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Synthesis and Structure–Activity Studies of Corticosteroid 17-Heterocyclic Aromatic Esters. 1. 9α,11β-Dichloro Series

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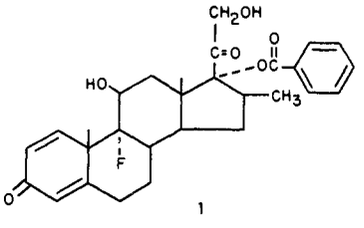
The preparation and topical antiinflammatory potencies of a series of 9α,11β-dichloro-16-methyl corticosteroid 17-heteroaryl carboxylates are described. The 17-acyl group was introduced to the 9α,11β-dichloro 21-acetate by direct acylation with the appropriate heteroaryl carbonyl chloride in the presence of 4-(dimethylamino)pyridine. Alternatively, the 21-functionalized 17-hydroxy $\Delta^{9(11)}$ compound was acylated at 17, followed by C-ring chlorination. The most extensively studied heterocyclic acyl functionality was the 2-furoyl, but the 3-furoyl, and 2- and 3-thenoyl derivatives were also investigated. Antiinflammatory potencies were measured in mice by a 5-day modification of the Tonelli croton oil ear assay. The most potent topical antiinflammatory compounds were 17-heteroaryl esters in the 16α-methyl series where the 21-substituent was chloro or fluoro. Thus **2p** [21-chloro 17-(2′-furoate)] was 8 times as potent as betamethasone valerate, while **2s** [21-fluoro 17-(2′-furoate)], **2r** [21-chloro 17-(2′-thenoate)], and **2v** [6α-fluoro 21-chloro 17-(2′-furoate)] were 3 times as potent as betamethasone valerate.

This paper describes a new class of corticosteroids with high topical antiinflammatory potencies.[1] Some of the compounds described in this paper have shown higher topical antiinflammatory potencies than any other topical corticosteroid tested in our laboratories.

This class of corticosteroids consists of aromatic heterocyclic ester derivatives of the 17-hydroxy function of the side chain. These include furoyl, thenoyl, and pyrrolylcarbonyl esters. The corticosteroids reported here are 9α,11β-dichloro compounds, while the 11-oxygenated analogues will be described elsewhere.

Corticosteroid 17-benzoates have demonstrated substantial topical antiinflammatory potency.[2,3] In particular, betamethasone 17-benzoate (1) has been used in clinical practice for a long time. We anticipated that similar esters



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of furan-, thiophene-, and pyrrolecarboxylic acids would exhibit topical antiinflammatory activity. Accordingly, a variety of these esters were synthesized. The results of

(1) Shapiro, E. L. U. S. Patent 4 472 393, Sept. 18, 1984; *Chem. Abstr.* **1985**, *102*, 95905*k*.
(2) DiPasquale, G.; Rassaert, C. L.; McDougall, E. *Steroids* **1970**, *16*, 679.
(3) Lutsky, B. N.; Berkenkopf, J.; Fernandez, X.; Monahan, M.; Shue, H. J.; Tiberi, R. L.; Green, M. J. *Arzneim.-Forsch.* **1979**, *29*, 1662.

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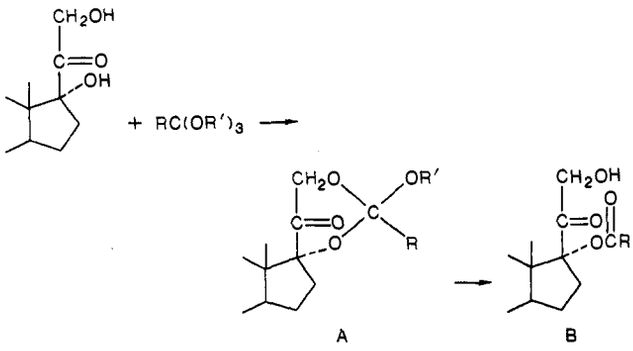
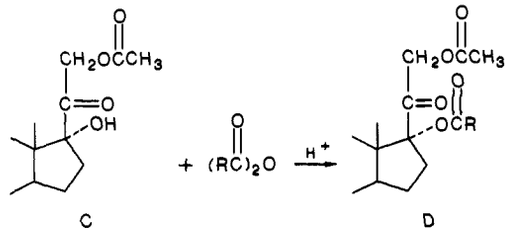
animal studies justified our expectations.

Chemistry

The preparation of a 17-ester derivative of a corticosteroid has been generally effected via the 17,21-(ortho ester) intermediate A, followed by hydrolytic cleavage to the 21-hydroxy 17-ester B[4] (with subsequent 21-esterification, if desired). Alternatively, the 21-ester C under acid



catalysis can be transformed to the 17,21-diester D. Each process suffers from certain disadvantages. The ortho

