of the hydrochloride salt began. Recrystallization from MeOH/EtOAc gave the pure monohydrochloride of compound **9** (3.08 g, 85%), mp 268 °C dec. Anal. (Table III).

The other compounds were prepared similarly. In cases where the monohydrochloride salt was not crystalline, recrystallization from MeOH/EtOAc/HCl gave the crystalline dihydrochloride salts (see Table II). Many of the compounds were hygroscopic and crystallized as hydrates.

Acknowledgment. This work was supported by the Auckland Division of the Cancer Society of New Zealand and the Medical Research Council of New Zealand. We thank Cherry Grimwade, Susan O'Rourke, and Kareen Clingin for assistance with antitumor testing, Claudia Bos for physicochemical measurements, and Margaret Snow for preparation of the manuscript.

Registry No. **1**, 51264-14-3; **3**, 88412-78-6; **4**, 88412-94-6; **5**, 108835-44-5; **5**·HCl, 108835-45-6; **6**, 108835-46-7; **6**·HCl, 108835-47-8; **7**, 108835-48-9; **7**·HCl, 108835-49-0; **8**, 90125-87-4; **8**·HCl, 108835-50-3; **9**, 88914-50-5; **9**·HCl, 88913-92-2; **10**, 88914-59-4; **10**·HCl, 88914-01-6; **11**, 82720-41-0; **12**, 88914-47-0; **12**·HCl, 88913-89-7; **13**, 108835-51-4; **13**·HCl, 108835-52-5; **14**, 108835-53-6; **14**·HCl, 108835-54-7; **15**, 88914-53-8; **15**·HCl, 88913-95-5; **16**, 88914-54-9; **16**·HCl, 88913-96-6; **17**, 88914-55-0; **17**·HCl, 88913-97-7; **18**, 108868-10-6; **18**·2HCl, 108835-55-8; **19**, 88914-52-7; **19**·HCl, 88913-94-4; **20**, 108835-56-9; **20**·HCl, 108835-57-0; **21**, 108835-58-1; **21**·HCl, 108835-59-2; **22**, 108835-60-5; **22**·HCl, 108835-61-6; **23**, 108835-62-7; **23**·HCl, 108835-63-8; **24**, 88914-58-3; **24**·2HCl, 88914-00-5; **25**, 108835-64-9; **25**·2HCl, 108835-65-0; **26**, 108835-66-1; **26**·HCl, 108835-67-2; **27**, 108835-68-3; **27**·2HCl, 108835-69-4; **28**, 108835-70-7; **28**·HCl, 108835-71-8; **29**, 88914-56-1; **29**·2HCl, 88913-98-8; **30**, 88914-57-2; **31**, 108835-72-9; **31**·HCl, 108835-73-0; **32**, 108835-74-1; **32**·2HCl, 108835-75-2; **33**, 108835-76-3; **33**·2HCl, 108835-77-4; **34**, 108835-78-5; **34**·2HCl, 108835-79-6; **35**, 108835-80-9; **35**·2HCl, 108835-81-0; **36**, 108835-82-1; **36**·2HCl, 108835-83-2; **37**, 108835-84-3; **37**·HCl, 108835-85-4; **38**, 108835-86-5; **38**·HCl, 108835-87-6; **39**, 108835-88-7; **39**·HCl, 108835-89-8; **40**, 108835-90-1; **40**·HCl, 108835-91-2; I, 55851-38-2; IIb, 108835-92-3; IIc, 108835-93-4; IV, 88914-75-4; Vb, 88914-83-4; Vc, 88914-78-7; 2-MeO-4-$NH_2C_6H_3NHCOPr$, 59988-64-6; 3-MeO-4$NHCoPrC_6H_3NHCO_2Me$, 88149-78-4; 3-NHMe-4-$NO_2C_6H_3NHCO_2Me$, 108835-94-5; 2-OMe-4-$NHAcC_6H_3NH_2$, 93973-25-2; 2-NHMe-4-$NHAcC_6H_3NH_2$, 108835-95-6; 2-NMe_2-4-$NHAcC_6H_3NH_2$, 108835-96-7; 3-OMe-4-$NH_2C_6H_3NHP(O)(OMe)_2$, 86187-37-3; MeOP(O)BrOMe, 24167-74-6; 3-Me_2N-4-$NH_2C_6H_3NHCO_2Me$, 88915-02-0; 3-N(Me)CH_2Ph-4-$NH_2C_6H_3NHP(O)(OMe)_2$, 108835-97-8; 3-NMe_2-4-$NH_2C_6H_3NHP(O)(OMe)_2$, 108835-98-9; 3-NHMe-4-$NH_2C_6H_3NHCO_2Me$, 88914-84-5; 9-chloroacridine, 1207-69-8; 9-chloro-2-methylacridine, 16492-09-4; 9-chloro-3-fluoroacridine, 2377-16-4; 3,9-dichloroacridine, 35547-70-7; 3-bromo-9-chloroacridine, 35547-72-9; 9-chloro-3-iodoacridine, 88914-90-3; 9-chloro-3-methylacridine, 16492-10-7; 9-chloro-3-methoxyacridine, 16492-14-1; 9-chloro-3-nitroacridine, 1744-91-8; 9-chloro-4-fluoroacridine, 3829-32-1; 4,9-dichloroacridine, 10166-44-6; 9-chloro-4-methylacridine, 16492-11-8; 9-chloro-4-methoxyacridine, 16492-15-2; 9-chloro-4-aminocarbonylacridine, 63178-96-1; 9-chloro-4-[(methylamino)carbonyl]acridine, 63178-97-2; 9-chloro-3-fluoro-5-methylacridine, 88914-95-8; 3,9-dichloro-5-methylacridine, 88914-96-9; 3-bromo-9-chloro-5-methylacridine, 88914-98-1; 9-chloro-3,5-dimethylacridine, 88914-93-6; 9-chloro-3-methoxy-5-methylacridine, 88914-94-7; 9-chloro-3-fluoro-5-methoxyacridine, 102940-93-2; 3,9-dichloro-5-methoxyacridine, 88914-97-0; 3-bromo-9-chloro-5-methoxyacridine, 6534-56-1; 9-chloro-3-methyl-5-methoxyacridine, 88914-99-2; 9-chloro-4,5-dimethylacridine, 63345-58-4; 9-chloro-4,5-dimetoxyacridine, 89784-84-9; 9-chloro-4-methyl-5-[(methylamino)carbonyl]acridine, 88915-00-8; 9-chloro-4-methoxy-5-[(methylamino)carbonyl]-acridine, 88377-34-8.

