Synthesis and Topical Antiinflammatory Properties of 17,21-Bis(acetyloxy)-6β,9-difluoro-11β-hydroxypregna-1,4-diene-3,20-dione and Related 2-Halogenated Compounds

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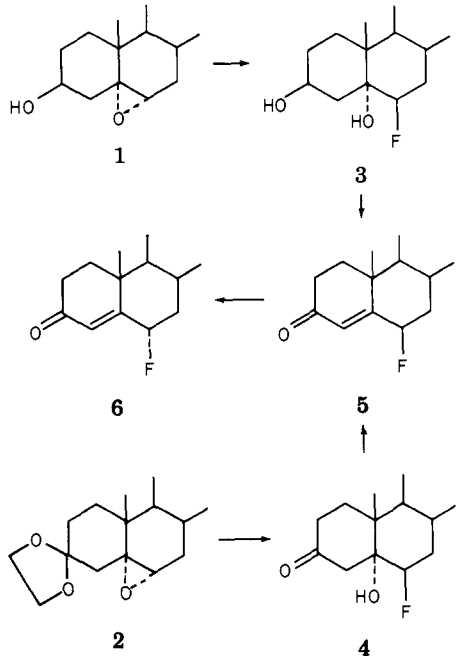
Introduction of a halogen atom at C-2 of steroid 3-ketofluorohydrins, obtained from the corresponding 5α,6α-epoxides by trans-diaxial opening with hydrofluoric acid, prevents the 6β-fluorine atom from undergoing rearrangement to the more stable 6α configuration when the 5-*tert*-hydroxyl is split off to yield a conjugated double bond. Two processes were investigated for the synthesis of 17,21-bis(acetyloxy)-6β-fluoro-1,4,9(11)-triene-3,20-dione (**24a**) and the related 2-bromo compound **24b** starting from the known 21-(acetyloxy)-6β-fluoro-5α,11α,17-trihydroxypregnane-3,20-dione (**13**). Successive reaction with hypobromous acid, epoxidation, and fluorination converted **24a** and **24b** into the title compound **27a** and the analogue 2-bromo compound **27b**. In addition, a synthesis of 17,21-bis(acetyloxy)-2-chloro-6β,9-difluoropregna-1,4-diene-3,20-dione (**27c**) is reported. The antiinflammatory activity of 17,21-bis(acetyloxy)-6β,9-difluoropregna-1,4-diene-3,20-dione (**27a**) and its 2-halogenated analogues **27b** and **27c** in comparison with the corresponding 6α,9-difluoro epimers was studied. Some 6β-fluoro compounds displayed high topical antiinflammatory activity without systemic effects.

Since it was found that fluorination of the corticoids may differentially affect their antiinflammatory and mineralcorticoid activity, a large number of fluoro corticoids and extensive data on their pharmacological activity have been accumulated over the past 20 years. Interesting observations were made by investigating the effects of fluorination in numerous positions of the cortisol molecule.[1,2] The presence of an electronegative fluorine atom at C-9 is particularly important for antiinflammatory activity.[3] The introduction of a 6α-fluorine atom not only enhances the thymolytic and antiinflammatory activity of cortisol but also decreases sodium retention.[2] In contrast, 6β-fluoro substitution was reported[4] to decrease thymolytic and antiinflammatory activity and increase sodium retention.

The combination of a 6α- and 9-fluorine atom in the prednisolone molecule enhances antiphlogistic and reduces sodium-retaining activity.[5] To our knowledge, until now, the influence of a 6β-fluorine atom in the 9-fluoroprednisolone molecule and its esters has not been biologically evaluated.

The aim of this report has been to compare the topical antiinflammatory effects of 6β,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (**28a**) and its acetyl esters with the corresponding 6α-fluoro epimers. Extending the investigation to the other compounds, we examined the electron-withdrawing effects of a halogen atom[6] at C-2 in both series. The oral activity of the diacetyl esters was evaluated too.

Chemistry. Preliminary examination of the numerous methods currently available for introducing a fluorine atom into the C-6β position of the steroids revealed that fluorination by a trans-diaxial opening of a 5α,6α-epoxide (**1** and **2**) to yield the vicinal fluorohydrin (**3** and **4**) was still one of the most frequently employed methods.[7] However, after oxidation of the 3-hydroxyl of the fluorohydrin (**3**), and subsequent dehydration of the 5-*tert*-hydroxyl to yield a conjugated double bond, the 6β-fluorine atom easily underwent rearrangement to the 6α configuration. Dehydration of 3-ketofluorohydrin (**4**) was also accompanied by inversion of the 6β-fluorine atom.[8] Attempts were made to isolate the 4,5 unsaturated 6β-fluoro-3-keto steroids, intermediates for the preparation of 1,4 unsaturated 6β-fluoro-3-keto steroids, by dehydration of 3-ketofluorohydrins, but the easy conversion of the 6β (axial) epimer to the more stable 6α (equatorial) epimer gave only moderate yields.[9]

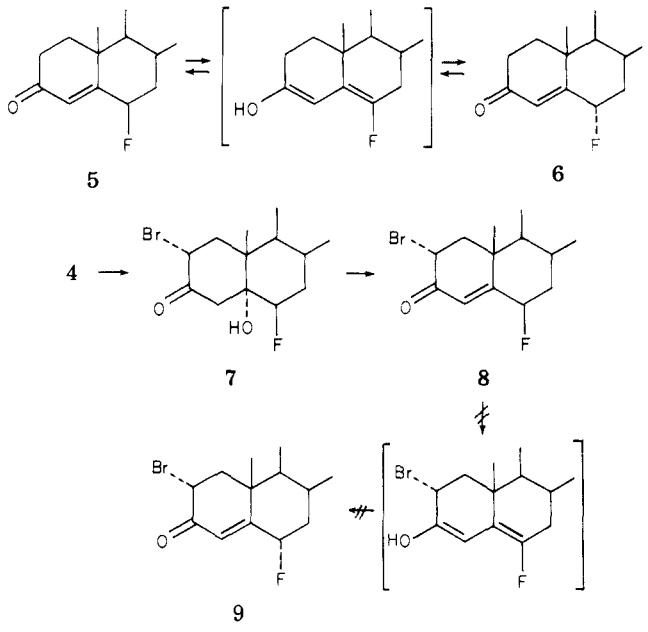


1 3 6 5 2 4

Since the origin of both 6α and 6β epimers might be rationalized by assuming that reversible enolization of **5** with concomitant isomerization could take place,[8] it seemed reasonable, therefore, to prevent the inversion of the 6β-fluorine atom by introducing a halogen atom at C-2 of the 3-ketofluorohydrin (**4**) before the dehydration reaction. The electron-withdrawing effect of this group would inhibit enolization of **8** toward C-6 and, consequently, the epimerization of **8** to **9**. For the same reason, an A-ring 1,2 unsaturation would stabilize the 6β configuration.

In analogy to reported procedures,[10] the C-3 keto group of the starting substance 21-(acetyloxy)-11α,17-dihydroxypregn-4-ene-3,20-dione (**10**)[11] was first ketalized (Scheme I) with ethylene glycol, in presence of pyridine hydrochloride, to give the corresponding 21-(acetyloxy)-3,3-(ethylenedioxy)-11α,17-dihydroxypregn-5-en-20-one (**11**). Formation of the cyclic ethylene ketal at C-3 was accompanied by typical migration of the double bond from the 4,5 to the 5,6 position.