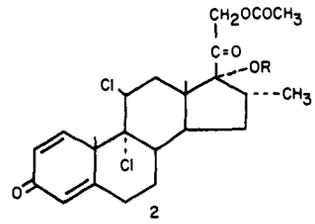


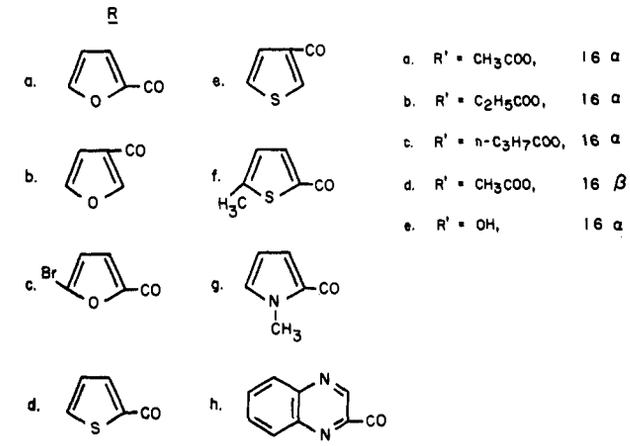
ester process requires the preparation of the appropriate reagent ortho ester, often difficult or inconvenient to prepare. The anhydride/acid catalytic process often leads to undesired rearrangements of the steroid.

In the search for an alternate process that would allow for the rapid synthesis of a large variety of 17-esters, it appeared that a procedure recently published for a specific application[5] might be applied for our purposes. Thus, with the use of the appropriate acid chloride and a nitrogen base such as 4-(dimethylamino)pyridine (4-DMAP), a large number of 17-heteroaromatic esters were prepared.

In the Experimental Section, we outline a generalized process for 17-esterification of 16-methyl substrates, illustrated with 2-furoyl chloride and 4-DMAP in dichloromethane, although other acid chlorides used generally followed this procedure. The yields are generally in the 30–65% range for first-time preparation of the desired esters in the 16α-methyl series. In the 16β-methyl series, uniformly lower yields were experienced.

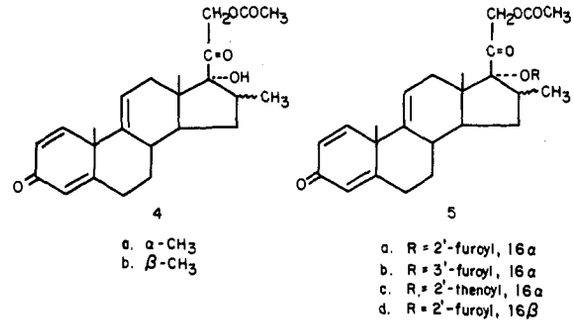
Table I lists the 9α,11β-dichloro 17-esters prepared. These include 2′- and 3′-furoates, 2′- and 3′-thenoates, and two nitrogen-containing heterocyclic carboxylates. Compounds **2a–h** were prepared by reaction with the appropriate acid chloride[6] and 9α,11β-dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-acetate (**3a**).[7] Similarly, **3d**, the 16β-methyl analogue[7] of **3a**, was converted to **2i**.





Selective 21-deacylation of **2a**, **2b**, and **2d** with $HClO_4$–MeOH[8] gave, respectively, the 21-hydroxy **2j**, **2k**, and **2l**. The 17-(2′-furoates) **2m** and **2n** were prepared from the corresponding 21-esters **3b** and **3c**, respectively, by using 2-furoyl chloride.

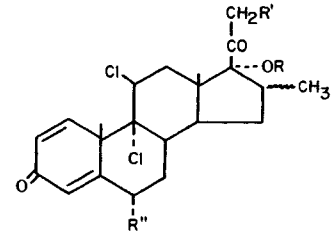
Our next objective was to synthesize the 21-halogenated 17-heterocyclic aromatic esters. Attempts to convert the 21-methanesulfonate derived from **2j** to the 21-chloro **2p** led to gross rearrangements involving the 9,11-dichloro moiety.[9] Therefore, the conversion of the 21-mesylates to 21-halocorticosteroids was carried out on the $\Delta^{9(11)}$ series, and these transformations are depicted in **4** → **5** → **6** → **2**.



The $\Delta^{9(11)}$ compounds **4a**[10] and **4b**[11] were esterified at 17 with the appropriate acid chloride to give the 17-esters **5a–d**, respectively. Selective hydrolysis of the 21-acetate with $HClO_4$–MeOH to **6a–d** followed by treatment with MsCl–pyridine gave the appropriate 21-mesylates, which

(4) Ercoli, A.; Gardi, R. Belgian Patent 619180, Dec. 20, 1962; *Chem. Abstr.* **1963**, *59*, 10187*d*.
(5) Kerb, U.; Stahnke, M.; Wiechert, R. German Patent 2748442, May 3, 1979; *Chem. Abstr.* **1980**, *93*, 168494*h*.
(6) Where not commercially available, the requisite acid chloride was prepared by standard methods ($SOCl_2$, benzene).
(7) Robinson, C. H.; Finckenor, L. E.; Tiberi, R. L.; Oliveto, E. P. *J. Org. Chem.* **1961**, *26*, 2863.
(8) Shapiro, E. L.; Finckenor, L. E.; Pluchet, H.; Weber, L.; Robinson, C. H.; Oliveto, E. P.; Herzog, H. L.; Tabachnick, I. I. A.; Collins, E. J. *Steroids* **1967**, *9*, 143.
(9) Heller, M.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1911.
(10) Oliveto, E. P.; Rausser, R.; Weber, L.; Nussbaum, A. L.; Gebert, W.; Coniglio, C. T.; Hershberg, E. B.; Tolksdorf, S.; Eisler, M.; Perlman, P. L.; Pechet, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 4431.
(11) Oliveto, E. P.; Rausser, R.; Herzog, H. L.; Hershberg, E. B.; Tolksdorf, S.; Eisler, M.; Perlman, P. L.; Pechet, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 6687.