17-Heteroaroyl Esters of Corticosteroids. 2. 11β-Hydroxy Series

Elliot L. Shapiro,* Margaret J. Gentles, Robert L. Tiberi, Thomas L. Popper,* Joseph Berkenkopf, Barry Lutsky, and Arthur S. Watnick

Pharmaceutical Research Division, Schering-Plough Corporation, Bloomfield, New Jersey 07003. *Received September 18, 1986*

The preparation and topical antiinflammatory potencies of a series of 17-furoyl and -thenoyl esters of 9α-fluoro-11β-hydroxy-16-methyl and 9α-chloro-11β-hydroxy-16-methyl corticosteroids are described. The 17α-esters were introduced to the 9α-fluoro 11-ketones or to the appropriate $\Delta^{9(11)}$ compounds by direct acylation with the appropriate heteroaryl carbonyl chloride in the presence of 4-(dimethylamino)pyridine. Functionalization of the C ring was completed by standard methods. The most extensively studied heterocyclic acyl group was 2-furoyl, but 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 agents were **1e**, dexamethasone 17-(2′-furoate) 21-propionate, and **2c**, the 21-chloro 17-(2′-furoate) in the 9α-chloro series, both being 6 times as potent as betamethasone 17-valerate. Several other 9α-chloro-11β-hydroxy-17-heteroaryl carboxylates (**2a**, **2b**, **2d**, and **2g**) were at least 4 times as potent as betamethasone 17-valerate. Evaluation of **2c** in the clinic confirmed that the compound is a potent topical antiinflammatory agent in humans.

In this paper we describe a new class of topical corticosteroids bearing 17-heteroaryl ester groups.[1] The preceding publication focused on 9α,11β-dichloro corticosteroids;[2] herein described are their 11β-oxygenated counterparts. The 17-position has been functionalized with furoyl and thenoyl esters. As introduction of the 17-heteroaromatic ester groups resulted in high topical antiinflammatory potencies in the 9,11-dichloro series,[2] we expected high topical antiinflammatory potencies in the 11β-hydroxy series. The potency in this class of 17-esters was generally high, and some of the compounds exceeded the potency of the most potent topical corticosteroids tested in our laboratories. The 9α-fluorinated compounds are delineated in Table I, while the 9α-chloro and 9-unsubstituted compounds are in Table II, with appropriate substitution at positions 6, 16, and 21.

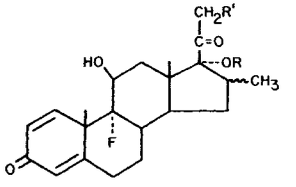
Chemistry

In the preceding paper we reported a process utilizing direct esterification of the 17-hydroxy group with the ap-

(1) Shapiro, E. L. U.S. Patent 4472393, Sept 18, 1984; *Chem. Abstr.* **1985**, *102*, 95905*k*.
(2) Shapiro, E. L.; Gentles, M. J.; Tiberi, R. L.; Popper, T. L.; Berkenkopf, J.; Lutsky, B.; Watnick, A. S. *J. Med. Chem.* **1987**, *30*, 1068.

0022-2623/87/1830-1581$01.50/0

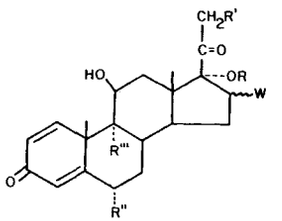
Table I. 9α-Fluoro-11β-hydroxy Corticosteroid 17α-Heterocyclic Esters[a]



no.	R	R′	C_{16}-CH_3	mp, °C	$[\alpha]^{26}_D$, deg (dioxane)	formula	mol wt	FAB (M + 1)	UV: λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)	topical potency[b] 5 h	topical potency[b] 5 day
1a	2′-furoyl	$OCOCH_3$	α	238–239	+0.9	$C_{29}H_{33}O_8F$	528.55	529	247 (25.89)	1.7 (1.04–2.11)	2.2 (1.53–2.90)
1b	2′-furoyl	$OCOCH_3$	β	241–243	+68.1	$C_{29}H_{33}O_8F$	528.55	529	248 (25.5)	0.5 (0.37–0.72)	0.2 (0.19–0.28)
1c	3′-furoyl	$OCOCH_3$	α	214–217	+9.0	$C_{29}H_{33}O_8F$	528.55	529	234 (16.78)	2.9 (0.69–7.40)	3.2 (1.45–4.64)
1d	2′-thenoyl	$OCOCH_3$	α	245–247[c]	−1.0	$C_{29}H_{33}O_7SF$	544.63	545	242 (22.31)	1.6 (0.65–3.99)	2.9 (2.23–3.84)
1e	2′-furoyl	$OCOC_2H_5$	α	226–228[c]	+3.3	$C_{30}H_{35}O_8F$	542.58	543	246 (26.30)	2.1 (0.93–3.67)	6.8 (4.24–9.19)
1f	2′-furoyl	$OCOC_3H_7$	α	235	+2.2	$C_{31}H_{37}O_8F$	556.61	557	247 (26.39)	1.1 (1.11–1.14)	–
1g	2′-furoyl	$OCOCH_2OCH_3$	α	180–208[f]	–	$C_{30}H_{35}O_9F$	558.58	559	246 (24.96)	0.8 (0.36–1.30)	3.2 (2.53–3.55)
1h	2′-furoyl	Cl	α	224–227[c]	+25.8	$C_{27}H_{30}O_6FCl$	504.97	505	247 (26.21)	1.6 (1.03–2.73)	2.3 (1.26–3.77)
1i	2′-furoyl	Cl	β	209–211	+82.8	$C_{27}H_{30}O_6FCl$	504.97	505	248 (24.8)	0.6 (0.42–0.77)	0.9[d]
1j	3′-furoyl	Cl	α	226–228	+36.9	$C_{27}H_{30}O_6FCl$	504.97	505	238 (18.4)	1.0 (1.0)	1.2 (0.83–1.54)
1k	2′-thenoyl	Cl	α	242–244[c]	+27.6	$C_{27}H_{30}O_5SFCl$	521.04	521	243 (24.46)	1.3 (0.89–1.71)	2.6 (1.46–3.82)
1l[e]	3′-furoyl	Cl	α	208–210	+86.2	$C_{27}H_{28}O_6FCl$	502.95	503	237 (18.57)	0.6 (0.54–0.75)	1.7[d]
1m	2′-furoyl	$OCOCH_3$	$=CH_2$	217–218	−44.8	$C_{29}H_{31}O_8F$	526.54	527	245 (25.27)	0.5[d]	1.1 (0.41–1.92)
1n	5′-methyl-2′-thenoyl	$OCOCH_3$	α	215–220[c]	−6.1	$C_{30}H_{35}O_7SF$	558.65	559	244 (21.77) 277 (13.45)	2.4 (1.62–3.09)	1.7 (1.18–2.12)
20	betamethasone 17-valerate									1.0 (standard)	1.0 (standard)

[a] NMR and infrared spectra were obtained for all targeted compounds, and NMR spectral data 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] Statistically derived estimated cumulative potencies relative to betamethasone valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of the pooled estimates. [c] Decomposition. [d] Single assay. [e] 11-Ketone. [f] Indeterminant.

