to sep. After 1 hr a 10% aq soln of AcOH (1 ml) was added, and the ppt (250 mg), mp 252–256°, was recovered by filtration. Crystallization (EtOH) gave IV; mp 252–256°; tlc, R_f 0.47; [α]D +170°. *Anal.* ($C_{29}H_{33}O_6F$) C, H. Identity with authentic IV, prepared from I by a conventional procedure, was established.

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6,6-Difluoro-19-norprogesterone†

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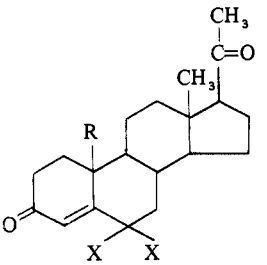
We recently described[1-8] the synthesis of several 6,6-difluoro-19-norsteroid progestational agents related to norethindrone and norgestrel. The oral progestational activities of 17α-ethynyl- and 17α-propadienyl-19-nortestosterones are enhanced by the *gem*-6,6-difluoro substitution,[1-4,7-9] so it was of interest to prepare some pregnanes with this γ,γ-difluoro-α,β-enone structural unit to see if a similar enhancement could be produced with subcutaneous progestational activities. The conversion of progesterone (1) to 6,6-difluoroprogesterone (2) has already been described,[1,10,11] and the present notice describes a parallel conversion of 19-norprogesterone (3)[12] to its 6,6-difluoro derivative (4). Unlike the estrane series, 6,6-difluoro substitution in the pregnane and 19-norpregnane series did not enhance their progestational activity, as illustrated in Table I. It is clear that the biological profiles of 17α-ethynyl-19-nortestosterones and pregnanes are distinct,[13] and modificiations to one series do not necessarily translate to the other series.

†Contribution No. 1905.

Table I. Subcutaneous Progestational Activities of Progesterone Derivatives

Compound	Activity[a]
1	1.0
2	~0.2
3	4–8[b]
4	<2

[a] Clauberg assay *vs.* progesterone standard using estrogen-primed rabbits, *cf.* ref 13. [b] See ref 14.



1, R = CH_3; X = H
2, R = CH_3; X = F
3, R = H; X = H
4, R = H; X = F

Experimental Section‡

6,6-Difluoro-19-norprogesterone (4). 19-Norprogesterone[12] (3) (5.0 g) was reduced (LiAlH(*O-tert*-Bu)$_3$–THF) to the corresponding 3β,20β-diol which was reoxidized (DDQ–dioxan) to 20β-hydroxy-19-nor-4-pregnen-3-one, mp 178–182°, in overall yield of 49% after recrystn (hexane–Me_2CO). This was converted[15] (Ac_2O–AcCl–C_5H_5N) in 73% yield to 3,20β-dihydroxy-19-nor-3,5-pregnadiene 3,20-diacetate, mp 148–154° dec, redn of which ($NaBH_4$–THF–EtOH), followed by reacetylation (Ac_2O–C_5H_5N), gave 3β,20β-dihydroxy-19-nor-5-pregnene 3,20-diacetate, mp 198–200°, in 52% yield. Treatment of the latter with NOF and Al_2O_3 chromatography gave a 53% yield of colorless crystalline 3β,20β-dihydroxy-5α-fluoro-19-norpregnan-6-one 3,20-diacetate, mp 144–150° dec. The 6-oxo function was converted to 6,6-*gem*-difluoro (SF_4) in 65% yield. 3β,20β-Dihydroxy-5α,6,6-trifluoro-19-norpregnane 3,20-diacetate, mp 115–117°, was hydrolyzed (MeOH–HCl) to the parent diol and oxidized (8 *N* CrO_3–Me_2CO) to 5α,6,6-trifluoro-19-norpregnane-3,20-dione, which was dehydrofluorinated (Al_2O_3 chromatography) to crude 4 (0.3040 g, 5.5% overall yield).

Two recrystallizations of 4 (Me_2CO–hexane) gave 0.1276 g of colorless crystalline 6,6-difluoro-19-norprogesterone: mp 101–102°; ν_{max}^{KBr} 1725 and 1690 cm^{-1}; λ_{max}^{EtOH} 330 (ε 40), 285 (53), and 226 nm (13,700); $[\alpha]^{25}D$ +16° (*c* 0.25, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{26}O_2F_2$: C, 71.40; H, 7.79; *m/e* 336.1900. Found: C, 71.84; H, 8.32; *m/e* 336.1902.

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‡Because the synthesis was a direct parallel to that used for 2[1,10,11] only the final product is described in detail. The structural assignments of intermediate products were in agreement with their ir, uv, and nmr spectra.