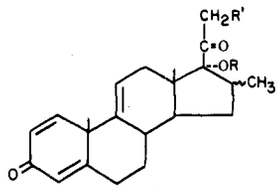
Table I. 9,11-Dichloro Corticosteroid 17α-Heterocyclic Esters[a]



no.	R	R′	R″	C_{16}-CH_3	mp, °C	$[\alpha]^{26}_D$, deg (dioxane)	formula	mol wt	FAB	UV: λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)	topical potency[c] 5 h	topical potency[c] 5 day
2a	2′-furoyl	$OCOCH_3$	H	α	237–241[d]	+65.7	$C_{29}H_{32}O_7Cl_2$	563.46	563	244 (26.3)	1.4 (0.92–1.78)	1.2 (0.74–2.10)
2b	3′-furoyl	$OCOCH_3$	H	α	228–234[d]	+65.7	$C_{29}H_{32}O_7Cl_2$	563.46	563	237 (17.68)	1.3 (0.85–1.92)	1.4 (1.25–1.61)
2c	5′-bromo-2′-furoyl	$OCOCH_3$	H	α	220[d]		$C_{29}H_{31}O_7Cl_2Br$	642.37	641, 643		0.6 (0.58–1.13)	
2d	2-′thenoyl	$OCOCH_3$	H	α	241–243[d]	+55.6	$C_{29}H_{32}O_6Cl_2S$	579.53	579	241 (22.9)	1.3 (1.2–1.4)	0.8 (0.23–1.34)
2e	3′-thenoyl	$OCOCH_3$	H	α	243–246[d]	+57	$C_{29}H_{32}O_6Cl_2S$	579.53	579	238 (22.39)	0.9 (0.35–1.29)	3.2 (2.10–4.27)
2f	5′-methyl-2′-thenoyl	$OCOCH_3$	H	α	205–207	+45.6	$C_{30}H_{34}O_6Cl_2S$	593.55	593	241 (20.57) 277 (14.1)	1.2 (0.98–1.30)	0.56 (0.54–0.58)
2g	1′-methyl-2′-pyrrolyl-carbonyl	$OCOCH_3$	H	α	213–217[d]		$C_{30}H_{35}O_6Cl_2N$	576.50	576	237, 380[b] 243 (47.2)	1.1[e]	
2h	2′-quinoxalinylcarbonyl	$OCOCH_3$	H	α	244–248[d]		$C_{33}H_{34}O_6Cl_2N_2$	625.53	625	284 (3.6) 315 (6.81) 245 (23.34)	0.3 (0.12–0.54)	
2i	2′-furoyl	$OCOCH_3$	H	β	240–242	+118.8	$C_{29}H_{32}O_7Cl_2$	563.46	563	252 (22.94)	1.3 (1.04–1.60)	1.7 (0.81–2.85)
2j	2′-furoyl	OH	H	α			$C_{27}H_{30}O_6Cl_2$	521.42	521	243 (20.91)	0.8 (0.59–1.13)	
2k	3′-furoyl	OH	H	α	185		$C_{27}H_{30}O_6Cl_2$	521.42	521	236 (17.4)	0.7 (0.63–0.78)	
2l	2′-thenoyl	OH	H	α			$C_{27}H_{30}O_5Cl_2S$	537.49	537	241 (22.3)	0.8 (0.68–0.89)	
2m	2′-furoyl	$OCOC_2H_5$	H	α	235–238[d]	+61.4	$C_{30}H_{34}O_7Cl_2$	577.49	577	244 (22.3)	1.1 (0.78–1.42)	0.9[e]
2n	2′-furoyl	$OCOC_3H_7$	H	α	238–244[d]		$C_{31}H_{36}O_7Cl_2$	591.51	591	245 (23.6)	1.0 (0.49–1.23)	
2o	2′-furoyl	$OCOCH_2OCH_3$	H	α	215–220[d]	+59.5	$C_{30}H_{34}O_8Cl_2$	593.49	594	245 (23.3)	1.0 (0.75–1.27)	3.0 (0.34–4.81)
2p	2′-furoyl	Cl	H	α	242–243[d]	+85.8	$C_{27}H_{29}O_5Cl_3$	539.87	540	245 (24.3)	1.9 (0.82–3.20)	8.2 (4.41–13.1)
2q	3′-furoyl	Cl	H	α	224–225[d]		$C_{27}H_{29}O_5Cl_3$	539.87	539	236 (16.3)	1.0 (0.72–1.38)	1.7 (1.18–2.68)
2r	2′-thenoyl	Cl	H	α	253–255	+74.5	$C_{27}H_{29}O_4Cl_3S$	555.94	555	236 (22.4)	0.7 (0.58–0.91)	3.3 (2.55–4.35)
2s	2′-furoyl	F	H	α	266–268[d]	+73	$C_{27}H_{29}O_5Cl_2F$	523.46	523	245 (22.76)	1.8[e]	4.0 (2.55–5.35)
2t	2′-furoyl	Cl	H	β	246–249[d]	+135.9	$C_{27}H_{29}O_5Cl_3$	539.87		245 (23.43)	1.2 (0.66–1.73)	0.8[e]
2u	2′-furoyl	$OCOCH_3$	F	α	240–241[d]	+60.6	$C_{29}H_{31}O_7Cl_2F$	581.45	581	243 (23.8)	3.3 (3.15–3.43)	1.8 (1.46–2.04)
2v	2′-furoyl	Cl	F	α	249[d]	+73.5	$C_{27}H_{28}O_5Cl_3F$	557.86	557	243 (23.0)	2.5 (1.85–3.12)	3.0 (1.23–4.87)
11	betamethasone	17-valerate									1.0 (standard)	1.0 (standard)