Epoxidation of the 5,6 double bond with monoperphthalic acid in ethyl ether, as reported previously by



Bowers et al.,[12] afforded the 5α,6α-epoxide (**12**). Treatment of **12** with aqueous hydrofluoric acid, according to Hogg et al.,[13] gave 21-(acetyloxy)-6β-fluoro-5α,11α,17-trihydroxypregnane-3,20-dione (**13**).

We have developed two processes (A and B) for the conversion of **13** into 17,21-bis(acetyloxy)-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24a**) and 17,21-bis(acetyloxy)-2-bromo-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24b**) uncontaminated by the corresponding 6α-fluoro epimers. The 17,21-bis(acetyloxy)-2-chloro-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24c**) from **13** was obtained only by the method B.

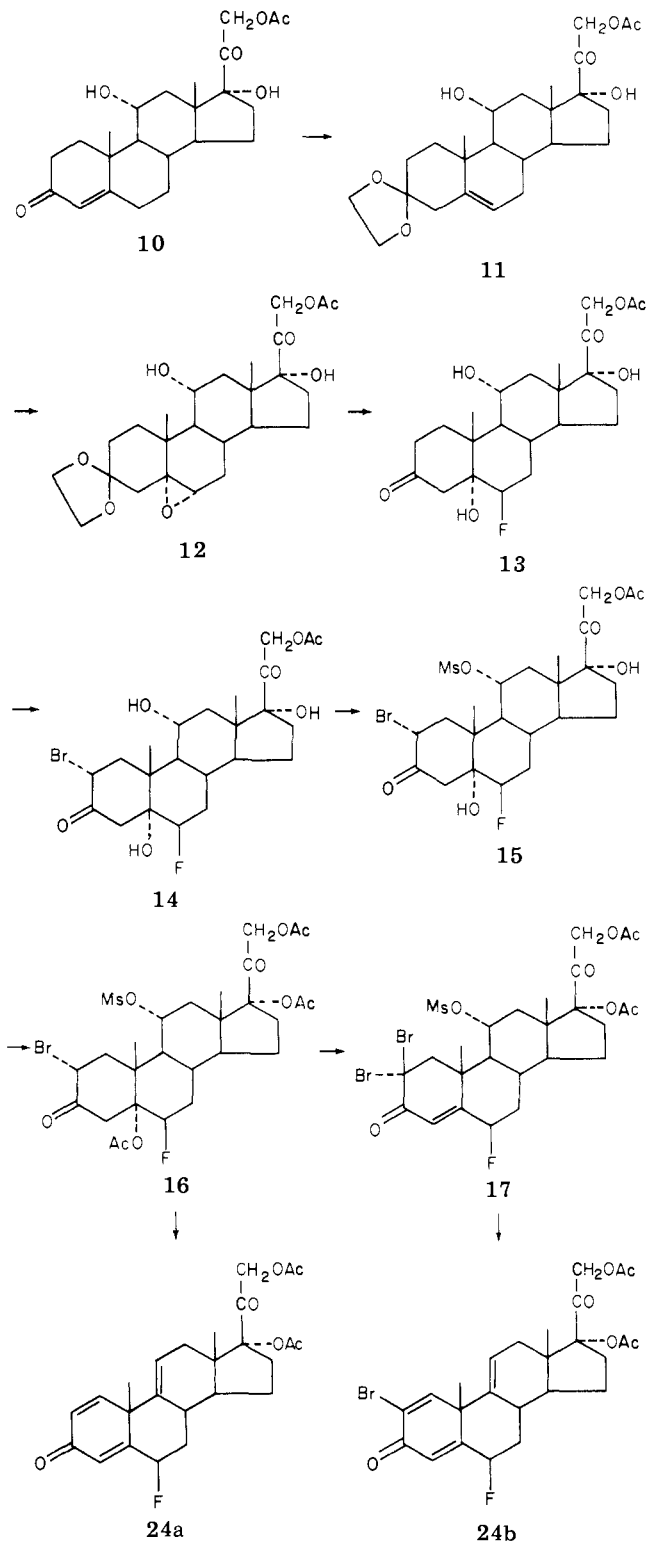
Method A (see Scheme I) involved the buffered bromination[14] of **13** with 1.1 equiv of bromine in dioxane to give 21-(acetyloxy)-2α-bromo-6β-fluoro-5α,11α,17-trihydroxypregnane-3,20-dione (**14**) which by treatment with sodium iodide in acetone[15] afforded the corresponding 2α-iodo compound. The assignment of the 2α configuration resulted from ir and uv spectra[15,16] of these two products. The C-3 carbonyl stretching region of both compounds was displaced by about 15–20 cm^{-1} to higher frequency. As expected, the introduction of the equatorial 2α-bromo group left the uv maximum unaffected whereas the equatorial 2α-iodo group produced an appreciable negative effect (−34 nm).

Addition of methanesulfonyl chloride[17] to **14** gave 21-(acetyloxy)-2α-bromo-6β-fluoro-5α,17-dihydroxy-11α-(methanesulfonyloxy)pregnane-3,20-dione (**15**), the *tert*-hydroxyl groups of which were further allowed to react with acetic anhydride and perchloric acid as the catalyst[18] to give **16**. In this case formation of the corresponding 3-enol acetate was not observed.

Base-catalyzed bromination of **16** with 1.1 equiv of bromine in acetic acid[14] afforded mainly **17**.

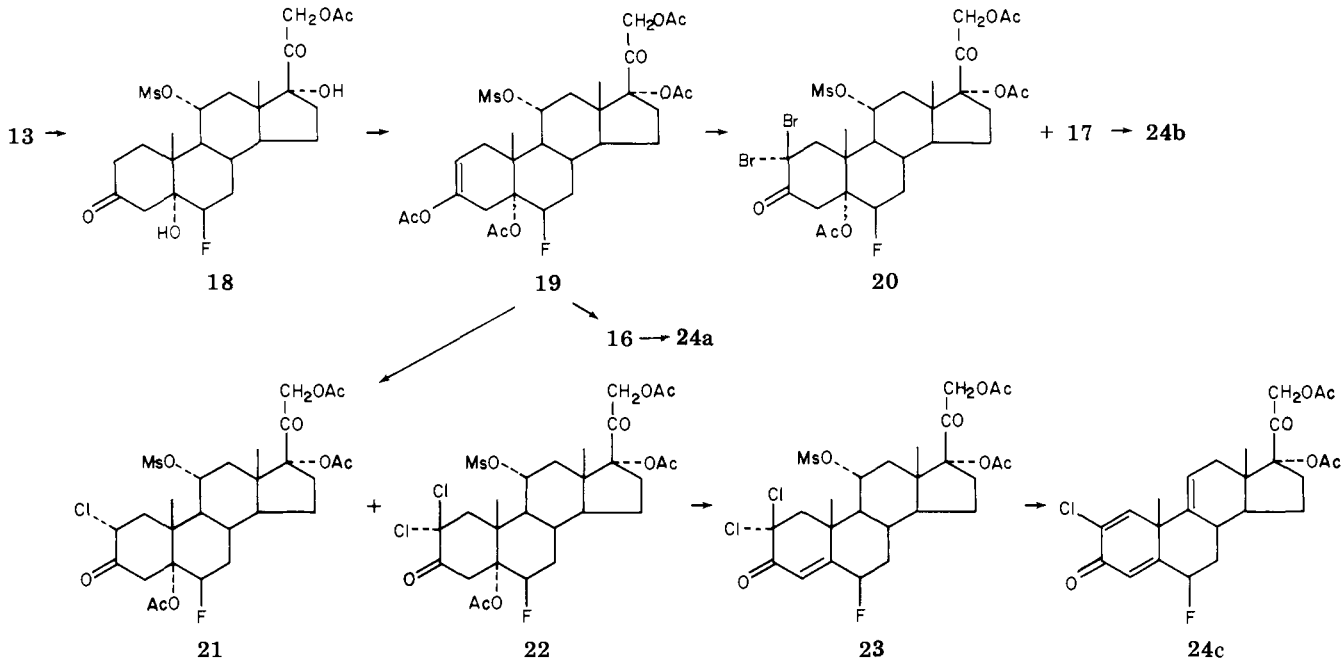
When **16** and **17** were refluxed in dimethylformamide with lithium bromide and lithium carbonate according to the method of Joly et al.,[19] they were converted respectively into 17,21-bis(acetyloxy)-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24a**) and 17,21-bis(acetyloxy)-2-bromo-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24b**). The ^1H NMR spectrum of the crude triene **24a** showed the C-6α proton as two triplets[20] centered at 346 and 296 Hz and the characteristic long-range spin–spin coupling of the protons at C-19 with the 6β-fluorine atom.[21] The ^1H NMR spectrum of the triene **24b** exhibited for the C-1 proton a singlet centered at 452 Hz and for the C-4 proton a