Table II. 9α-Chloro-11β-hydroxy and 9-Unsubstituted 11β-Hydroxy Corticosteroid 17α-Heterocyclic Esters[a]



no.	R	R′	R″	R‴	W	mp, °C	$[\alpha]^{26}_D$, deg (dioxane)	formula	mol wt	FAB (M + 1)	UV: λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)	topical potency[b] 5 h	topical potency[b] 5 day
2a	2′-furoyl	$OCOCH_3$	H	Cl	α-CH_3	254–255	+25.9	$C_{29}H_{33}O_8Cl$	545.01	545	247 (23.32)	1.7 (1.49–1.82)	4.4 (1.28–7.82)
2b	2′-furoyl	$OCOCH_2OCH_3$	H	Cl	α-CH_3	247–249[c]	+33.6	$C_{30}H_{35}O_9Cl$	575.04	575	247 (25.68)	–	4.3 (0.88–7.90)
2c	2′-furoyl	Cl	H	Cl	α-CH_3	218–220	+58.3	$C_{27}H_{30}O_6Cl_2$	521.42	521	247 (26.3)	1.0 (0.99–1.05)	6.1 (2.50–11.55)
2d	2′-thenoyl	Cl	H	Cl	α-CH_3	245[c]	+49.0	$C_{27}H_{30}O_5Cl_2S$	537.49	537	243 (23.5)	1.2 (1.15–1.26)	4.5 (3.40–5.52)
2e	2′-furoyl	F	H	Cl	α-CH_3	281–282[c]	+32.2	$C_{27}H_{30}O_6ClF$	504.96	505	–	1.4[d]	4.4 (2.36–7.67)
2f	2′-furoyl	$OCOCH_3$	F	H	α-CH_3	–	−1.4	$C_{29}H_{33}O_8F$	528.55	–	247 (27.80)	2.7 (1.62–3.43)	2.1 (1.10–3.07)
2g	2′-furoyl	Cl	F	Cl	α-CH_3	–	–	$C_{27}H_{29}O_6Cl_2F$	539.41	–	245 (24.78)	1.1 (0.70–1.37)	5.1 (4.50–5.70)
2h	2′-furoyl	$OCOCH_3$	H	H	$=CH_2$	161–163	−50.9	$C_{29}H_{32}O_8$	508.55	509	–	2.7 (0.84–5.09)	1.2 (0.58–2.20)
2i	2′-furoyl	$OCOCH_3$	H	Cl	$=CH_2$	210[c]	−15.4	$C_{29}H_{31}O_8Cl$	543.00	543	246 (24.37)	2.3[d]	2.2 (2.01–2.48)
2j	2′-furoyl	$OCOC_2H_5$	H	H	α-CH_3	205–207	+1.0	$C_{30}H_{36}O_8$	524.59	525	250 (25.83)	1.1[d]	1.5 (0.94–2.06)
2k	2′-furoyl	$OCOCH_3$	H	H	H	221–222	+22.9	$C_{28}H_{32}O_8$	496.54	–	249 (26.51)	1.3 (0.90–1.87)	0.9 (0.64–1.11)
20	betamethasone 17-valerate											1.0 (standard)	1.0 (standard)

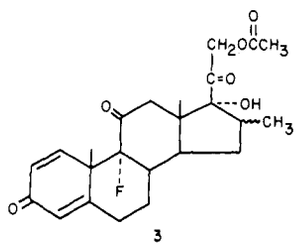
[a] NMR and infrared spectra were obtained for all targeted compounds, and NMR spectral data are in the Experimental Section for selected compounds. Mass spectra (EI) were also taken of all compounds reported, although not listed in this report. Microanalyses were determined for most targeted compounds.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

propriate acid chloride or anhydride. Activation of the acylating agent was achieved by use of a reactive base such as 4-(dimethylamino)pyridine (4-DMAP).[2,3] Use of the generally available acid chlorides[4] avoided the necessity of synthesizing the less accessible heteroaromatic ortho ester reagents.[5]

Most of the steroid substrates used in the 17-esterification have an 11-keto, 9β,11β-oxido, or $\Delta^{9(11)}$ moiety with the only unprotected hydroxyl function at 17. Some results on selective 17-hydroxyl esterification of a few 11,17-dihydroxy substrates are reported.

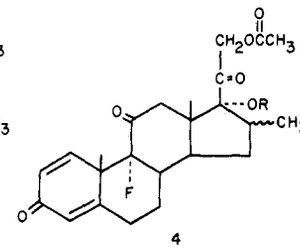
Esterification of the 17-hydroxy group was generally effected with the appropriate heteroaromatic acid chloride, although occasionally for the preparation of the 2′-furoates, 2-furoic anhydride (2-FA)[6] was used instead of 2-furoyl chloride (2-FC). Our generalized process consisted of reaction of the 17-hydroxy steroid (1 equiv), the appropriate acid chloride (2–3 equiv), and 4-DMAP (4–10 equiv) in methylene chloride. Yields were generally 30–50% with the 16α-methyl-9α-fluoro 11-ketones for first-time preparation. In the 16β-methyl series the yields of the 17-acylation step were lower.

Thus, **3a**[7] gave the 17-(2′-furoate) **4a**, the 17-(3′-furoate) **4c**, and the 17-(2′-thenoate) **4d**. The isomeric **3b**[8] gave the 2′-furoate **4b**.



3

a. 16α
b. 16β

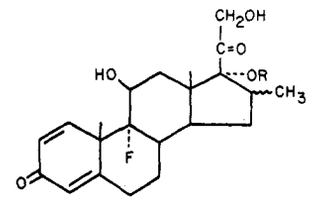


4

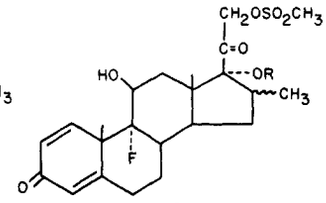
a. R = 2′-furoyl; 16α
b. R = 2′-furoyl; 16β
c. R = 3′-furoyl; 16α
d. R = 2′-thenoyl; 16α

Selective reduction of the 11-ketone in **4a–d** with sodium borohydride proceeded in high yield to give the desired 11β-hydroxy **1a–d** (Table I). Hydrolysis of the 21-acetate with perchloric acid in methanol[9] proceeded selectively in **1a–d** with retention of the 17-ester function to afford **5a–d**. Acylation of **5a** with the appropriate acylating agents gave the 21-propionate **1e**, the 21-butyrate **1f**, and the 21-methoxyacetate **1g** (Table I).

The preparation of the 21-chloro 17-esters was effected by conversion of the 21-hydroxy **5a–d** to the 21-mesylates **6a–d**. Reaction of the 21-mesylates with lithium chloride afforded the 21-chloro steroids **1h–k** (Table I) in 55–78% yields. The 21-chloro 17-(3′-furoate) **1j** was oxidized to the corresponding 11-ketone **11** with chromic acid. In the



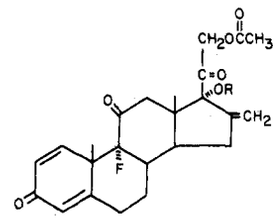
5



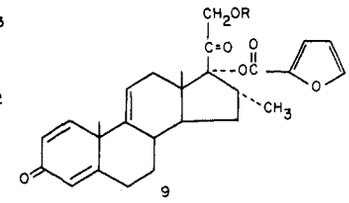
6

a. R = 2′-furoyl; 16α
b. R = 2′-furoyl; 16β
c. R = 3′-furoyl; 16α
d. R = 2′-thenoyl; 16α

16-methylene series, acylation of **7**[10] with 2-furoic anhydride gave the 17-(2′-furoate) **8** in low yield. Reduction of the 11-ketone afforded the fluorohydrin **1m** (Table I) in modest yield.