[a] NMR and infrared spectra were obtained for all targeted compounds and are in the Experimental Section for selected compounds. Mass spectra (EI) were also taken of all compounds reported, although not listed in this report. Microanalyses were determined for most targeted compounds. However, persistent solvation was experienced with many compounds. [b] Ultraviolet spectrum is qualitative. [c] Statistically derived estimated cumulative potencies relative to betamethasone valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of the pooled estimates. [d] Decomposition. [e] Single assay.

on treatment with LiCl afforded the 21-chloro **6e–h** in good yield.[12] C-ring chlorination to **2p–r** and **2t** was effected



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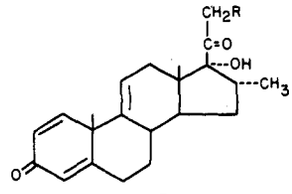
a. R = 2'-furoyl; R' = OH, 16α
b. R = 3'-furoyl; R' = OH, 16α
c. R = 2'-thenoyl; R' = OH, 16α
d. R = 2'-furoyl; R' = OH, 16β
e. R = 2'-furoyl; R' = Cl, 16α
f. R = 3'-furoyl; R' = Cl, 16α
g. R = 2'-thenoyl; R' = Cl, 16α
h. R = 2'-furoyl; R' = Cl, 16β



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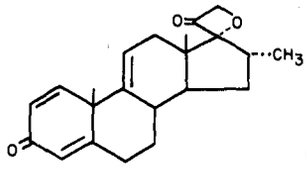
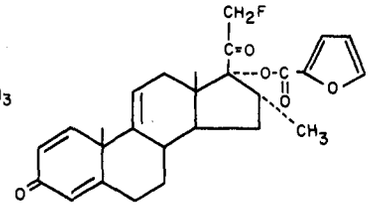
a. R=OH
b. R=F

in a CCl_4–CH_2Cl_2 medium containing Cl_2 and pyridine hydrochloride. Because of the difficulties in converting the 21-mesylate to 21-fluoro in the presence of a 17-ester, the transformation had to be carried out on a 17-hydroxy substrate. Thus, the 21-fluoro **2s** was prepared from the 21-hydroxy **7a** via the mesylate, which was heated with KF in DMF, affording the 21-fluoro **7b** in 70% yield. In the same reaction, the 17,21-oxide **8** was also formed as a by-product.[13] Compound **9** was obtained in 58% yield by using furoic anhydride–DMAP. Chlorination of **9** gave **2s** in 72% yield.

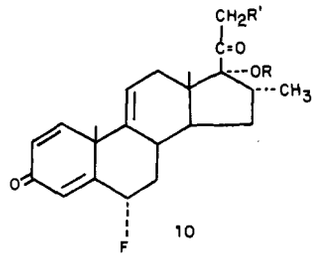
Finally, the 6α-fluoro compounds **2u** and **2v** were prepared by using essentially similar reaction sequences, but commencing with the 6α-fluoro **10a**.[14]



8



9



10

a. R = H, R' = $OCOCH_3$
b. R = 2'-furoyl, R' = $OCOCH_3$
c. R = 2'-furoyl, R' = OH
d. R = 2'-furoyl, R' = -Cl

Esterification of the 17-hydroxy **10a** with 2-furoyl chloride gave **10b**, which on chlorination yielded **2u**. Hydrolysis of the 21-acetate **10b** gave the 21-hydroxy **10c**, which was converted to the 21-chloro **10d** via the 21-mesylate. Chlorination of $\Delta^{9(11)}$ **10d** gave **2v**, in overall yield of 24% from **10b**.

Biological Results and Discussion

Topical antiinflammatory activity was measured by a modification[15] of the croton oil ear assay of Tonelli et al.[16] The topical potencies of the 9,11-dichlorocorticosteroid 17-heterocyclic aromatic esters relative to betamethasone 17-valerate (**11**) are listed in Table I.

For establishing structure–activity relationships, the potencies measured in the 5-day (chronic) assay were used. Since topical corticosteroids are mostly used chronically in clinical practice, the 5-day assay appears to be more relevant. The 5-h assay is, however, useful for identification of lead compounds.