Scheme I. Method A



doublet centered at 374 Hz ($J_{6\beta F\text{-}4H}$ = 4 Hz), attributable to fluorine-proton 1,3 coupling,[20] while the C-6α proton appeared as two triplets centered at 334 and 286 Hz. Also, the ^1H NMR spectrum of **24b** showed the characteristic spin–spin coupling of the protons at C-19 with the 6β-fluorine atom. TLC and HPLC analyses of the crude **24a** and **24b**, by comparison with authentic samples of their corresponding 6α-fluoro epimers, established the absence of these compounds in the reaction mixture. The conversion of **16** and **17** into **24a** and **24b** appeared to be facilitated by the presence of the bromine atom at C-2. A priori the electron-withdrawing effect of the bromine atom

Scheme II. Method B



was expected to prevent the reversible enolization of **16** and **17** toward C-6 and, consequently, the inversion of the 6β configuration.

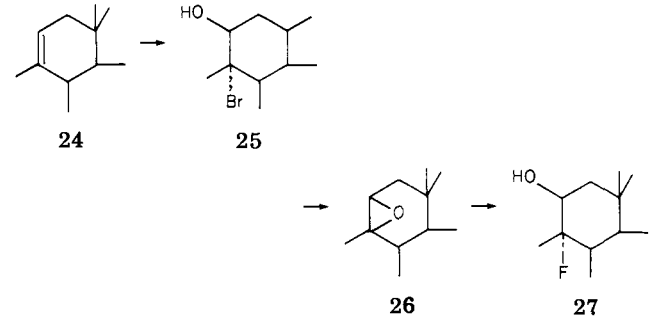
Method B (see Scheme II) involved conversion of **13** into 3,5α,17,21-tetrakis(acetyloxy)-6β-fluoro-11α-(methanesulfonyloxy)-pregn-2-en-20-one (**19**) by reaction with methanesulfonyl chloride in pyridine, followed by treatment with acetic anhydride and perchloric acid as catalyst.[18]

Monobromination of **19** with hypobromous acid generated from 1,3-dibromo-5,5-dimethylhydantoin and perchloric acid in tetrahydrofuran[22] gave **16**, the ir spectrum and other physical constants of which were in agreement with the structure of **16** prepared by procedure A. Bromination of **19** with 2.2 equiv of bromine in dioxane afforded rapidly a mixture of 5α,17,21-tris(acetyloxy)-2,2-dibromo-6β-fluoro-11α-(methanesulfonyloxy)pregnane-3,20-dione (**20**) and 17,21-bis(acetyloxy)-2,2-dibromo-6β-fluoro-11α-(methanesulfonyloxy)pregn-4-ene-3,20-dione (**17**). The uv and ^{1}H NMR spectra of this mixture indicated that the conjugated ketone was present in about 40% amount. The two compounds were separated by fractional crystallization from methanol. When **19** was treated with 2.2 equiv of chlorine in tetrahydrofuran, a 80:20 mixture of **21** and **22** was obtained. The percent composition of **21** and **22** was determined in the crude product by integration of their ^{1}H NMR spectra after proton bands were identified and assigned following separation and purification of **21** from **22** by successive crystallizations from methanol. The doublet of triplets at 360 and 310 Hz was assigned to the C-6α proton of **21**. No further chlorination was observed by repeating this experiment with a fivefold excess of chlorine. In contrast, chlorination of the mixture to give **23** was completed with further 1.2 equiv of chlorine in acetic acid at 90 °C in the presence of anhydrous sodium acetate.[14]

Both compound **23** and the mixture of **20** and **17** were refluxed in dimethylformamide in the presence of lithium bromide and lithium carbonate,[19] respectively yielding 17,21-bis(acetyloxy)-2-chloro-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24c**) and 17,21-bis(acetyloxy)-2-bromo-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (**24b**), uncontaminated by the corresponding 6α-fluoro epimers. The product **24b** was identical with a sample obtained by the method A. The ^{1}H NMR spectrum of triene **24c** exhibited for the C-1 proton a singlet centered at 435 Hz, for the C-4 proton a doublet centered at 372 Hz ($J_{6\beta F\text{-}4H}$ = 4 Hz), for the C-6α proton two triplets centered at 330 and 280 Hz, and for the three C-19 protons a doublet centered at 93 Hz ($J_{6\beta F\text{-}19H}$ = 2 Hz).

The fluorine atom at the C-6β position of **24a–c** was considered to be in the stable configuration on the basis of the following observation. Attempts to isomerize **24a–c** with dry hydrochloric acid in ethanol-containing chloroform[13] at 0 °C for 2 h did not alter the optical rotation of the crude products identical in all aspects with the starting samples **24a–c**.

Conversion of the 1,4,9(11)-trienes **24** to the corresponding 6β,9-difluoro compounds **27** was carried out in conformity with Fried and Sabo's method.[17,23] Reaction of **24** with hypobromous acid generated from 1,3-dibromo-5,5-dimethylhydantoin and perchloric acid in tetrahydrofuran gave the bromohydrins **25** which were closed with potassium carbonate in acetone to give the



9(11)-epoxides **26**. Finally, rupture of the epoxide with aqueous hydrofluoric acid by a modification[10,24] of Fried and Sabo's original method gave the 6β,9-difluoro compounds **27**.[25] The structure of **27b** was based on spectroscopic data. The 1,4 unsaturated 2-bromo-6β-fluoro-3-keto structure was indicated by the uv spectrum, which had an absorption maximum at 246 nm (ε 12 500). The ir spectrum had bands at 1680, 1650, and 1610 cm^{-1}, characteristic[26] of 1,4 unsaturated 3-keto steroids with the electron-withdrawing substituent at C-2. The ^{1}H NMR

