

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 01-063014- -00011-0000
Rec: 2006-12-21 16:23:05 Dep. 2020 NUECREACIONES
Fol: 2 PATENTES
Eve: 1 REGUESTO
Act 444 RESPUESTA REQUE Folios: 38

E. _____ S. _____ D. _____

Re: P1.-GLAXO GROUP LIMITED.-Solicitud de Patente de
Invencción para "NUEVOS DERIVADOS DE ANDROSTANO
ANTI-INFLAMATORIOS".-Clase A.61.-Expediente número
01-063.014.-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 19 de Octubre de 2006.
2. De acuerdo con el Concepto Técnico No. **1623** se tiene que:

"SOLICITUD DE SUMINISTRO DE INFORMACION

"Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existen en el estado de la técnica los siguientes documentos que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- **ISOGAI, MITSUTAKA ET AL: "Binding affinities of mometasone furoate and related compounds including its metabolites for the glucocorticoid receptor of rat skin tissue". J. STEROID BIOCHEM. MOL. BIOL. (1993), 44(2), 141-5, XP002182261.**
- **PHILLIPPS G H ET AL: "Synthesis and structure-activity relationships in a series of anti-inflammatory corticosteroid analogues, halomethyl androstane-17beta-carbothioates and 17-beta-carboselenoates". Journal of**

Medicinal chemistry, American Chemical Society. Washington. US. Vol. 37, No. 22, 1 October 1994, pages 3717-3729, XP002025925. ISSN: 0022-2623.

- **POPPER T L ET AL: "Structure-activity relationship of a series of novel topical corticosteroids". Journal of Steroid biochemistry, Pergamon Press PLC, GB, Vol 27, no. 4-6, 1987, pages 837-843, XP000972215. ISSN: 0022-4731. PAGE 840-841, examples 21-24, 29-32.**
- **SHAPIRO E L ET AL: "17 Heteroaroyl esters of corticosteroids 2. 11-beta hydroxy series" Journal of Medicinal chemistry, American Chemical Society. Washington, US, vol. 30, no. 9, 1987, pages 1581-1588, XP...2153839. ISSN: 0022-2623. Page 1582; examples 1 H-IK; table 1; page 1583; examples 2C-2E, 2G; table II.**

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión 486, anexo me permito presentar a ese Despacho copia de los siguientes documentos solicitados:

- **ISOGAI, MITSUTAKA ET AL: "Binding affinities of mometasone furoate and related compounds including its metabolites for the glucocorticoid receptor of rat skin tissue". J. STEROID BIOCHEM. MOL. BIOL. (1993), 44(2), 141-5, XP002182261.**
- **PHILLIPPS G H ET AL: "Synthesis and structure-activity relationships in a series of anti-inflammatory corticosteroid analogues, halomethyl androstane-17beta-carbothioates and 17-beta-carboselenoates". Journal of Medicinal chemistry, American Chemical Society. Washington. US. Vol. 37, No. 22, 1 October 1994, pages 3717-3729, XP002025925. ISSN: 0022-2623.**
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4. En vista de todo lo anterior, ruego a usted proceder de conformidad y conceder el privilegio de patente solicitado.

Señor Superintendente,


GUSTAVO TAMAYO

T.P. 37.172

XP-002182261

1993

141-145

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BINDING AFFINITIES OF MOMETASONE FUROATE AND RELATED COMPOUNDS INCLUDING ITS METABOLITES FOR THE GLUCOCORTICOID RECEPTOR OF RAT SKIN TISSUE

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(Received 29 May 1992; accepted 15 October 1992)

Summary—The binding affinities of mometasone furoate (MF), its metabolites and related compounds for the glucocorticoid receptor of rat epidermis and dermis were measured. MF and its main metabolite exhibited binding affinities higher than those of alclomethasone dipropionate (ADP) and betamethasone dipropionate (BDP), but equivalent to betamethasone 17-valerate (BMV). For compound I (metabolite of MF), ADP, BDP and BMV, the binding affinity was found to be higher in epidermis relative to dermis. This difference in the dermal/epidermal binding ratio may be a favorable sign leading to a possible reduction of dermal collagen atrophy, a known side effect of glucocorticoids. In structure-binding relationship studies, esterification of the 17-OH by furoylation and introduction of the 9 α -Cl caused a marked increase of the binding affinity, whereas the 6 β -hydroxylation led to a pronounced decrease.