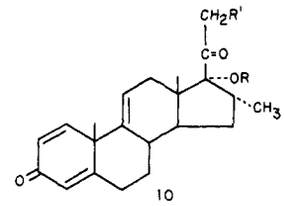


7 R = H
8 R = 2′-furoyl



9

a. R = $COCH_3$
b. R = $COCH_2OCH_3$
c. R = H



10

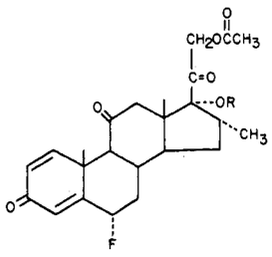
a. R = 2′-furoyl; R′ = Cl
b. R = 2′-thenoyl; R′ = Cl
c. R = 2′-furoyl; R′ = F

In Table II are listed the 17-heteroaromatic esters bearing 9α-chloro and 9α-hydrogen substituents with various 21-functionalities. The chlorohydrins **2a–e** (Table II) were obtained from the appropriate $\Delta^{9(11)}$ compounds[2] by using 1,3-dichloro-5,5-dimethylhydantoin (DDH) in aqueous tetrahydrofuran containing perchloric acid. Under these conditions small amounts of the 9,11-dichloro compounds were also obtained as byproducts. The $\Delta^{9(11)}$ steroid **9a** gave chlorohydrin **2a**. The 21-methoxyacetate **9b**, prepared from 21-hydroxy steroid **9c** with methoxyacetyl chloride, was converted to the 9α-chloro-11β-hydroxy corticosteroid **2b**. The chlorohydrins **2c** [21-chloro 17-(2′-furoate)] and **2d** [21-chloro 17-(2′-thenoate)] were obtained from **10a** and **10b**, respectively. The 9α-chloro-21-fluoro steroid **2e** was prepared from the 21-fluoro-$\Delta^{9(11)}$ steroid **10c** with DDH.

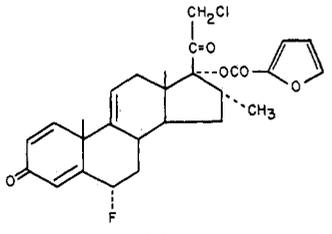
Preparation of the two 6α-fluoro analogues **2f** and **2g** was initiated by esterification of 11-keto **11a**[11] to afford the 17-(2′-furoyl) **11b** in low yield. Reduction of the 11-ketone in **11b** gave the 9-unsubstituted 11β-hydroxy steroid **2f**. Exposure of **12**[2] to DDH afforded the 6α-fluoro-9α-chloro steroid **2g**.

In order to complete the structure–activity relationship studies, the 9-unsubstituted 16-methylene steroid **2h** and its 9-chloro analogue **2i** were prepared. Also prepared were **2j**, 16α-methylprednisolone 17-(2′-furoate) 21-propionate,

(3) Kerb, U.; Stahnke, M.; Wiechert, R. German Patent 2748442, May 3, 1979; *Chem. Abstr.* **1980**, *93*, 168494*h*.
(4) Where not commercially available, the requisite acid chloride was prepared by standard methods ($SOCl_2$, benzene).
(5) Generally, 17-esters of corticosteroids are obtained via the 17,21-ortho ester, prepared from an appropriate ortho ester reagent and the 17,21-dihydroxy corticosteroid.
(6) Adkins, H.; Thomson, Q. E. *J. Am. Chem. Soc.* **1949**, *71*, 2242.
(7) Muller, G. U.S. Patent 3115491, Dec 24, 1963; *Chem. Abstr.* **1964**, *60* 10759*f*.
(8) Scherico Ltd. British Patent 901093, July 11, 1962; *Chem. Abstr.* **1963**, *58*, 3489*g*.
(9) Shapiro, E. L.; Finckenor, L.; Pluchet, H.; Weber, L.; Robinson, C. H.; Oliveto, E. P.; Herzog, H. L.; Tabachnick, I. A.; Collins, E. J. *Steroids* **1967**, *9*, 143.
(10) Irmscher, K.; Orth, D. British Patent 1213118, Nov 18, 1970; *Chem. Abstr.* **1971**, *74*, 63183*k*.
(11) Upjohn Co. British Patent 902294, Aug 1, 1962; *Chem. Abstr.* **1963**, *59*, 14078*c*.



11

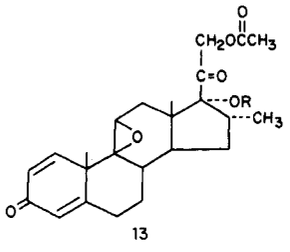


12

a. R = H
b. R = 2'-furoyl

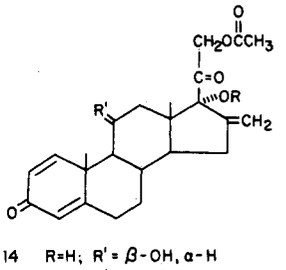
and **2k**, prednisolone 17-(2'-furoate) 21-acetate. The latter compound lacks both the potency-enhancing 9α-halo and 16α-methyl groups. The syntheses of **2h–k** followed known sequences of transformations and are presented in the Experimental Section.

An alternative route to the 9α,11β-halohydrins is exemplified in the preparation of the 9,11-chlorohydrin **2a**. Acylation of the 9,11-epoxide **13a**[12] with 2-FA gave the 17-(2'-furoate) **13b**. Treatment of the epoxide **13b** with HCl in acetic acid gave **2a** in 92% yield. A distinct advantage of this process over the DDH treatment of the $\Delta^{9(11)}$ compound is the avoidance of the competitive formation of the undesired 9,11-dichloro compound.

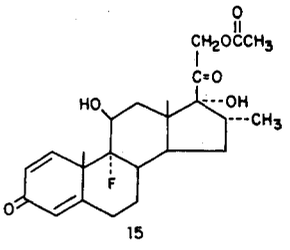


13

a. R = H
b. R = 2'-furoyl



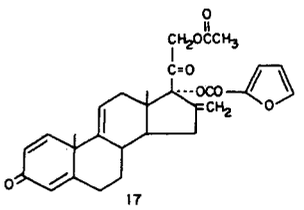
14 R=H; R' = β-OH, α-H
16a. R=H; R' = O
16b. R=2'-furoyl; R' = O



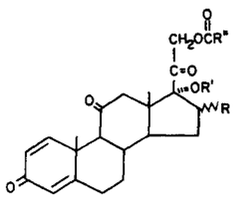
15

An alternative process for the preparation of **2a** involves direct and selective esterification of the 17-hydroxyl function in 11β,17α-dihydroxy corticosteroids. Generally, the presence of another hydroxyl function is avoided because of the difficulty of preventing multiple esterification. Thus, exposure of 16-methyleneprednisolone 21-acetate (**14**)[13] to 2-FC and 4-pyrrolidinopyridine (4-PP) (1 mmol of **14**, 1.2 mmol of 2-FC, and 6.1 mmol of 4-PP in methylene chloride) gave the 17-(2'-furoate) **2h** in 12% yield. When dexamethasone 21-acetate (**15**) was exposed to similar conditions, **1a** was obtained only in 2% yield.