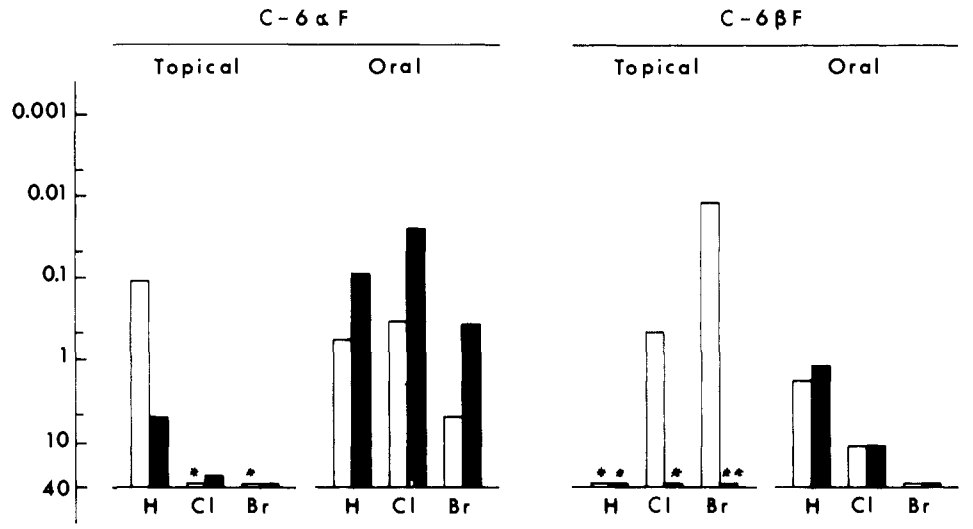


Figure 1. Antiinflammatory and thymolytic activity of 17,21-bis(acetyloxy)-6,9-difluoro-11β-hydroxypregna-1,4-diene-3,20-dione and its 2-halogenated analogues. The log scale on the ordinate represents the ED_{30} in μg/pellet or mg/kg die for topical or oral treatment, respectively. The substituent at C-2 is reported at the bottom of each column. Open columns refer to antiinflammatory activity; shaded columns refer to thymolytic activity. *, ED_{30} >40 μg/pellet (or 40 mg/kg die); **, ED_{30} >1000 μg/pellet.

spectrum exhibited a singlet centered at 465 Hz for the C-1 proton, a doublet centered at 387 Hz ($J_{6\beta F\text{-}4H}$ = 4 Hz) for the C-4 proton, two triplets centered at 346 and 396 Hz for the C-6α proton, and a doublet centered at 97 Hz ($J_{6\beta F\text{-}19H}$ = 2 Hz) for the C-19 protons. Similarly, elemental analysis, ^1H NMR, and other physical constants were in agreement with the structures of **27a** and **27c**.

Hydrolysis of the 6β,9-difluoro compounds **27** with methanolic potassium hydroxide at 0 °C yielded the corresponding 17,21-dihydroxy derivatives **28**.[27] Esterification of these with acetic anhydride in pyridine afforded the 21-monoacetates **29**.[28]

Following the Schering method,[29] **30b** and **30c** were obtained by treatment of **30a** with *N*-bromosuccinimide–hydrobromic acid and *N*-chlorosuccinimide–hydrochloric acid, respectively.

The known compounds **30a** and **32** were prepared from 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (**31**)[13] using reported procedures.[12,30]

Results and Discussion

The topical antiinflammatory and thymolytic activity in terms of ED_{30} of all the compounds examined is reported in Table I in comparison with fluocinolone acetonide.

Marked increase in activity was observed when both the C-17 and C-21 hydroxyl groups of **28a–c** and **31** were acetylated. This result was not unexpected since the higher topical antiinflammatory activity of steroid esters compared to their corresponding hydroxy derivatives was reported elsewhere.[31] Therefore, the diacetyl esters were selected for direct comparison of 6α- and 6β-fluoro epimers. Compound **27a** compared unfavorably with the analogue **30a** in terms of topical antiinflammatory activity. However, the presence of a halogen atom at C-2 brought about interesting changes in the properties of these compounds. The introduction of a bromine or chlorine atom at C-2 of **30a** greatly reduced the topical antiinflammatory activity. In contrast, the substitution of a halogen atom at C-2 of **27a** surprisingly yielded compounds endowed with high topical antiinflammatory properties but completely devoid of thymolytic activity. Compound **27b**, the most active of the 6β-fluoro compounds, was in fact unable to reduce the thymus weight at doses as high as 1000 μg/pellet. It is therefore apparent that the concomitant presence of a halogen atom at C-2 and a fluorine atom at C-6β position in the 17,21-bis(acetyloxy)-9-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione molecule is necessary to evoke high topical antiinflammatory activity without influencing the thymus weight.

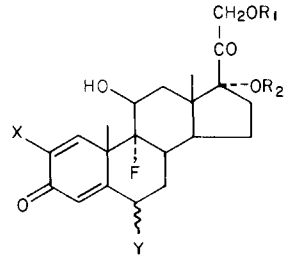
In contrast to the activity profile on topical application, a substantial decrease in oral antiinflammatory and thymolytic activity (Figure 1) was observed by introduction of a halogen atom at C-2 of **27a**. No similar modification resulted from the same C-2 substitution in the corresponding 6α-fluoro compound **30a**. The complete dissociation between topical and oral antiinflammatory activity of **27b** and **27c**, as well as the absence of thymolytic activity on their topical application, makes all diesters of 6β,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (**28a**) halogenated at C-2 potentially topical steroids devoid of systemic effects. At present there is no explanation for the striking difference in biological activity between **27b,c** and **30b,c**. It may only be suggested that the former compounds, due to very low liposolubility, are not easily removed from their original site or very weakly absorbed from the gastrointestinal tract. It may also be speculated that, if they enter the body fluids, they might be firmly bound to proteins or rapidly metabolically inactivated. Experiments are now in progress to confirm or reject these hypotheses.

In additional experiments it was observed that **27b** did not modify sodium retention when given subcutaneously up to a dose of 1 mg/kg body weight. This compound (halopredone acetate),[32] showing the highest topical antiinflammatory activity and devoid of thymolytic activity, was selected for a more extensive pharmacological evaluation and preliminary clinical trials.

Experimental Section

Elemental analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Elbach über Engelskirchen, West Germany. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values. All melting points were taken in open capillary tubes using a Tottoli apparatus (N. Büchi, Flawil, Switzerland) and are uncorrected. Optical rotations were determined at 24–25 °C in 1% (unless otherwise specified) $CHCl_3$ or dioxane solutions with a Schmidt-Haentsch polarimeter. Uv spectra were measured in MeOH (unless otherwise indicated) using a Beckman DU spectrophotometer. Ir spectra were obtained on a Perkin-Elmer 257 spectrophotometer for KBr disks. ^1H NMR spectra were

Table I. 6α,9- and 6β,9-Difluoro-11β-hydroxypregna-1,4-diene-3,20-dione and Their 2-Halogenated Derivatives and Acetyl Esters