INTRODUCTION

A variety of glucocorticosteroids are widely used as potent local antiinflammatory agents. The skin is one important target organ in the topical treatment with glucocorticoids.

It is well known that a specific receptor protein for glucocorticoids is present in the skin of mouse [1], rat [2-4] and human [5, 6]. The receptor occurs in both the epidermis and dermis and appears physico-chemically similar in each tissue [3]. Since the main side effect of glucocorticoid is dermal collagen atrophy, development of topical glucocorticoids with high binding affinity for the epidermis and associated low affinity for dermal tissue is now required.

Mometasone furoate (MF) is a new glucocorticoid recently developed as a potent topical antiinflammatory agent with a favorable ratio between local and systemic effects [7-9]. Therefore, it is interesting to determine the binding affinities of MF, its metabolites, and related compounds for the glucocorticoid receptor in rat epidermis and dermis. These were the aims of this study.

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EXPERIMENTAL

Chemicals

[6,7-³H]Triamcinolone acetonide (sp. act. 42.5 Ci/mmol) was obtained from Du pont NEN Research Products. Unlabeled triamcinolone acetonide was obtained from Sigma. MF [9 α ,21-dichloro-11 β ,17 α -dihydroxy-16 α -methyl-1,4-pregnadiene-3,20-dione 17-(2'-furoate)], its synthetic precursor, compound VIII and reference steroids alclomethasone dipropionate (ADP), betamethasone dipropionate (BDP) and betamethasone 17-valerate (BMV) were all supplied by Schering-Plough Corporation. Among putative metabolites of MF, compounds I, II, III, V and VI were prepared starting from compound VIII according to the procedure of Shapiro *et al.* [10, 11]. Compounds IV and VII were obtained, respectively, by direct selenium dioxide oxidation of MF and compound V [12]. The bromohydrin analog of compound V was converted via dehydrohalogenation (KOAc) of its 21-TBDMS derivative, followed by deprotection (HOAc) to compound IX [13]. Oxidation (PDC) of the latter compound followed by epoxide ring cleavage (HCl) and successive methylation gave compound X [13]. Compound XI was obtained from

compound VIII by periodic acid oxidation and subsequent internal acylation followed by similar epoxide-ring cleavage and methylation [13, 14].

Preparation of cytosols

Cytosols were prepared by a modification of the method of Smith and Shuster [15]. Rat neonates (3 days old) of the Sprague-Dawley strain SPF (Charles River Inc.) were killed by decapitation and the skin was rapidly removed from the body and incubated in buffer 1 (88 mM K_2HPO_4 , 12 mM KH_2PO_4 , 10 mM sodium molybdate, 100 mM mercaptoethanol, pH 7.0) at 4°C. After 3 h, the epidermis was removed from the dermis. The tissues were minced using scissors and homogenized in 12 vol of buffer 2 (10 mM Tris, 2 mM $MgCl_2 \cdot 6H_2O$, 5 mM dithiothreitol, 10 mM sodium molybdate, 10% glycerol, pH 7.25) using a Polytron homogenizer at speed setting 6. The homogenates were centrifuged at 100,000 *g* for 1 h at 2°C. The resulting supernatant cytosol fractions were used immediately for binding assays.

[³H]Triamcinolone acetone binding assays

This assay was carried out according to the report of Smith and Shuster [15].

In all experiments, 0.2 ml cytosols (1.5–3 mg protein/ml) were incubated with 0.22–0.26 nM [³H]triamcinolone acetone in the presence of different concentrations of various steroids (prepared in buffer 2 containing 20% ethanol) in a total volume of 0.5 ml of buffer 2 at 4°C. After 20 h, the reaction was terminated by adding 0.25 ml dextran-charcoal solution (3.75% activated charcoal, 0.357% dextran T-500, 10 mM Tris, 2 mM $MgCl_2 \cdot 6H_2O$, 10% glycerol, 0.1% gelatin, pH 7.25). The mixture was incubated for 30 min at 4°C and then centrifuged at 1600 *g* for 15 min at 4°C. The radioactivity of [³H]triamcinolone acetone in the supernatant was counted by a liquid scintillation counter (Aloka, LSC-900) after addition of 10 ml scintillator (Atomlight, Du pont NEN). The nonspecific binding was determined in the presence of 10 μ M nonradioactive triamcinolone acetone. Accordingly, the specific binding was defined as the difference between the nonspecific and total bindings. All the assays were conducted in duplicate. Dose-response curves for various steroids were plotted to obtain the concentration (IC_{50}) necessary to displace 50% of the specific binding of [³H]triamcinolone acetone. Cytosol proteins were measured by the method of Lowry *et al.* [16]. The maximum number of binding sites