In contrast, exposure of **15** to 2-(5-methyl)thenoyl chloride in the presence of 4-DMAP resulted in formation of the 17-monoester **1n** in 11% yield. Studies on selective esterification of 11β,17α-dihydroxy substrates are being published in a separate paper.[14]



17



18a. R=CH_3; R'=H; R"=C_2H_5
18b. R=CH_3; R'=2'-furoyl; R"=C_2H_5
19a. R=H; R'=H; R"=CH_3
19b. R=H; R'=2'-furoyl; R"=CH_3

Biological Results and Discussion

Topical antiinflammatory activity was measured by a modification of the croton oil ear assay of Tonelli et al.[15] Listed in Table I are potencies of the 9α-fluoro-11β-hydroxy corticosteroid 17-heteroaromatic esters relative to betamethasone 17-valerate (**20**). The potencies of the 9-chloro and 9-unsubstituted analogues are listed in Table II.

Structure–activity relationships were established by using the potencies derived in the 5-day (chronic) assay because topical corticosteroids are used chronically in clinical practice. The 5-h (acute) assay is, however, useful for identification of lead compounds. Among the 9α-fluoro compounds (Table I), the 17,21-diesters showed consistently higher activity than the standard in the 16α-methyl (dexamethasone) series. The most potent compound was **1e**, the 17-(2'-furoate) 21-propionate, being 6 times as potent as betamethasone valerate. Other compounds in the series with high potency were **1g**, 17-(2'-furoate) 21-methoxyacetate, **1c**, 17-(3'-furoate) 21-acetate, and **1d**, 17-(2'-thenoate) 21-acetate, which were 3 times as potent as betamethasone valerate.

The 21-chloro 17-esters **1h** and **1k** were twice as potent as the standard; thus in the 9α-fluoro series the 21-halo has not shown the strong potency-enhancing effect observed in the 9α,11β-dichloro series[2] or in the 9α-chloro-11β-hydroxy series below.

In the 9α-chloro series (Table II) with one exception the 17-ester was kept constant as the 2'-furoate. In this series most of the compounds prepared have shown high antiinflammatory potency. Thus, **2c**, the 21-chloro 17-(2'-furoate), was 6 times as potent as the standard, whereas **2d**, the 21-chloro 17-(2'-thenoate), **2e**, the 21-fluoro 17-(2'-furoate), and **2g**, the 6α-fluoro analogue of **2c**, were at least 4 times as potent as betamethasone valerate. In this series the 17,21-diesters **2a** and **2b** have shown equally high topical antiinflammatory potency.

A few representative 16β-methyl compounds were prepared: **1i** and **1b** showed lower antiinflammatory potencies respectively than their 16α-methyl analogues. These findings parallel those observed in the 9α,11β-dichloro series.[2]

The structure–activity studies were extended to the 16-methylene series to include **1m** and **2i**. These compounds were less potent than the analogous 16α-methyl compounds, although **2i** was still twice as potent as betamethasone valerate.

In summary, introduction of the 2'-furoate function into the 17-position of 9α-fluoro-16α-methyl and 9α-chloro-

(12) 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.

(13) Taub, D.; Wendler, N. L.; Hofsommer, R. D. U.S. Patent 3 068 226, Dec 11, 1962; *Chem. Abstr.* **1963**, *58*, 11451g.

(14) A more extensive study on selective esterification of 11β,17α-dihydroxy corticosteroids and on other products of the reaction will be the subject of a communication by three of us (E.L.S., M.J.G., and T.L.P.).

(15) Tonelli, G.; Thibault, L.; Ringler, I. *Endocrinology (Baltimore)* **1965**, *77*, 625.

16α-methyl corticosteroids results in significant topical antiiflammatory potency enhancement. The 9,21-dichloro 17-(2′-furoate) **2c** (mometasone furoate, Elocon) as 0.1% ointment and cream has been clinically evaluated and was found to be a highly efficacious, long-acting topical antiiflammatory agent. Similarly, the 9α-fluoro 17-(2′-furoate) **1a** was found to be highly efficacious on clinical evaluation as a 0.1% ointment.

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 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 in a Finnigan MAT-312 mass spectrometer operating at an accelerating voltage of 3 kV. Silica gel preparative-layer chromatography (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.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (1a). 4-(Dimethylamino)pyridine (4-DMAP) (2.8 g, 23 mmol) and 2-furoyl chloride (2-FC) (0.46 mL, 4.6 mmol) were mixed in CH_2Cl_2 (14 mL) while the temperature was maintained at 0–5 °C. After removal of the cooling bath, 9α-fluoro-17α,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,11,20-trione 21-acetate (**3a**)[7] (1.0 g, 2.3 mmol) was added with stirring. After 72 h the reaction mixture was evaporated to a residue, which was triturated with water. The precipitate was collected and dried, and the crude **4a** (1.1 g) was purified by silica gel preparative-layer chromatography (PLC) ($CHCl_3$–EtOAc, 39:1), affording **4a**, 0.6 g (50%), crystallized from CH_2Cl_2–hexane: mp 228–231 °C; $[\alpha]^{26}_D$ +48.9°; λ_{max} 248 nm (25.3 × 10^3); FAB MS, *m/e* 527 (M + 1); NMR δ 0.96 (16α-CH_3, d, 6 Hz), 4.82 and 5.07 (21-CH_2, d's, 17 Hz), 6.07 (4 H), 6.1 (2 H, d of d, 10 Hz, 1 Hz), 6.63–6.67 (4′-H, q, 1.5 Hz), 7.27–7.40 (1-H and 3′-H), 7.98 (5′-H).

To a solution of **4a** (0.986 g, 1.87 mmol) in DMF (26 mL), MeOH (30 mL), and water (3 mL) under N_2 was added $NaBH_4$ (0.212 g, 5.6 mmol) at 0–2 °C. After 20 min 1 N HCl (6 mL) was added, and the reaction mixture was added to saturated NaCl. The white solid was collected and purified by PLC ($CHCl_3$–EtOAc, 9:1) to afford **1a**, 0.78 g (79%), crystallized from CH_2Cl_2–Et_2O: NMR δ 4.19 (11α-H, 9 Hz), 5.45 (11β-OH, br), 6.68 (4′-H, q, 1.9 Hz), 7.13–7.22 (5′-H), 7.99 (3′-H).

9α-Fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (1b). As in the previous experiment, **3b**[8] was converted to **4b** (18%), which on reduction with $NaBH_4$ afforded **1b** (80% from **4b**), crystallized from CH_2Cl_2–EtOAc.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(3′-Furoate) 21-Acetate (1c). As in the preparation of **1a**, **3a** was converted to **4c** (48%), which on reduction with $NaBH_4$ afforded **1c** (76%), crystallized from CH_2Cl_2–Et_2O.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) 21-Acetate (1d). As in the preparation of **1a**, **3a** was converted to **4d** (39%), which on reduction with $NaBH_4$ afforded **1d** (62%), crystallized from CH_2Cl_2–Et_2O.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Propionate (1e). The 21-acetoxy steroid **1a** (0.67 g, 12.7 mmol), 70% $HClO_4$ (0.86 mL), and MeOH (18 mL) were stirred for 24 h at room temperature and then added to saturated NaCl solution. The insolubles were collected, washed with water, and dried, to obtain crude **5a** (0.625 g). Purification via PLC ($CHCl_3$–EtOAc, 5:1) and evaporation from EtOAc gave **5a** (0.616 g, 99%), which was used in subsequent preparations.