The most potent compounds were 17α-heterocyclic aromatic esters where the 21-substituent was either chloro or fluoro. Thus, in the 16α-methyl series, **2p** [21-chloro 17-(2'-furoate)], **2s** [21-fluoro 17-(2'-furoate)], and **2r** [21-chloro 17-(2'-thenoate)] were found at least 3 times as potent as the standard betamethasone valerate, with **2p** being by far the most potent. The potency-enhancing effect of the 21-halogen carried through to the 6α-fluoro series, where **2v**, the 21-chloro 17-(2'-furoate), was 3 times as potent as the standard.

In the 16α-methyl series 17,21-diesters where the 17-acyl group derived from furan- or thiophenecarboxylic acid, the 21-ester being mostly acetate, the topical antiinflammatory potency was not significantly different from that of betamethasone valerate. The only exceptions were **2o**, the 17-(2'-furoyl) 21-methoxyacetate, and **2e**, the 17-(3'-thenyl) 21-acetate, which were 3 times as potent as the standard.

There was no significant potency-enhancing effect of 17-heterocyclic aromatic esterification in the 16β-methyl series (**2t** and **2i**). This was not surprising, as other esters of 16β-methyldichlorisone have also shown low topical antiinflammatory potencies.[17]

The high topical antiinflammatory potency of the 21-halo 17-heterocyclic aromatic esters **2p**, **2r**, **2s**, and **2v** is somewhat unexpected, as the related 17,21-diesters showed little enhancement of potency over betamethasone valerate. It is known, however, that replacement of a 21-acyloxy function with chlorine can lead to highly potent topical corticosteroids such as the clinically used clobetasol propionate[18] or halcinonide.[19]

Experimental Section

Melting points were taken on either a Hoover melting point capillary apparatus or a Fisher-Johns hot-stage apparatus and are uncorrected. Optical rotations were determined at 26 °C in dioxane. NMR spectra were obtained in Me_2SO-d_6 at 79.5 or 100 MHz on either a Varian CFT-20 or an XL-100-15 spectrometer, respectively, and chemical shifts (δ) are reported in parts per million downfield from an internal $Si(CH_3)_4$ standard in Me_2SO-d_6. Electron ionization (EI) mass spectra were recorded at 70 eV by using a Varian MAT CH5 medium-resolution mass spectrometer at a probe temperature of 160–200 °C and a source temperature of 250 °C. The fast-atom-bombardment (FAB) mass spectra were obtained on a Finnigan MAT-312 mass spectrometer operating at accelerating voltage of 3kV. Silica gel preparative (1000 μM, PLC) and analytical thin-layer chromatography (250 μM, TLC) plates were obtained from Analtech, Inc. Silica gel used for column chromatography was 60–200 mesh, grade 62, supplied by the Davison Chemical Division of Grace, Inc.

Formation of 17-Heterocyclic Aromatic Esters. General

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Procedure. The heterocyclic aromatic carbonyl chloride (or anhydride) and 4-DMAP were mixed with dry CH_2Cl_2 with cooling (0–15 °C). After the mixture was stirred for 10–30 min, the steroid was added at ambient temperature. In general, 1 equiv of steroid, 2 equiv of acid chloride or anhydride, and 4–10 equiv of 4-DMAP were used. Reaction was monitored by TLC and worked up when no further consumption of starting material was observed. The solvent was evaporated and the residue treated with HCl, dilute sodium carbonate, and water, and solids were collected. Alternatively, the reaction mixture was diluted with additional CH_2Cl_2, washed successively with dilute HCl, water, and dilute Na_2CO_3, and then evaporated to a residue. Purification of the residue was by crystallization or by chromatography followed by crystallization.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2a). 2-Furoyl chloride (2 mL, 0.02 mol) was added to a cooled solution of 4-DMAP (12 g, 0.098 mol) in CH_2Cl_2 (62 mL), followed by continued stirring for 30 min. 9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-acetate (**3a**) (4.8 g, 0.0102 mol) was added, and stirring was continued at room temperature for 4 days. The reaction mixture was evaporated to an oily residue, and dilute HCl was added. The resulting solids were collected and washed (water). The solids were stirred with aqueous Na_2CO_3, collected by filtration, dried, and crystallized from CH_2Cl_2–ether to give 3.53 g (61%) of **2a**. An analytical sample was obtained by PLC and crystallization from CH_2Cl_2–Et_2O: NMR 0.91 (16α-CH_3, d, 7 Hz), 1.14 (13-CH_3), 1.68 (10-CH_3), 2.08 (21-$OCOCH_3$), 4.85 and 5.07 (21-CH_2, d's, 17 Hz), 5.04 (11α-H), 6.00 (4-H), 6.28 (2-H, d of d, 10 Hz, 2 Hz), 6.67–6.75 (4′-H, q, 1.8 Hz), 7.17–7.28 (3′-H, m), 7.23 (1-H, d, 10 Hz), 8.00 (5′-H, m).