Compd	X	Y	R_1	R_2	Crystn solvent[a]	Mp, °C	[α]D, deg	Uv max, nm (ε × 10^{-3})	Yield, %[b]	Formula	Analyses	Granuloma wt inhibn, ED_{30}, μg/pellet	Thymus wt inhibn, ED_{30}, μg/pellet
27a	H	6β-F	$COCH_3$	$COCH_3$	A-B	210-212[c]	−6[d]	241 (12.6)	78	$C_{25}H_{30}F_2O_7$	C, H, F	40	>40
27b	Br	6β-F	$COCH_3$	$COCH_3$	A	290-292[e]	−36[d]	246 (12.5)	69.5	$C_{25}H_{29}BrF_2O_7$	C, H, Br, F	0.01 (0.002-0.045)	>1000
27c	Cl	6β-F	$COCH_3$	$COCH_3$	A	285-286[e,f]	−24[g]	245 (12.7)	85.5	$C_{25}H_{29}ClF_2O_7$	C, H, Cl, F	0.45 (0.1-1.9)	>40
28a	H	6β-F	H	H	C-D	221-222	+20[h]	240 (11.8)	81	$C_{21}H_{26}F_2O_5$	C, H, F	>40	>40
28b	Br	6β-F	H	H	E	228-230[e]	−6[d]	246 (11.7)	67	$C_{21}H_{25}BrF_2O_5$	C, H, Br, F	>40	>40
28c	Cl	6β-F	H	H	E-F	219-221[e]	+5[d]	245 (11.8)	77.5	$C_{21}H_{25}ClF_2O_5$	C, H, Cl, F	>40	>40
29a	H	6β-F	$COCH_3$	H	C-B	218-221	+31[d]	241 (12.3)	86.5	$C_{23}H_{28}F_2O_6$	C, H, F	>40	>40
29b	Br	6β-F	$COCH_3$	H	C-B	194-196[e]	+12[d]	246 (11.8)	86	$C_{23}H_{27}BrF_2O_6$	C, H, Br, F	40	>40
29c	Cl	6β-F	$COCH_3$	H	C-B	225-227[e]	+21[d]	245 (12.1)	72	$C_{23}H_{27}ClF_2O_6$	C, H, Cl, F	9	>40
30a	H	6α-F	$COCH_3$	$COCH_3$	C	284-286[i,j]	+34[k,l]	241 (14.6)	51	$C_{25}H_{30}F_2O_7$		0.10 (0.02-0.42)	5
30b	Br	6α-F	$COCH_3$	$COCH_3$	C-B	246-248[e,m]	+4[d]	247 (13.3)	30.5	$C_{25}H_{29}BrF_2O_7$	C, H, Br, F	>40	>40
30c	Cl	6α-F	$COCH_3$	$COCH_3$	C-B	244-247[e,n]	+10[d]	245 (15.2)	74	$C_{25}H_{29}ClF_2O_7$	C, H, Cl, F	>40	40
31	H	6α-F	H	H	C	248-250[o]	+89[h,p]	240 (14.0)		$C_{21}H_{26}F_2O_5$		40	20
32	H	6α-F	$COCH_3$	H	C-B	233-235[q]	+100[h,r]	240 (15.3)[s]	86	$C_{23}H_{28}F_2O_6$		40	20
Fluocinolone acetonide												1.02 (0.16-6.52)	5

[a] A, C_6H_6; B, hexane; C, MeOH; D, H_2O; E, dichloroethane; F, petroleum ether; G, Me_2CO. [b] No attempts were made to optimize yields. [c] ^1H NMR (Me_2SO-d_6) 350, 300 (dt, 1, C-6 H), 96, 94 Hz (d, 3, C-10 CH_3). [d] Optical rotation was determined in 1% $CHCl_3$ solution. [e] With decomposition. [f] ^1H NMR (Me_2SO-d_6) 452 (s, 1, C-1 H), 390, 386 (d, 1, C-4 H), 346, 296 (dt, 1, C-6 H), 98, 96 Hz (d, 3, C-10 CH_3). [g] Optical rotation was determined in 0.5% $CHCl_3$ solution. [h] Optical rotation was determined in 1% dioxane solution. [i] ^1H NMR (Me_2SO-d_6) 88 Hz (s, 3, C-10 CH_3). [j] Lit.[30] mp 280-283 °C. [k] Optical rotation was determined in 0.4% $CHCl_3$ solution. [l] Lit.[30] [α]D +31° (c 0.5, dioxane). [m] ^1H NMR (Me_2SO-d_6) 360, 310 (dm, 1, C-6 H), 93 Hz (s, 3, C-10 CH_3). [n] ^1H NMR (Me_2SO-d_6) 360, 310 (dm, 1, C-6 H), 92 Hz (s, 3, C-10 CH_3). [o] Lit.[13] mp 250-257 °C. [p] Lit.[13] [α]D +84° (Me_2CO). [q] Lit.[12] mp 224-226 °C. [r] Lit.[12] [α]D +114° (dioxane). [s] Lit.[12] uv max (95% EtOH) 238 nm (ε 15 100).

obtained on a Varian T-60A spectrometer at room temperature in $CDCl_3$ or Me_2SO-d_6 with Me_4Si used as an internal standard. Mass spectra were determined with a LKB Model 9000 mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 210 °C. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck, F-254). "Florisil" refers to magnesium silicates (100–200 mesh) from Floridin Co, Pa.

21-(Acetyloxy)-3,3-(ethylenedioxy)-11α,17-dihydroxypregn-5-en-20-one (11). A mixture of 8 g (0.0198 mol) of 21-(acetyloxy)-11α,17-dihydroxypregn-4-ene-3,20-dione (**10**), 200 ml of C_6H_6, 80 ml of ethylene glycol, and 4.8 g of C_5H_5N·HCl was refluxed for 8 h, collecting the condensate in a Dean-Stark trap packed with about 2 g of anhydrous Na_2SO_4 to remove the water formed in the reaction. After the reaction was completed 200 ml of 5% aqueous $NaHCO_3$ was added, and the mixture was further concentrated until crystals appeared and then poured into cold water. The resulting precipitate was removed by filtration, washed neutral with water, dried, and crystallized from Me_2CO–hexane to yield 6 g (67.5%) of **11**: mp 233–234 °C; $[\alpha]_D$ +12° ($CHCl_3$). Anal. ($C_{25}H_{36}O_7$) C, H.

21-(Acetyloxy)-5α,6α-epoxy-3,3-(ethylenedioxy)-11α,17-dihydroxypregnan-20-one (12). It was prepared by epoxidation of **11** (6 g, 0.0134 mol) in Et_2O with monoperphthalic acid as previously described by Bowers et al.[12] The product was recrystallized from EtOH (72.5%): mp 281–283 °C; $[\alpha]_D$ ±0° (dioxane). Anal. ($C_{25}H_{36}O_8$) C, H.

21-(Acetyloxy)-6β-fluoro-5α,11α,17-trihydroxypregnane-3,20-dione (13). To 45 ml of 70% aqueous HF, contained in a polyethylene flask chilled to −65 °C, was added, with stirring, 4.5 g (0.0097 mol) of **12** in small amounts while maintaining the temperature below −60 °C. The reaction mixture was stirred for 0.5 h and poured into 650 ml of cold water. The solid was dissolved in 400 ml of EtOAc, the solution was washed with 250 ml of 5% aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The crude solid was purified by column chromatography on Florisil (1:50 ratio), using $CHCl_3$–MeOH (99:1) as eluent, to yield 3 g (70.5%) of **13**: mp 223–224 °C; $[\alpha]_D$ +51° ($CHCl_3$); uv max 290 nm (ε 97); ir 3640, 3440 (br), 1745, 1730, 1705, 1230 cm^{-1}. Anal. ($C_{23}H_{33}FO_7$) C, H, F.

21-(Acetyloxy)-2α-bromo-6β-fluoro-5α,11α,17-trihydroxypregnane-3,20-dione (14). A solution of 4 g (0.025 mol) of Br_2 in 50 ml of dioxane was added dropwise at 30 °C over a period of about 3 min to a stirred mixture of 2 g of anhydrous NaOAc, 10 g (0.0227 mol) of **13**, and 100 ml of dioxane. When the addition of Br_2 was completed, the reaction mixture was poured into 1500 ml of a cold 5% aqueous NaCl solution. After stirring for 1 h at room temperature, a white crystalline product was collected by filtration, washed with water, and dried. Several crystallizations from Me_2CO–MeOH–$CHCl_3$ (1:10:20) gave 6 g (51%) of **14**: mp 139–140 °C dec; $[\alpha]_D$ +49° (dioxane); uv max 288 nm (ε 124); ir 3530, 3430, 3250 (br), 1760, 1720, 1220 cm^{-1}. Anal. ($C_{23}H_{32}BrFO_7$) C, H, Br, F. The 2α-iodo analogue was obtained refluxing **14** with NaI in acetone:[15] mp 174–176 °C dec; $[\alpha]_D$ +42° (dioxane); uv max 256 nm (ε 725); ir 3640, 3560, 3430, 1725 (br), 1235 cm^{-1}. Anal. ($C_{23}H_{32}JFO_7$) C, H, I, F.