The 21-hydroxy compound **5a** (0.2 g, 0.4 mmol) was stirred with propionic anhydride (0.3 mL, 2.2 mmol) in pyridine (2 mL) at room temperature for 18 h and then added to water. The insolubles were collected and placed on PLC plates ($CHCl_3$–EtOAc, 15:1) to give 0.15 g (68%) of **1e**, crystallized from CH_2Cl_2–hexane: NMR δ 1.20 (21-$OCOCH_2CH_3$, t).

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Butyrate (1f). The 21-butyrate **1f** was prepared from **5a** in 58% yield, crystallized from CH_2Cl_2–hexane.

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Methoxyacetate (1g). The 21-methoxyacetate **1g** was prepared from **5a** in 68% yield, crystallized from EtOAc–hexane.

21-Chloro-11β,17α-dihydroxy-9α-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (1h). The 21-hydroxy steroid **5a** (0.27 g, 0.55 mmol), methanesulfonyl chloride (0.44 mL, 5.6 mmol), and pyridine (2.75 mL) were stirred at 0–2 °C for 1 h, and then the mixture was added to a saturated NaCl solution. The insolubles were collected and dried to obtain **6a**, which was used directly in the next step. The 21-mesylate **6a** (0.297 g, 0.49 mmol) and lithium chloride (0.35 g) in DMF (4 mL) were heated at 80 °C for 20 h. Addition to saturated NaCl solution and collection of the resulting solids gave 0.22 g of crude **1h**, which was purified via PLC ($CHCl_3$–EtOAc, 8:1) to give 21-chloro steroid **1h** (0.184 g, 74%), crystallized from CH_2Cl_2–hexane: NMR δ 4.47 and 4.57 (21-CH_2, d's, 15 Hz).

21-Chloro-11β,17α-dihydroxy-9α-fluoro-16β-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (1i). As in the preparation of **5a**, **1b** was converted to **5b** (80%), and after mesylation, treatment with LiCl in DMF afforded **1i** (67%), crystallized from CH_2Cl_2–hexane.

21-Chloro-11β,17α-dihydroxy-9α-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(3′-Furoate) (1j). As in the preparation of **5a**, **1c** was converted to **5c** (88%), and after mesylation, treatment with LiCl in DMF afforded **1j** (69%), crystallized from CH_2Cl_2–hexane.

21-Chloro-11β,17α-dihydroxy-9α-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) (1k). As in the preparation of **5a**, **1d** was converted to **5d** (90%), and after mesylation, treatment with LiCl in DMF afforded **1k** (71%), crystallized from CH_2Cl_2–hexane.

21-Chloro-9α-fluoro-17α-hydroxy-16α-methyl-1,4-pregnadiene-3,11,20-trione 17-(3′-Furoate) 21-Acetate (1l). A chromic acid solution (0.075 g of CrO_3, 0.15 mL of water, and 2 mL of acetic acid) was added to a stirred suspension of **1j** (0.25 g, 0.5 mmol) in acetic acid (3 mL) at 18 °C in 10 min. After 90 min the reaction mixture was added to 100 mL of water containing $NaHSO_3$ (0.3 g). The collected insolubles were purified by PLC ($CHCl_3$–EtOAc, 19:1) to afford **1l** (0.2 g, 81%), crystallized from acetone–Et_2O–hexane: NMR δ 4.55 (21-CH_2), 6.12 (4-H), 6.18 (2-H, d of d, 10 Hz, 2 Hz), 7.32 (1-H, d, 10 Hz).

9α-Fluoro-16-methylene-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (1m). 9α-Fluoro-16-methyleneprednisone 21-acetate (**7**) (2.15 g, 5 mmol), 2-FA (1.7 g, 8.2 mmol), 4-DMAP (2.44 g, 20 mmol), and CH_2Cl_2 (12 mL) were stirred at room temperature for 24 h. Evaporation gave a residue, which was triturated with water, then aqueous HCl, and water to afford solids (2.7 g). Purification on PLC ($CHCl_3$–EtOAc, 12:1, then 18:1, followed by hexane–EtOAc, 2:1) gave **8** (0.513 g, 20%), which was used in the reduction step. The 11-keto steroid **8** (0.5 g, 0.95 mmol), $NaBH_4$ (0.113 g, 3 mmol), DMF (1.1 mL), and MeOH (41 mL) were stirred as in the preparation of **1a**, to afford, after PLC ($CHCl_3$–EtOAc, 6:1) purification, **1m** (0.046 g, 33%), crystallized from CH_2Cl_2–hexane: NMR δ 4.78 and 4.99 (21-CH_2, d's, 15 Hz), 5.30 (11-OH, and 16-CH_2, 11-OH exchangeable).

9α-Chloro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2a). 16α-Methyl-17α,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) 21-acetete (**9a**) (0.618 g, 1.25 mmol) was dissolved in THF (12.5 mL) and maintained at 0–2 °C under N_2. A solution of 70% $HClO_4$ (0.23 mL) in 0.53 mL of water was added, followed by 1,3-dichloro-5,5-dimethylhydantoin (DDH) (0.173 g, 0.88

mmol). After 5 min, the cooling bath was removed and the mixture was stirred at room temperature for 4 h. The reaction mixture was added to water (250 mL) containing $NaHSO_3$ (1.6 g), followed by addition of solid NaCl, and the precipitate was collected, dried, and placed on PLC plates ($CHCl_3$–EtOAc, 9:1), affording **2a** (0.37 g, 54%), crystallized from CH_2Cl_2–Et_2O: NMR δ 4.27–4.43 (11α-H, br), 5.55 (11β-OH, d, 4 Hz).

9α-Chloro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Methoxyacetate (2b). 16α-Methyl-17α,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**9c**) (0.5 g, 1.12 mmol) and methoxyacetyl chloride (0.16 mL, 1.75 mmol) were mixed in pyridine (3 mL) at 0–2 °C. After 105 min and the usual workup with aqueous NaCl solution, the isolated solids of **9b** (0.5 g) were used directly in the next step.

As in the preparation of **2a**, **9b** (0.48 g, 0.92 mmol) with 70% $HClO_4$ (0.17 mL) in water (0.42 mL), DDH (0.127 g, 0.64 mmol), and THF (9 mL) gave chlorohydrin **2b** in 45% yield, crystallized from CH_2Cl_2–Et_2O: NMR δ 4.33–4.43 (11α-H), 5.99 (11β-OH, d, 4 Hz). The related 9α,11β-dichloro steroid was also obtained, in 7% yield.