(B_{max}) and dissociation constant (K_d) for epidermal and dermal cytosols were estimated from Scatchard analysis [17] of the saturation data over the concentration range of 0.08–4 nM [³H]triamcinolone acetone. The inhibition constant (K_i) of each steroid was calculated from the following equation of Cheng and Prusoff [18], with the concentration (*C*) of [³H]triamcinolone acetone used in the experiment.

$$K_i = \frac{IC_{50}}{1 + \frac{C}{K_d}}$$

RESULTS AND DISCUSSION

The specific binding of [³H]triamcinolone acetone at a concentration of 0.08–4 nM in rat epidermis and dermis showed saturation curves. Scatchard analysis of the specific binding data was compatible with a single population of binding sites. In the epidermis, the dissociation constant (K_d) was 0.178 ± 0.027 nM ($n = 4$) and the number of receptor sites (B_{max}) was 213 ± 7 fmol/mg protein ($n = 4$). In the dermis, K_d was 0.180 ± 0.023 nM ($n = 4$) and B_{max} was 439 ± 40 fmol/mg protein ($n = 4$). Values for K_d in the epidermis and dermis did not differ significantly ($P > 0.05$). The number of receptors in the dermis were more than that in the epidermis, which corresponds to the results of Smith and Shuster [15]. This behavior of receptor binding in rat skin is also similar to previous findings for the receptor in mouse, rat and human skin [1, 3, 6].

The inhibition of [³H]triamcinolone acetone binding by MF analogs, ADP, BDP and BMV was determined by incubating [³H]triamcinolone acetone (0.22–0.26 nM) at 5 to 7 concentrations in epidermal and dermal cytosols. The inhibition constants (K_i) of these compounds are shown in Table I. MF and most of its metabolites exhibited binding affinities higher than those of ADP and BDP but equivalent to that of BMV. The relative binding potency for each of the compounds is expressed as the ratio of the inhibition constants in dermis and epidermis. The values (dermis/epidermis) listed in Table I show the degree of the binding affinity in epidermis relative to that in dermis which was given a potency of 1. For all steroids examined, the relative potency was calculated to be higher than 1. In particular, the binding affinities of compound I, ADP and BDP were significantly