21-(Acetyloxy)-2α-bromo-6β-fluoro-5α,17-dihydroxy-11α-(methanesulfonyloxy)pregnane-3,20-dione (15). To a solution of 10 g (0.0193 mol) of **14** in 50 ml of anhydrous C_5H_5N was added at −5 °C with stirring over a 20-min period 8 g (0.07 mol) of CH_3SO_2Cl. After 1.5 h at 0 °C, the mixture was poured into 400 ml of cold water and the mesylate **15** was recovered from the reaction mixture with $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated to a syrup under reduced pressure at a bath temperature not exceeding 25 °C. The solid was crystallized many times from C_6H_6 to give 8.9 g (77%) of **15**: mp 122–123 °C dec; $[\alpha]_D$ +47° ($CHCl_3$). Anal. ($C_{24}H_{34}BrFO_9S$) C, H, Br, F, S.

5α,17,21-Tris(acetyloxy)-2α-bromo-6β-fluoro-11α-(methanesulfonyloxy)pregnane-3,20-dione (16). A mixture of 10 g (0.0167 mol) of **15**, 75 ml of Ac_2O, 0.5 ml of 70% $HClO_4$, and 450 ml of EtOAc was stirred at 30 °C for 0.5 h and then washed with 500 ml of 5% aqueous $NaHCO_3$. The EtOAc solution was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. Crystallization of the residue from MeOH gave 9 g (79%) of **16**: mp 131–132 °C dec; $[\alpha]_D$ −12° ($CHCl_3$); uv max 285 nm (ε 104); ir 1740 (br), 1370, 1230 (br), 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 355, 307 (dt, 1, C-6 H), 304–290 (m, 2, C-2 and C-11 H), 300, 284, 278, 262 (dd, 2, $COCH_2O$), 224, 210 (d, 1, C-4 αH), 184 (s, 3, OSO_2CH_3), 124 (s, 6, OAc), 120 (s, 3, OAc), 94, 90 (d, 3, C-10 CH_3), 48 Hz (s, 3, C-13 CH_3). Anal. ($C_{28}H_{38}BrFO_{11}S$) C, H, Br, F, S.

17,21-Bis(acetyloxy)-2,2-dibromo-6β-fluoro-11α-(methanesulfonyloxy)pregn-4-ene-3,20-dione (17). A solution of 15 g of anhydrous NaOAc in 60 ml of HOAc was added at 90 °C to a solution of 6.8 g (0.01 mol) of **16** in 330 ml of HOAc, followed immediately by 1.75 g (0.011 mol) of Br_2 in 25 ml of HOAc, added in one lot. Heating at 90 °C was continued until the Br_2 color disappeared (after ~3 min). The solution was then cooled as rapidly as possible to room temperature and poured into cold water. The solid was collected by filtration, washed thoroughly with water, dried to a constant weight, and crystallized from MeOH to afford 6.5 g (93%) of **17**: mp 140–142 °C dec; $[\alpha]_D$ −18° ($CHCl_3$); uv max 243 nm (ε 10 200); ir 1745, 1730, 1697, 1625, 1340, 1230, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 362, 358 (d, 1, C-4 H), 328, 278 (dt, 1, C-6 H), 320–290 (m, 1, C-11 H), 302, 286, 280, 264 (dd, 2, $COCH_2O$), 228, 212, 204, 188 (dd, 2, C-1 αH and C-1 βH), 190 (s, 3, OSO_2CH_3), 130 (s, 3, OAc), 128 (s, 3, OAc), 108, 104 (d, 3, C-10 CH_3), 52 Hz (s, 3, C-13 CH_3). Anal. ($C_{26}H_{33}Br_2FO_9S$) C, H, Br, F, S.

21-(Acetyloxy)-6β-fluoro-5α,17-dihydroxy-11α-(methanesulfonyloxy)pregnane-3,20-dione (18). Using the general procedure for the preparation of **15**, 10 g (0.0227 mol) of **13** was treated with CH_3SO_2Cl in C_5H_5N to afford, after crystallization from EtOH–H_2O, 8.5 g (72%) of **18**: mp 159–161 °C dec; $[\alpha]_D$ +35° ($CHCl_3$); uv max 288 nm (ε 140). Anal. ($C_{24}H_{35}FO_9S$) C, H, F, S.

3,5α,17,21-Tetrakis(acetyloxy)-6β-fluoro-11α-(methanesulfonyloxy)pregn-2-en-20-one (19). Using the general procedure for the preparation of **16**, 21 g (0.04 mol) of **18** was treated with Ac_2O and 70% $HClO_4$ in EtOAc to yield, after crystallization from MeOH, 25 g (97%) of **19**: mp 135–136 °C dec; $[\alpha]_D$ −27° ($CHCl_3$); uv max 286 nm (ε 103); ir 1755, 1740, 1370, 1235, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 355, 307 (dt, 1, C-6 H), 322–310 (m, 1, C-2 H), 305–296 (m, 1, C-11 H), 300, 284, 278, 262 (dd, 2, $COCH_2O$), 182 (s, 3, OSO_2CH_3), 128 (s, 6, OAc), 124 (s, 3, OAc), 122 (s, 3, OAc), 74, 72 (d, 3, C-10 CH_3), 46 Hz (s, 3, C-13 CH_3). Anal. ($C_{30}H_{41}FO_{12}S$) C, H, F, S.

17,21-Bis(acetyloxy)-6β-fluoropregna-1,4,9(11)-triene-3,-20-dione (24a). Method A (See Scheme I). To a mixture of 34 ml of DMF, 6.8 g of Li_2CO_3, and 3.4 g of LiBr was added under stirring 3 g (0.0044 mol) of **16**. The reaction mixture was then warmed at 130 °C, under N_2 for 1.5 h, cooled, and poured into cold water. The precipitate was filtered off, washed with water, dried to a constant weight, and crystallized from MeOH to afford 1.7 g (87%) of **24a**: mp 227–229 °C; $[\alpha]_D$ −51° ($CHCl_3$); uv max 241 nm (ε 15 400); ir 1755, 1740, 1670, 1630, 1232 cm^{-1}; ^1H NMR (Me_2SO-d_6) 448, 438 (d, 1, C-1 H), 378–360 (m, 2, C-2 and C-4 H), 346, 296 (dt, 1, C-6 H), 340–330 (m, 1, C-11 H), 284 (s, 2, $COCH_2O$), 125 (s, 3, OAc), 121 (s, 3, OAc), 96, 94 (d, 3, C-10 CH_3), 40 Hz (s, 3, C-13 CH_3). Anal. ($C_{25}H_{29}FO_6$) C, H, F.