9α,21-Dichloro-11β,17α-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2c). As in the preparation of **2a**, 21-chloro-16α-methyl-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**10a**) (0.24 g, 0.5 mmol) with 70% $HClO_4$ (0.09 mL), water (0.21 mL), and DDH (0.059 g) in THF (8 mL) and the usual workup including PLC ($CHCl_3$–EtOAc, 9:1) purification gave chlorohydrin **2c** (0.169 g, 65%), crystallized from aqueous MeOH: NMR δ 4.35–4.52 (11α-H, br), 5.62 (11β-OH, d, 4 Hz). The related 9α,11β-dichloro steroid was also obtained, in 9% yield.

9α,21-Dichhloro-11β,17α-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Thenoate) (2d). As in the preparation of **2a**, 21-chloro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-thenoate) (**10b**) (1.07 g, 2.2 mmol) with DDH (0.26 g), 70% $HClO_4$ (0.36 mL) in water (0.84 mL), and THF (28.5 mL) afforded, after PLC ($CHCl_3$–EtOAc, 9:1) purification, the 9,11-chlorohydrin **2d** (0.47 g, 41%), crystallized from CH_2Cl_2–hexane: NMR δ 4.25–4.58 (11α-H, br), 5.57 (11β-OH, d, 5 Hz). The related 9α,11β-dichloro steroid was also obtained, in 8% yield.

9α-Chloro-11β,17α-dihydroxy-21-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2e). As in the preparation of **2a**, 21-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**10c**)[2] (0.35 g) with DDH (0.086 g), 70% $HClO_4$ (0.12 mL) in water (0.28 mL), and THF (6 mL) afforded, after PLC purification ($CHCl_3$–EtOAc, 9:1) the 9,11-chlorohydrin **2e** (0.22 g, 67%), crystallized from CH_2Cl_2–hexane. The related 9α,11β-dichloro steroid was also obtained, in 8% yield.

6α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2f). As in the preparation of **4a**, **11a**[11] was converted to **11b** (11%) which on reduction with $NaBH_4$ afforded **2f** (41%), crystallized from EtOAc–hexane.

9α,21-Dichloro-11β,17α-dihydroxy-6α-fluoro-16α-methyl-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) (2g). As in the preparation of **2a**, 21-chloro-6α-fluoro-17α-hydroxy-16α-methyl-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) (**12**) (0.97 g, 2 mmol) was treated with DDH (0.24 g, 1.2 mmol) and 70% $HClO_4$ (0.3 mL) in water (0.7 mL) and THF (25 mL). After the usual workup and purification via silica gel G-60, **2g** (0.35 g, 32%) was obtained and crystallized from CH_2Cl_2–Et_2O: EI MS, m/e 489 (M – CH_2Cl); NMR δ 4.34–4.57 (21-CH_2 and 11α-H), 5.30 and 5.90 (6α-H, br), 5.66 (11β-OH, d, 5 Hz).

16α-Methylene-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2h). As in the preparation of **4a**, **16a**[13] was converted to **16b** (40%), which on reduction with $NaBH_4$ afforded **2h** (30%), crystallized from EtOAc–hexane.

9α-Chloro-16-methylene-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2i). To a solution of the 11β-hydroxy steroid **2h** (1.0 g, 2 mmol) in DMF (7.5 mL) and collidine (2.5 mL) at 5 °C was added with stirring 0.6 mL of methanesulfonyl chloride (1.41 g of mesyl chloride/mL of solution) in SO_2 under N_2.[16] The cooling bath was removed, and the mixture was allowed to remain at room temperature for 95 min. The reaction mixture was added to water, and the resultant solids were collected and purified by PLC ($CHCl_3$–EtOAc, 12:1, and hexane–EtOAc, 4:1) to obtain 17α,21-dihydroxy-16-methylene-1,4,9(11)-pregnatriene-3,20-dione 17-(2′-furoate) 21-acetate (**17**) (0.414 g, 43%), used directly in the next step: NMR δ 5.43 (16-CH_2), 5.58 (11-H).

As in the preparation of **2a**, the $\Delta^{9(11)}$ **17** (0.216 g, 0.44 mmol) and DDH (0.1 g, 0.5 mmol) in the presence of 70% $HClO_4$ (0.08 mL) in water (0.19 mL) and THF (4 mL) gave, after the usual workup and PLC ($CHCl_3$–EtOAc, 10:1), **2i** (0.094 g, 39%), crystallized from CH_2Cl_2–hexane: NMR δ 4.42 (11α-H), 5.45 (16-CH_2), 5.68 (11β-OH, d, 5 Hz).

16α-Methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Propionate (2j). As in the preparation of **4a**, **18a**[17] was converted to **18b**, which on reduction with $NaBH_4$ afforded **2j** (35% from **18a**), crystallized from CH_2Cl_2–hexane.

11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2k). As in the preparation of **4a**, prednisone 21-acetate (**19a**) was converted to **19b** (35%), which on reduction with $NaBH_4$ afforded **2k** (58%), solid from CH_2Cl_2–Et_2O–hexane: EI MS, m/e 496.

Preparation of 2a via 9,11-Oxide. To a prepared mixture of 4-DMAP (0.49 g, 4 mmol), 2-FA (0.412 g, 2 mmol), and CH_2Cl_2 (4 mL) at room temperature and being stirred was added 17α,21-dihydroxy-16α-methyl-9,11β-oxido-1,4-pregnadiene-3,20-dione 21-acetate (**13a**) (0.414 g, 1 mmol). After being stirred for 6 days at room temperature, the reaction mixture was evaporated to a residue, which was triturated with water. The solids were filtered, and purification via PLC ($CHCl_3$–EtOAc, 19:1) afforded **13b** (0.294 g, 58%), which was used in the following step.

To **13b** (0.17 g, 0.33 mmol) with stirring in acetic acid (1.5 mL) was added at 0–2 °C a 0.3-mL solution of HCl–acetic acid (0.0213 g HCl). The cooling bath was removed, and the reaction mixture was stirred for 45 min. Water was added and the precipitate collected, washed (dilute aqueous Na_2CO_3, water), and dried (50 °C), giving **2a** (0.16 g, 92%).

Direct 17-Esterification of 11,17-Dihydroxy Substrates. 16-Methylene-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2′-Furoate) 21-Acetate (2h). Essentially as in the preparation of **4a**, but with 4-pyrrolidinopyridine (4-PP), a mixture of 16-methylene-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate (**14**) (0.414 g, 1 mmol), 4-PP (0.96 g, 6.1 mmol), and 2-FC (0.12 mL, 1.2 mmol) in CH_2Cl_2 (7 mL) was stirred at room temperature for 4 days. The solvent was evaporated and the residue triturated successively with dilute aqueous HCl, water, dilute Na_2CO_3, and water. The collected solids were purified via PLC ($CHCl_3$–EtOAc, 7:1, 19:1) to give **2h** (12% yield).

9α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnatriene-3,20-dione 17-(5′-Methyl-2′-thenoate) 21-Acetate (1n). A mixture of dexamethasone 21-acetate (**15**) (1 g, 2.3 mmol), 2-(5-methyl)thenoyl chloride (0.71 g, 4.9 mmol), 4-DMAP (3 g, 24.6 mmol) in CH_2Cl_2 (10 mL), and DMF (2.5 mL) was stirred at room temperature for 3 days. The usual workup and purification via PLC ($CHCl_3$–EtOAc, 50:1, 10:1, 20:1) afforded **1n** (0.146 g, 11%), crystallized from CH_2Cl_2–Et_2O: NMR δ 4.18 (11α-H), 5.44 (11β-OH, exchangeable); NMR δ ($CDCl_3$) 2.53 (5′-CH_3).