9α,11β-Dichloro-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2i). 9α,11β-Dichloro-17α,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-acetate (0.47 g) with 2-furoyl chloride gave 0.1 g of **2i**.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(3′-Furoate) 21-Acetate (2b). 9,11-Dichloro **3a** (0.47 g, 1 mmol) with 3-furoyl chloride gave **2b** (59%). Compound **2b** was obtained in 21% yield by using 4-pyrrolidinopyridine instead of 4-DMAP.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(5′-Bromo-2′-furoate) 21-Acetate (2c). Treatment of **3a** (0.47 g) with 5-bromo-2-furoyl chloride with 4-DMAP in CH_2Cl_2 and DMF gave **2c** in 5% yield.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) 21-Acetate (2d). Treatment of **3a** (0.47 g) with 2-thenoyl chloride gave 0.23 g (40%) of **2d**: NMR 0.95 (16α-CH_3, d, 7 Hz), 1.13 (13-CH_3), 1.72 (10-CH_3), 2.07 (21-$OCOCH_3$), 4.77 and 5.08 (21-CH_2, d's, 9 Hz), 5.01 (11α-H), 5.97 (4-H), 6.26 (2-H, d of d, 10 Hz, 2 Hz), 7.11–7.32 (1-H and 4′-H), 7.75 and 7.94 (3′-H and 5′-H).

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(3′-Thenoate) 21-Acetate (2e). Treatment of **3a** (1 g) with 3-thenoyl chloride gave 0.5 g (37%) of **2e**.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(5′-Methyl-2′-thenoate) 21-Acetate (2f). Exposure of **3a** (1 g) to 5-methyl-2-thenoyl chloride gave 0.65 g (53%) of **2f**.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(1′-Methylpyrrole-2′-carboxylate) 21-Acetate (2g). Reaction of **3a** (3 g) with *N*-methylpyrrole 2-carbonyl chloride afforded 14 mg of **2g**: NMR 0.94 (16α-CH_3, d, 6 Hz), 1.18 (13-CH_3), 1.72 (10-CH_3), 2.08 (21-$OCOCH_3$), 3.78 (N-CH_3), 4.82–5.14 (21-CH_2, br), 6.00 (4-H), 6.18 (2-H, d of d, 10 Hz, 2 Hz), centered at 6.13, 6.9, 7.14 (pyrrol H's, br m's), 7.28 (1-H, d, 10 Hz).

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Quinoxalinoate) 21-Acetate (2h). Compound **3a** (0.23 g) with 2-quinoxalinecarbonyl chloride afforded 54 mg (18%) of **2h**.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2j). The 17-(2′-furoate) 21-acetate **2a** (0.0563 g) was treated with 70% $HClO_4$ (0.1 mL) in MeOH (3.5 mL) at 0–5 **C** for 24 h, followed by 3 h at room temperature. After aqueous workup followed by EtOAc extraction, the product was purified by chromatography (PLC), affording **2j** (47%), which was solidified with ether–hexane.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(3′-Furoate) (2k). Similarly to the preparation of **2j**, the 21-acetate **2b** (0.1 g) with 70% $HClO_4$ in MeOH gave 53 mg (60%) of **2k**, crystallized from CH_2Cl_2–ether–hexane.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) (2l). Similarly to the formation of **2j**, the 21-acetate **2d** (0.060 g) was exposed to 70% $HClO_4$ in MeOH to give **2l** in 70% yield, solidified from ether–hexane.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Propionate (2m). 21-Propionate **3b** (0.24 g, 0.5 mmol), prepared from the 21-hydroxy **3e** with propionyl chloride, was treated with 2-furoyl chloride (0.1 mL) as in the general procedure to give **2m** (41%), with soldification from ether.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Butyrate (2n). 21-Butyrate **3c** (0.249 g, 0.5 mmol), prepared from the 21-hydroxy **3e** with butyryl chloride, was treated with 2-furoyl chloride as in the general procedure to give **2n** (33%), with solidification from ether.

9α,11β-Dichloro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Methoxyacetate (2o). Methoxyacetyl chloride (0.15 mL, 1.64 mmol), pyridine (5 mL), and 21-hydroxy **2j** (0.521 g, 1 mmol) were mixed at 0–5 °C and then held at room temperature for 3 h. Aqueous workup and purification on PLC ($CHCl_3$–EtOAc, 9:1) gave 0.465 g (82%) of **2o** crystallized from CH_2Cl_2–hexane.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) 21-Acetate (5a). 17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 21-acetate (**4a**) (9.96 g, 25 mmol) was treated with 2-furoyl chloride as in the general procedure to afford **5a** (44%), crystallized from CH_2Cl_2–Et_2O. Another experiment afforded a 68% yield of **5a**.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(3′-Furoate) 21-Acetate (5b). Five grams (10.6 mmol) of **4a** with 3-furoyl chloride as in the general procedure gave 2.94 g of **5b**, with solidification from EtOAc–hexane.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Thenoate) 21-Acetate (5c). Five grams (10.6 mmol) of **4a** with 2-thenoyl chloride as in the general procedure gave **5c** (41%) solidified from EtOAc–hexane.