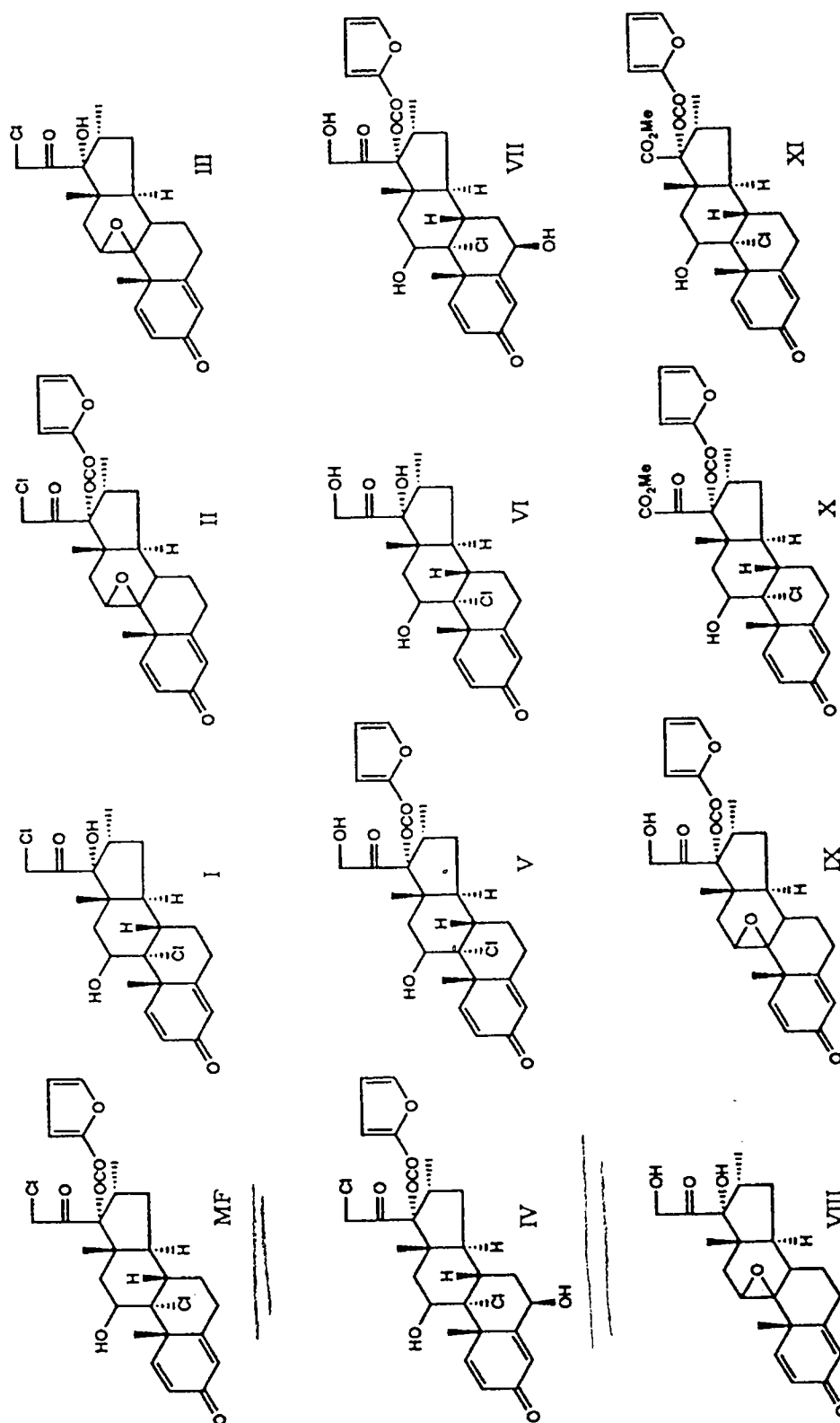


Fig. 1. Structural formulae of MF, its metabolites (I-VII) and related compounds (VIII-XI).

Table 1. Binding affinities of MF, its metabolites and related compounds in epidermis and dermis

Compound	K_d value (nM)		Relative potency
	Epidermis	Dermis	
MF	0.177 ± 0.029	0.194 ± 0.014	1.10
I	0.189 ± 0.025	0.307 ± 0.035*	1.62
II	0.221 ± 0.034	0.359 ± 0.049	1.62
III	4.42 ± 0.68	6.52 ± 1.36	1.48
IV	0.392 ± 0.049	0.428 ± 0.040	1.42
V	0.144 ± 0.020	0.171 ± 0.013	1.19
VI	0.314 ± 0.043	0.438 ± 0.063	1.39
VII	0.582 ± 0.061	0.811 ± 0.126	1.39
VIII	96.9 ± 12.6	153 ± 41	1.58
IX	1.57 ± 0.28	2.52 ± 0.68	1.61
X	4.69 ± 0.93	5.50 ± 1.11	1.17
XI	0.576 ± 0.062	0.804 ± 0.082	1.40
ADP	0.443 ± 0.043	1.05 ± 0.16*	2.37
BDP	0.689 ± 0.079	1.36 ± 0.24*	1.97
BMV	0.158 ± 0.013	0.224 ± 0.016*	1.42

Values are means ± standard error of 3 experiments. *Significantly different from the corresponding epidermal value at $P < 0.05$.

higher in epidermis than in dermis. Smith and Shuster [15] have shown that the binding potencies of RO 12 7024, dexamethasone, corticosterone and cortisone among several steroids were higher in epidermis than in the dermis. These differences in binding in epidermis and dermis show a favorable response in view of glucocorticoid therapy since they may account for a reduction in the side effects which accompany dermal collagen atrophy.