Test Methods. Croton Oil Induced Ear Inflammation in Mice. Topical antiinflammatory activity was determined in mice by a modification of the method of Tonelli et al.[15] Compounds ranging in concentration from 10^{-4}% to 10^{-6}% (w/v) were dissolved in a mixture of 0.6–0.7% croton oil in a vehicle containing 20% pyridine, 5% water, and 74% diethyl ether (v/v). Ten-microliter aliquots of each test solution were applied to the inner aspect of both pinnae of the test animals, daily, for 5 days. Five hours following the last treatment, the animals were sacrificed, and 6-mm punch biopsies of both ears were removed and weighed. Potencies were determined relative to betamethasone 17-valerate (**20**) by using the mean of left plus right ear punch weights.

The 5-h assay was carried out identically, but the test animals were sacrificed 5 h following a single drug treatment.

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

Registry No. **1a**, 83880-70-0; **1b**, 83880-73-3; **1c**, 83880-71-1; **1d**, 83880-72-2; **1e**, 83880-75-5; **1f**, 83881-10-1; **1g**, 83880-97-1; **1h**, 83880-77-7; **1i**, 83880-78-8; **1j**, 83880-79-9; **1k**, 83880-80-2; **1l**, 83881-16-7; **1m**, 83881-13-4; **1n**, 83880-83-5; **2a**, 83897-05-6; **2b**, 109218-04-4; **2c**, 83919-23-7; **2d**, 83881-14-5; **2e**, 83881-02-1; **2f**, 83880-86-8; **2g**, 83880-93-7; **2h**, 109183-48-4; **2i**, 83881-15-6; **2j**, 109183-49-5; **2k**, 83880-81-3; **3a**, 2995-86-0; **3b**, 4772-08-1; **4a**, 83880-69-7; **4b**, 83881-17-8; **4c**, 83881-18-9; **4d**, 83881-19-0; **5a**, 83880-74-4; **5b**, 109218-05-5; **5c**, 109183-50-8; **5d**, 109183-51-9; **6a**, 83880-76-6; **7**, 3872-52-4; **8**, 109183-52-0; **9a**, 83880-61-9; **9b**, 83881-05-4; **9c**, 83880-62-0; **10a**, 83880-65-3; **10b**, 107742-73-4; **10c**, 83881-01-0; **11a**, 1526-72-3; **11b**, 83880-85-7; **12**, 83880-91-5; **13a**, 2884-51-7; **13b**, 109183-56-4; **14**, 2325-61-3; **16a**, 912-24-3; **16b**, 109183-53-1; **17**, 109183-54-2; **18a**, 98422-34-5; **18b**, 109183-55-3; **19a**, 125-10-0; **19b**, 94813-60-2; 2-furoyl chloride, 527-69-5; 3-furoyl chloride, 26214-65-3; 2-thenoyl chloride, 5271-67-0; butyryl chloride, 141-75-3; methoxyacetyl chloride, 38870-59-6; dexamethasone 21-acetate, 1177-87-3; 5-methyl-2-thenoyl chloride, 31555-59-6.

Structure–Activity Relationships in an Imidazole-Based Series of Thromboxane Synthase Inhibitors

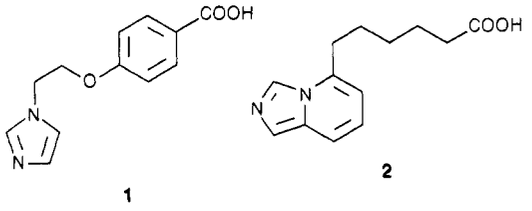
Paul W. Manley,*† Nigel M. Allanson,† Robert F. G. Booth, Philip E. Buckle,† Edward J. Kuzniar, Nagin Lad, Steve M. F. Lai,† David O. Lunt, and David P. Tuffin

Departments of Biology and Medicinal Chemistry, Searle Research and Development, Division of G. D. Searle & Co. Ltd., High Wycombe, Buckinghamshire HP12 4HL, U.K. *Received July 29, 1986*

Analogues of 4-[[2-(1*H*-imidazol-1-yl)-1-[[(4-methoxyphenyl)methoxy]methyl]ethoxy]methyl]benzoic acid (**5m**) were prepared and evaluated as thromboxane synthase inhibitors. A series of esters of **5m** showed a parabolic relationship between lipophilicity and inhibition of TxB_2 generation in intact platelets, with activities up to 50 times greater than that of dazoxiben. However, on administration to rabbits the ethyl ester **5d** had a short duration of action, due to rapid metabolism and excretion via deesterification and β-glucuronidation. Attempts at replacing the carboxylate group with other potential pharmacophores were unsuccessful.

The prostaglandin endoperoxide PGH_2 and its metabolites thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) have been implicated in a number of physiological processes.[1-5] Thus TxA_2, in addition to being a constrictor of vascular smooth muscle, is a potent inducer of shape change, aggregation, and secretion in blood platelets, thereby playing an important role in hemostasis, thrombosis, and vasospasm. TxA_2 is produced from PGH_2 by the enzyme thromboxane synthase predominantly located within the cellular membrane of blood platelets, whereas PGI_2, which in many respects antagonizes the actions of TxA_2 in being a potent vasodilator and antiaggregatory agent, is formed from PGH_2 by prostacyclin synthase located in vascular endothelial cells. Currently used antiaggregatory drugs such as aspirin and sulfinpyrazone inhibit the prostaglandin cyclooxygenase enzyme responsible for the production of the PGH_2 precursor, prostaglandin endoperoxide PGG_2, in both platelets and endothelial cells, thereby indirectly reducing both PGI_2 and TxA_2 levels. Clearly, a compound that specifically inhibits TxA_2 synthase, while leaving PGI_2 levels unaffected or even increased, may be of clinical benefit in a wide range of vasospastic diseases.[6]

Purified TxA_2 synthase is a P-450 hemoprotein,[7] and studies suggest that the heme thiolate group of the enzyme is responsible for the coordination of the 9-O atom of the endoperoxide bond of PGH_2, which results in its cleavage and rearrangement to the oxetane acetal TxA_2 (Scheme I). The structure of TxA_2 has recently been confirmed by chemical synthesis.[8] The majority of the known inhibitors of TxA_2 synthase possess a basic nitrogen heterocycle, which is usually imidazole or pyridine.[9-17] Representatives of this class of compounds, such as dazoxiben (**1**) and CGS 13080 (**2**), inhibit Fe–CO complexation of the enzyme, suggesting that they act, at least in part, through



1 **2**

the nitrogen heterocycle displacing a 6-hydroxyl ligand from the heme and coordinating in its place to the Fe^{3+}

*Address for correspondence: Dr. P. W. Manley, Preclinical Research Department, Sandoz Ltd., CH-4002 Basel, Switzerland.
†Department of Medicinal Chemistry.

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