17α,21-Dihydroxy-16β-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) 21-Acetate (5d). Five grams (10.6 mmol) of 17α,21-dihydroxy-16β-methyl-1,4,9(11)-pregnatriene-3,20-dione 21-acetate (**4b**) with 2-furoyl chloride as in the general procedure gave 0.85 g of **5d**, with solidification from EtOAc–hexane.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) (6a). Similarly to the preparation of **2j**, compound **5a** (4.47 g, 9.1 mmol) was exposed to 70% $HClO_4$ in MeOH to give **6a** (80%), crystallized from EtOAc–hexane.

21-Chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) (6e). 21-Hydroxy **6a** (3 g, 6.7 mmol), pyridine (43 mL), and CH_3SO_2Cl (5.1 mL) were mixed at 0–2 °C and after 90 min added to ice water. The resulting precipitate was collected, yielding 3.63 g of essentially pure 21-mesylate. The mesylate (0.5 g, 0.9 mmol) and LiCl (0.5 g) were heated in DMF (5 mL) at 80 °C for 7 h. The reaction mixture was added to saturated NaCl solution, and the resultant precipitate was collected. Purification via PLC ($CHCl_3$–EtOAc, 19:1) gave **6e**, 0.35 g, with solidification from ether–hexane, mp 229–232 °C dec.

17α-Hydroxy-16α-methyl-9α,11β,21-trichloro-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2p). A CCl_4 solution of chlorine (5.88 mmol of Cl_2/3.26 mL of CCl_4) was added to a solution of **6e** (2.3 g, 4.9 mmol) and pyridine hydrochloride (1.43 g, 12.3 mmol) in CH_2Cl_2 (37 mL) at −35 °C over 20 min. Workup by evaporation gave a residue of **2p**, 2.71 g (trace impurities by TLC). Crystallization of a 0.30-g portion from CH_2Cl_2–ether gave 0.22 g of **2p**.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(3′-Furoate) (6b). Similarly to the preparation of **2j**, 2.73 g (5.54 mmol) of **5b** was treated with $HClO_4$ in MeOH, affording **6b** (trace impurities), which was used directly in the 21-mesylate formation.

21-Chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(3′-Furoate) (6f). As in the preparation of

6e, mesyl chloride with **6b** (2.3 g) afforded the crude mesylate (2.6 g). A 2.44-g portion of the mesylate with LiCl gave 2.26 g of crude **6f**. A 0.3-g portion was purified by PLC ($CHCl_3$–EtOAc, 19:1), affording 0.22 g of pure **6f**, solidified from ether.

17α-Hydroxy-16α-methyl-9α,11β,21-trichloro-1,4-pregnadiene-3,20-dione 17-(3′-Furoate) (2q). As in the preparation of **2p**, 21-chloro **6f** (0.25 g, 0.46 mmol) with chlorine gave 64% of trichloro **2q** with PLC ($CHCl_3$–EtOAc, 39:1), with crystallization from CH_2Cl_2–hexane.

17α,21-Dihydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Thenoate) (6c). The 17-(2′-thenoate) 21-acetate **5c** (2.56 g, 5 mmol), as in preparation of **6a** with $HClO_4$ in MeOH, afforded **6c** (2.35 g, 98%), which by TLC revealed only trace impurities and was used directly in the mesylation step.

21-Chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Thenoate) (6g). As in the preparation of **6e**, 21-hydroxy **6c** (2.34 g) with mesyl chloride gave 2.43 g of crude mesylate. A 2.28-g portion of the mesylate with LiCl gave crude **6g**, which, after purification by PLC and crystallization from CH_2Cl_2–ether, gave **6g** (1.7 g).

17α-Hydroxy-16α-methyl-9α,11β,21-trichloro-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) (2r). 21-Chloro **6g** (0.37 g) was reacted with chlorine as in the preparation of **2p**, giving 0.35 g (83%) of **2r**, with crystallization from CH_2Cl_2–hexane.

17α,21-Dihydroxy-16β-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) (6d). The 17-(2′-furoate) 21-acetate **5d** (0.74 g) was mixed with $HClO_4$ in MeOH, as described for the preparation of **6a**, to afford crude **6d** (0.393 g), which was used directly for 21-mesylation.

21-Chloro-17α-hydroxy-16β-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-Furoate) (6h). As in the preparation of **6e**, 21-hydroxy **6d** (0.36 g) with mesyl chloride gave crude mesylate (0.43 g). Lithium chloride and the crude mesylate (0.39 g) gave crude **6h**. PLC purification gave **6h** (0.24 g).

17α-Hydroxy-16β-methyl-9α,11β,21-trichloro-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2t). Compound **6h** (0.338 g, 0.49 mmol) was treated with chlorine as in the preparation of **2p** to afford **2t** (0.164 g, 63%), crystallized from CH_2Cl_2–hexane.

9α,11β-Dichloro-21-fluoro-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2s). The 17-hydroxy **7a**[20] (0.98 g, 2.75 mmol) with methanesulfonyl chloride gave the 21-mesylate (1 g, 85%) after purification by PLC and solidification from ether. A portion of the mesylate (0.43 g, 1 mmol) and KF (0.29 g, 5 mmol) in DMF (10 mL) were heated at 124 °C for 4 h. The solvent was evaporated and the residue triturated with water. The solids were purified by PLC, and evaporation from EtOAc gave 21-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione (**7b**) (0.25 g, 70%). Also isolated was 17% of 17,21-oxide **8**.