The structure-binding relationships of MF analogs including its metabolites were also investigated in rat epidermis and dermis. Esterification of the 17-OH (furolylation) markedly increased the binding affinity (I → MF, III → II, VI → V, VIII → IX). During the conversion of 9 β ,11 β -epoxide to 9 α ,11 β -halohydrin, introduction of the 9 α -Cl as well as 9 α -F caused a dramatic increase in affinity (II → MF, III → I, VIII → VI, IX → V). Substitution of the 21-OH by Cl also led to a pronounced increase in affinity (VI → I, IX → II, VIII → IX, VII → IV) with the exception of one case (V → MF) in which the compound retained almost the same affinity. On the other hand, a decrease in affinity was observed for the 6 β -hydroxylation (MF → IV, V → VII), which is also one of the important metabolic pathways for glucocorticoids. This loss of the binding affinity agrees with the general principle of corticoid inactivation by such a metabolic route.

These findings are in good agreement with those in cultured human skin cells [19]. Namely, the presence of 9 α -halogen as in 9 α -fluorohydrocortisone or 9 α -fluoro-prednisolone, the esterification of 17-OH as in hydrocortisone-17-butyrate or BMV and the introduction of Cl

at the 21 position as in clobetasol, lead to an increase of the steroid affinity for receptor. These structure-binding relationships are important in the development of new topical glucocorticoids.

Acknowledgements—The authors are grateful to Dr Masuhisa Nakamura for his valuable discussions and advice.

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J. Med. Chem. 1994, 37, 3717-3729

PD. 10/1994

P 3717-3729

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(13)

Synthesis and Structure-Activity Relationships in a Series of Antiinflammatory Corticosteroid Analogues, Halomethyl Androstane-17 β -carbothioates and -17 β -carboselenoates

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Glaxo Research and Development Limited, Greenford Road, Greenford, Middlesex UB6 OHE, U.K.

Received September 20, 1993*

The preparation and topical antiinflammatory potencies of a series of halomethyl 17 α -(acyloxy)-11 β -hydroxy-3-oxoandrostane-1,4-diene-17 β -carbothioates, carrying combinations of 6 α -fluoro, 9 α -fluoro, 16-methyl, and 16-methylene substituents, are described. Key synthetic stages were the preparation of carbothioic acids and their reaction with dihalomethanes. The carbothioic acids were formed from 17 β -carboxylic acids by initial reaction with dimethylthiocarbamoyl chloride followed by aminolysis of the resulting rearranged mixed anhydride with diethylamine, or by carboxyl activation with 1,1'-carbonyldiimidazole (CDI) or 2-fluoro-*N*-methylpyridinium tosylate (FMPT) and reaction with hydrogen sulfide, the choice of reagent being governed by the 17 α -substituent. Carboxyl activation with FMPT and reaction with sodium hydrogen selenide led to the halomethyl 16-methyleneandrostane-17 β -carboselenoate analogues. Anti-inflammatory potencies were measured in humans using the vasoconstriction assay and in rats and mice by a modification of the Tonelli croton oil ear assay. Best activities were shown by fluoromethyl and chloromethyl carbothioates with a 17 α -propionyloxy group. S-Fluoromethyl 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androstane-1,4-diene-17 β -carbothioate (fluticasone propionate, FP) was selected for clinical study as it showed high topical antiinflammatory activity but caused little hypothalamic-pituitary-adrenal suppression after topical or oral administration to rodents.

The successful development of corticosteroid analogues designed to show high potency on local application to inflamed tissue has been reviewed.¹⁻⁴ Although the available compounds showed only weak undesirable systemic side effects after topical administration, we continued to seek further improvement. In this paper we describe a series of potent and novel corticosteroidal halomethyl esters of androstane-17 β -carbothioic acids with promising separations of activity.⁵

Earlier we reported that the normal two-carbon 17 β -side chain of pregnanes was not necessary for corticoid activity, androstane-17 β -carboxylates showing high topical antiinflammatory activity if both the 17 α -hydroxy and 17 β -carboxylic acid functions were esterified, with the greatest activity being shown by 17 α -propionates as fluoromethyl carboxylates.^{1,6-8}