Method B (See Scheme II). A solution of 4 g (0.0062 mol) of **19** in 50 ml of pure peroxide-free THF was cooled at 15 °C and treated with 4 ml of 0.46 N aqueous $HClO_4$ followed by 2.3 g (0.008 mol) of 1,3-dibromo-5,5-dimethylhydantoin. After stirring 2 h in the dark at 25–30 °C, enough saturated Na_2SO_3 solution was added to the reaction mixture to discharge the excess hypobromous acid. The mixture was poured into cold water and the resulting precipitate was collected by filtration, washed neutral with water, and allowed to air dry. Crystallization from MeOH yielded 3.9 g (92%) of **16**: mp 129–131 °C dec, undepressed with a sample of **16** obtained by Scheme I. Following the above procedure the reaction residue was treated with Li_2CO_3 and LiBr in DMF to afford, after crystallization from MeOH, 2.3 g (83.5%) of **24a**: mp 226–228 °C; $[\alpha]_D$ −50° ($CHCl_3$). The product was identical (ir, uv, and ^1H NMR) with that prepared by the method A.

17,21-Bis(acetyloxy)-2-bromo-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (24b). Method A (See Scheme I). Using the general procedure for the preparation of **24a** (method A), 7 g (0.01 mol) of **17** was converted into 4.8 g (91.5%) of **24b** (crystallized from Me_2CO): mp 270–271 °C dec; $[\alpha]_D$ −89° ($CHCl_3$); uv max

246 nm (ε 12750); ir 1740 (br), 1675, 1645, 1600, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) 452 (s, 1, C-1 H), 376, 372 (d, 1, C-4 H), 342–332 (m, 1, C-11 H), 334, 286 (dt, 1, C-6 H), 300, 284, 278, 262 (dd, 2, $COCH_2O$), 130 (s, 3, OAc), 123 (s, 3, OAc), 94, 92 (d, 3, C-10 CH_3), 45 Hz (s, 3, C-13 CH_3). Anal. ($C_{25}H_{28}BrFO_6$) C, H, Br, F.

Method B (See Scheme II). A solution of 4.4 g (0.0275 mol) of Br_2 in 44 ml of dioxane was added at 20 °C, under stirring, over a period of 30 min, to a solution of 8 g (0.0124 mol) of **19** in 40 ml of dioxane. After addition was completed the mixture was stirred for 20 min, while maintaining the temperature at 20 °C, and then poured into 500 ml of water and 20 g of NaCl. The product was collected by filtration, washed neutral with water, and air-dried, giving 6 g of a ca. 60:40 mixture of **20** and **17**: uv max 241 nm (ε 4300); ir 1740 (br), 1700 (sh), 1370, 1235, 1170 cm^{-1}. By fractionated crystallization from MeOH it was possible to separate analytically pure 5α,17,21-tris(acetyloxy)-2,2-dibromo-6β-fluoro-11α-(methanesulfonyloxy)pregnane-3,20-dione (**20**) [mp 143–145 °C dec; $[\alpha]_D$ +41° ($CHCl_3$); ir 1740 (br), 1700 (sh), 1370, 1235, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 355, 305 (dt, 1, C-6 H), 300, 284, 280, 264 (dd, 2, $COCH_2O$), 304–290 (m, 1, C-11 H), 220–200 (m, 4, C-1 and C-4 H), 188 (s, 3, OSO_2CH_3), 128 (s, 3, OAc), 126 (s, 3, OAc), 120 (s, 3, OAc), 102, 98 (d, 3, C-10 CH_3), 48 Hz (s, 3, C-13 CH_3). Anal. ($C_{28}H_{37}Br_2FO_{11}S$) C, H, Br, F, S] and **17**, identical in all respects with that prepared by method A. The percent composition of the two compounds was determined in the reaction residue by uv spectrum and by integration of the signals at 52 (C-13 CH_3 of **17**) and 48 Hz (C-13 CH_3 of **20**) present in their ^1H NMR spectra after protons bands were identified and assigned. Using the general procedure for the preparation of **24a** (method A), the entire crude mixture of **20** and **17** was converted after crystallization from Me_2CO into 4 g (61.5%) of **24b**: mp 270–272 °C dec, undepressed with a sample obtained by method A. Ir, uv, and ^1H NMR spectra and optical rotation were identical with those of **24b** (method A).

17,21-Bis(acetyloxy)-2-chloro-6β-fluoropregna-1,4,9(11)-triene-3,20-dione (24c). Method B (See Scheme II). A solution of 15.75 g (0.024 mol) of **19** in 180 ml of dioxane containing 3.97 g (0.0506 mol) of Cl_2 was stirred at 5–10 °C for 1 h and then poured into 1000 ml of cold water and 45 g of NaCl. The product was collected by filtration, washed neutral with water, and allowed to air dry giving 14.6 g of a solid. The ^1H NMR spectrum and elemental analysis (Cl: found, 6.65) of the crude reaction mixture showed the presence of 5α,17,21-tris(acetyloxy)-2α-chloro-6β-fluoro-11α-(methanesulfonyloxy)pregnane-3,20-dione (**21**) and 5α,17,21-tris(acetyloxy)-2,2-dichloro-6β-fluoro-11α-(methanesulfonyloxy)pregnane-3,20-dione (**22**) (4:1 ratio). Several crystallizations from MeOH gave 9.7 g (62.5%) of the major compound **21**: mp 134–135 °C dec; $[\alpha]_D$ −10° ($CHCl_3$); uv max 284 nm (ε 120); ir 1740 (br), 1370, 1235, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) 360, 310 (dt, 1, C-6 H), 305, 289, 283, 267 (dd, 2, $COCH_2O$), 190 (s, 3, OSO_2CH_3), 134 (s, 3, OAc), 126 (s, 3, OAc), 100, 96 (d, 3, C-10 CH_3), 54 Hz (s, 3, C-13 CH_3). Anal. ($C_{28}H_{39}ClFO_{11}S$) C, H, Cl, F, S. To the crude mixture of **21** and **22** (14.6 g) dissolved in 500 ml of HOAc was added at 90 °C a solution of 38.5 g of anhydrous NaOAc in 500 ml of HOAc, followed immediately by 20 ml (0.02 mol) of 1 M Cl_2 solution in HOAc, added in one portion. The reaction mixture was stirred at 90 °C for 20 min, cooled at 20 °C, stirred for 0.5 h, and poured into ice–water. The resulting precipitate was collected by filtration and dissolved in $CHCl_3$. The solution was washed with 5% aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated under reduced pressure to give, after crystallization from EtOH, 7 g (75%) of 17,21-bis(acetyloxy)-2,2-dichloro-6β-fluoro-11α-(methanesulfonyloxy)pregn-4-ene-3,20-dione (**23**): mp 173–175 °C dec; $[\alpha]_D$ −12° ($CHCl_3$); uv max 243 nm (ε 11200); ir 1745, 1730, 1710, 1625, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) 364, 360 (d, 1, C-4), 328, 278 (dt, 1, C-6 H), 320–290 (m, 1, C-11 H), 302, 286, 280, 264 (dd, 2, $COCH_2O$), 190 (s, 3, OSO_2CH_3), 130 (s, 3, OAc), 128 (s, 3, OAc), 106, 102 (d, 3, C-10 CH_3), 52 Hz (s, 3, C-13 CH_3). Anal. ($C_{26}H_{33}Cl_2FO_9S$) C, H, Cl, F, S.

Using the general procedure for the preparation of **24a** (method A), 7 g (0.0115 mol) of **23** was converted into 5 g of a crude residue which was purified on Florisil (1:100 ratio) using $CHCl_3$ as eluent. The collected fractions were crystallized from C_6H_6 to afford 4 g (73%) of **24c**: mp 264–266 °C dec; $[\alpha]_D$ −73° ($CHCl_3$); uv max (dioxane) 249 nm (ε 10400); ir 1740, 1680, 1650, 1610, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) 435 (s, 1, C-1 H), 374, 370 (d, 1, C-4 H), 344–334 (m, 1, C-11 H), 330, 280 (dt, 1, C-6 H), 300, 284, 280, 264 (dd, 2, $COCH_2O$), 128 (s, 3, OAc), 122 (s, 3, OAc), 94, 92 (d, 3, C-10 CH_3), 45 Hz (s, 3, C-13 CH_3). Anal. ($C_{25}H_{28}ClFO_6$) C, H, Cl, F.