A mixture of **7b** (0.017 g, 0.04 mmol), 2-furoyl chloride (0.02 mL, 0.2 mmol), and 4-DMAP (0.057 g, 0.47 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 40 °C for 27 h. Workup in the usual manner and purification via PLC followed by solidification from ether–hexane gave 21-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**9**) in 23% yield. The reaction when carried out with 2-furoic anhydride[21] at ambient temperature for 20 h gave **9** in 58% yield.

As in the preparation of **2p**, 21-fluoro **9** (0.34 g, 0.75 mmol) when treated with chlorine afforded, after the usual isolation and PLC purification, **2s** (0.28 g, 72%).

9α,11β-Dichloro-17α,21-dihydroxy-6α-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2u). As outlined in the general procedure, 9 g of 17α,21-dihydroxy-6α-fluoro-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 21-acetate (**10a**) with 2-furoyl chloride and 4-DMAP gave, after purification via descending silica gel G-60 chromatography (hexane–EtOAc, 2:1) **10b** (5.8 g, 53%), crystallized from CH_2Cl_2–Et_2O.

A portion of **10b** (0.5 g, 0.98 mmol) with chlorine gave **2u** (0.41 g, 70%), crystallized from CH_2Cl_2–Et_2O.

6α-Fluoro-17α-hydroxy-16α-methyl-9α,11β,21-trichloro-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2v). Similarly to the preparation of **6a**, the 21-acetate **10b** (5.2 g) was selectively hydrolyzed with $HClO_4$ in MeOH to give the 21-hydroxy 17-(2′-furoate) **10c** (4.69 g), essentially one component by TLC.

A portion of **10c** (4.4 g) was treated similarly as in the preparation of **6e** with mesyl chloride to afford the crude 21-mesylate (5.5 g), which with LiCl gave 21-chloro-6α-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**10d**), used directly in the next step. Via the procedure for the preparation of **2p**, treatment of **10d** (3 g) with chlorine gave 1.47 g of crude **2v**. Purification of 700 mg with PLC gave **2v** (490 mg, 24% from **10b**).

Acknowledgment. We thank Dr. Mohinder Puar for helpful discussions concerning interpretation of NMR spectra and Dr. Birendra Pramanik and Peter Bartner for helpful discussions concerning interpretation of mass spectral data. We also thank Mrs. Pier for expert typing of the text.

Registry No. **2a**, 83880-57-3; **2b**, 83880-59-5; **2c**, 83899-77-8; **2d**, 83897-04-5; **2e**, 107742-62-1; **2f**, 83880-82-4; **2g**, 83880-84-6; **2h**, 107742-63-2; **2i**, 83880-58-4; **2j**, 83880-98-2; **2k**, 83881-11-2; **2l**, 83880-96-0; **2m**, 83880-60-8; **2n**, 107742-64-3; **2o**, 83880-99-3; **2p**, 83880-66-4; **2q**, 83880-68-6; **2r**, 94838-09-2; **2s**, 83881-12-3; **2t**, 83880-67-5; **2u**, 83880-88-0; **2v**, 83880-92-6; **3a**, 27031-76-1; **3b**, 14647-98-4; **3c**, 107742-65-4; **3d**, 73082-60-7; **3e**, 4732-48-3; **4a**, 10106-41-9; **4b**, 910-99-6; **5a**, 83880-61-9; **5b**, 107742-66-5; **5c**, 107742-67-6; **5d**, 107742-68-7; **6a**, 83880-62-0; **6a** 21-mesylate, 83880-63-1; **6b**, 107768-20-7; **6b** mesylate, 107742-69-8; **6c**, 107742-70-1; **6c** mesyl chloride, 107798-05-0; **6d**, 107742-71-2; **6d** mesylate, 83880-64-2; **6e**, 83880-65-3; **6f**, 107742-72-3; **6g**, 107742-73-4; **6h**, 94813-59-9; **7a**, 13209-41-1; **7a** 21-mesylate, 23776-75-2; **7b**, 83881-00-9; **8**, 107742-74-5; **9**, 83881-01-0; **10a**, 19788-77-3; **10b**, 83880-87-9; **10c**, 83880-89-1; **10c** 21-mesylate, 83880-90-4; **10d**, 83880-91-5; 2-furoyl chloride, 527-69-5; 3-furoyl chloride, 26214-65-3; 5-bromo-2-furoyl chloride, 26726-16-9; 2-thenoyl chloride, 5271-67-0; 3-thenoyl chloride, 41507-35-1; 5-methyl-2-thenoyl chloride, 31555-59-6; *N*-methylpyrole-2-carbonyl chloride, 26214-68-6; 2-quinoxalinecarbonyl chloride, 54745-92-5; propionyl chloride, 79-03-8; butyryl chloride, 141-75-3; methoxyacetyl chloride, 38870-89-2; 2-furoic anhydride, 615-08-7.

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