17,21-Bis(acetyloxy)-2,9-dibromo-6β-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione (25b). To a suspension of 10 g (0.019 mol) of **24b** in 200 ml of pure peroxide-free THF and 10 ml of 0.46 N $HClO_4$ was added in the dark at 25–30 °C, with stirring, over 0.5-h period 7.1 g (0.025 mol) of 1,3-dibromo-5,5-dimethylhydantoin. During the addition the suspension begins to thin and after a total reaction time of 45 min all the starting material was dissolved. After an additional 2 h, 10% aqueous Na_2SO_3 was added under stirring until KI–starch paper no longer turned blue. The solution was slowly poured into cold water. The precipitate was collected by filtration, washed neutral with water, allowed to air dry, and crystallized from Me_2CO–hexane to afford 9.8 g (83%) of **25b**: mp 208–210 °C dec; $[\alpha]_D$ −18° ($CHCl_3$). Anal. ($C_{25}H_{29}Br_2FO_7$) C, H, Br, F.

17,21-Bis(acetyloxy)-9-bromo-6β-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione (25a). Following the above procedure, 4.44 g (0.01 mol) of **24a** was converted to 4.33 g (79%) of **25a**, used crude in the next step.

17,21-Bis(acetyloxy)-9-bromo-2-chloro-6β-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione (25c). Similarly 3.63 g (0.0076 mol) of **24c** was converted to 3.92 g (90%) of **25c**: mp 212–214 °C dec, crystallized from Me_2CO–hexane; $[\alpha]_D$ −11° ($CHCl_3$). Anal. ($C_{25}H_{29}BrClFO_7$) C, H, Br, Cl, F.

17,21-Bis(acetyloxy)-2-bromo-9β,11β-epoxy-6β-fluoropregna-1,4-diene-3,20-dione (26b). A stirred solution of 9.0 g (0.0145 mol) of **25b** in 200 ml of Me_2CO was treated at 20 °C with 40 ml of 14% aqueous K_2CO_3 added dropwise over a period of 20 min. Stirring was continued for 4 h and then ice–water was added, upon which crystallization occurred rapidly. The crystalline material was isolated by filtration, washed neutral with water, and allowed to air dry giving 7.2 g (92%) of **26b**: mp 240–242 °C dec, raised by crystallization from C_6H_6–cyclohexane to 248–249 °C; $[\alpha]_D$ −88° (*c* 0.5, $CHCl_3$); uv max 254 nm (ε 12680). Anal. ($C_{25}H_{28}BrFO_7$) C, H, Br, F.

17,21-Bis(acetyloxy)-9β,11β-epoxy-6β-fluoropregna-1,4-diene-3,20-dione (26a). Following the procedure above described for preparing **26b**, compound **25a** gave **26a** (89%): mp 228–229 °C, crystallized from C_6H_6–hexane; $[\alpha]_D$ −54° ($CHCl_3$). Anal. ($C_{25}H_{29}FO_7$) C, H, F.

17,21-Bis(acetyloxy)-2-chloro-9β,11β-epoxy-6β-fluoropregna-1,4-diene-3,20-dione (26c). Similarly **26c** was obtained in 73% yield: mp 255–256 °C dec, crystallized from C_6H_6–hexane; $[\alpha]_D$ −78° ($CHCl_3$). Anal. ($C_{25}H_{28}ClFO_7$) C, H, Cl, F.

17,21-Bis(acetyloxy)-2-bromo-6β,9-difluoro-11β-hydroxypregna-1,4-diene-3,20-dione (27b) (Table I). According to known procedures,[10,24] treatment of **26b** (10 g, 0.0185 mol) with 70% aqueous HF yielded (69.5%) **27b**, homogeneous on TLC ($CHCl_3$–Me_2CO–cyclohexane, 6:3:2): mp 290–292 °C dec, crystallized from C_6H_6; $[\alpha]_D$ −36° ($CHCl_3$); uv max 246 nm (ε 12500); ir 3520, 1758, 1733, 1705, 1680, 1650, 1610, 1235 cm^{-1}; ^1H NMR (Me_2SO-d_6) 465 (s, 1, C-1 H), 389, 385 (d, 1, C-4 H), 346, 296 (dt, 1, C-6 H), 336, 330 (d, 1, C-11 OH), 285 (s, 2, $COCH_2O$), 264–234 (m, 1, C-11 H), 127 (s, 3, OAc), 122 (s, 3, OAc), 98, 96 (d, 3, C-10 CH_3), 57 Hz (s, 3, C-13 CH_3); mass spectrum *m/e* 560/558 (M^+), 73 (base peak).

2-Bromo-6β,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (28b) (Table I). It was prepared by MeOH–KOH hydrolysis of **27b** (10 g, 0.0179 mol) using standard procedures.[9] The product was obtained in 67% yield after crystallization from dichloroethane: mp 228–230 °C dec; $[\alpha]_D$ −6° ($CHCl_3$); uv max 246 nm (ε 11700); *m/e* 476/474 (M^+), 219/217 (base peak).

21-(Acetyloxy)-2-bromo-6β,9-difluoro-11β,17-dihydroxypregna-1,4-diene-3,20-dione (29b) (Table I). The product was obtained (86%) from **28b** (5 g, 0.0105 mol) in the usual way (anhydrous C_5H_5N–Ac_2O): mp 194–196 °C dec; $[\alpha]_D$ +12° ($CHCl_3$); uv max 246 nm (ε 11800).

17,21-Bis(acetyloxy)-2-chloro-6α,9-difluoro-11β-hydroxypregna-1,4-diene-3,20-dione (30c) (Table I). According to the Schering method,[29] **30c** was obtained from 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (**31**)[13] in 74% yield after crystallization from Me_2CO–hexane: mp 245–247 °C dec;

$[\alpha]_D$ +10° ($CHCl_3$); uv max 245 nm (ε 15 200).

Antiinflammatory Assay. The antiinflammatory action was evaluated in the rat by the cotton-pellet induced granuloma test according to Meier et al.[33] In the test procedure for the evaluation of topical antiinflammatory activity, the compounds suspended in CMC (0.5% of carboxymethylcellulose in water) were applied directly to pellets at different doses up to 40 μg/pellet. Oral activity was measured by giving the compounds suspended in CMC daily for seven consecutive days at different dose levels up to 12.5 mg/kg die. In both oral and topical tests at least eight rats were used for each dose. The granuloma and thymus weights were converted to their relative body weights (mg/100 g body weight). The ED_{30} (dose inhibiting the inflammatory reaction or thymus weight by 30%) was obtained with 95% confidence limits from log dose–response regression lines by the least-squares method. Where regression lines could not be obtained statistically, approximate ED_{30} values were extrapolated from "eye-fit" linear plots of the average results at different doses.

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References and Notes

(1) Trivial names employed are cortisol (11β,17,21-trihydroxypregn-4-ene-3,20-dione), prednisolone (11β,17,21-trihydroxypregna-1,4-diene-3,20-dione), 9-fluoroprednisolone (9-fluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione), and fluocinolone acetonide (16α,17-acetonido-6α,9-difluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione).
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