We first explored the synthesis of 17 α -unsubstituted 17 β -carbothioates in making compounds with anaesthetic activity.^{9,10} Kertesz and Marx¹¹ overcame many difficulties while employing carboxyl-activation procedures followed by reactions with alkanethiols in the synthesis of some alkyl 17 α -acyloxy 17 β -carbothioates which showed good topical antiinflammatory activity. Their synthetic methods could not, however, be applied to the preparation of halomethyl carbothioates (analogues of the potent 21-halopregnan-20-ones¹⁻³) as halomethanethiols are not known and would be expected to be very unstable. We therefore devised new methods of preparing 17 α -hydroxy and 17 α -acyloxy 17 β -

carbothioic acids, which could then be esterified by reacting their salts with dihalomethanes. Furthermore, 17 α -acylation of haloalkyl 17 α -hydroxy 17 β -carbothioates was likely to be unselective in the presence of an 11 β -ol, so it would be preferable to 17 α -acylate at the carbothioic acid stage, as with the carboxylic acids.^{7,8} The antiinflammatory potencies of the halomethyl 17 α -acyloxy 17 β -carbothioates were in general high, as delineated in Table 3.

Chemistry

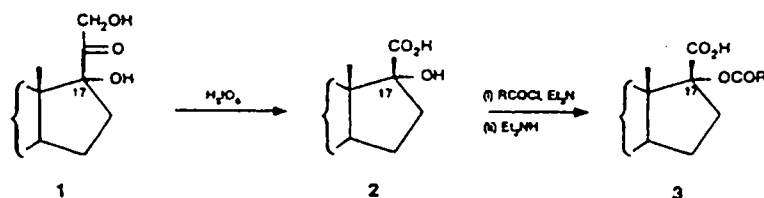
The 17 α -hydroxyandrostane-17 β -carboxylic acid intermediates **2** for the desired carbothioates were prepared by oxidative cleavage of 21-hydroxypregnan-20-ones **1** with periodic acid in aqueous dioxane or THF. They were readily 17 α -acylated, without concomitant 11 β -acylation, by reaction with excess acyl chloride and triethylamine followed by aminolysis of the resulting 17 α -acyloxy 17 β -carboxylic acid mixed anhydrides with diethylamine^{1,7,8} to give the corresponding acids **3** (Scheme 1).

Our first synthesis of carbothioic acids resulted while studying the aminolysis of the mixed anhydride formed by reaction of the 17 α -propionyloxy 17 β -carboxylic acid **3d**¹¹ with dimethylthiocarbamoyl chloride in pyridine. The mixed anhydride was initially believed to be the thione **4a**, but aminolysis with diethylamine gave the 17 β -carbothioic acid **6i** and it now has been assigned the rearranged structure **4bc**;³ this was supported by its synthesis as the major product from the reaction of thioacid **6i** with dimethylcarbonyl chloride and by the lack of a carbonyl IR absorption above 1740 cm⁻¹, in contrast to that observed (1783 cm⁻¹) for the oxygen

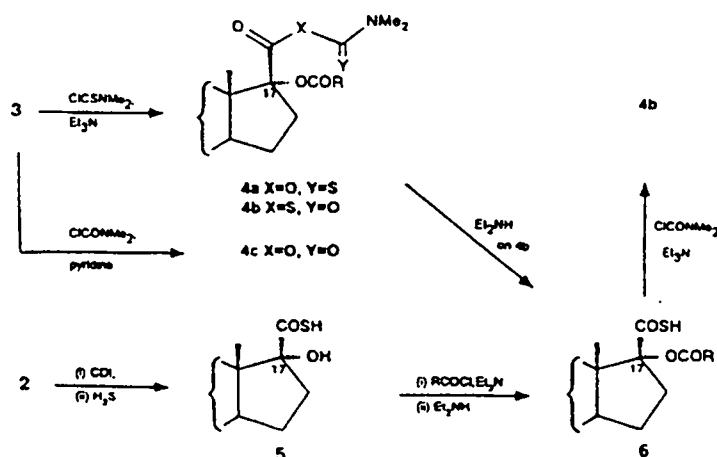
* External Scientific Affairs Department, to whom communications should be sent.

* Abstract published in *Advance ACS Abstracts*, September 15, 1994.

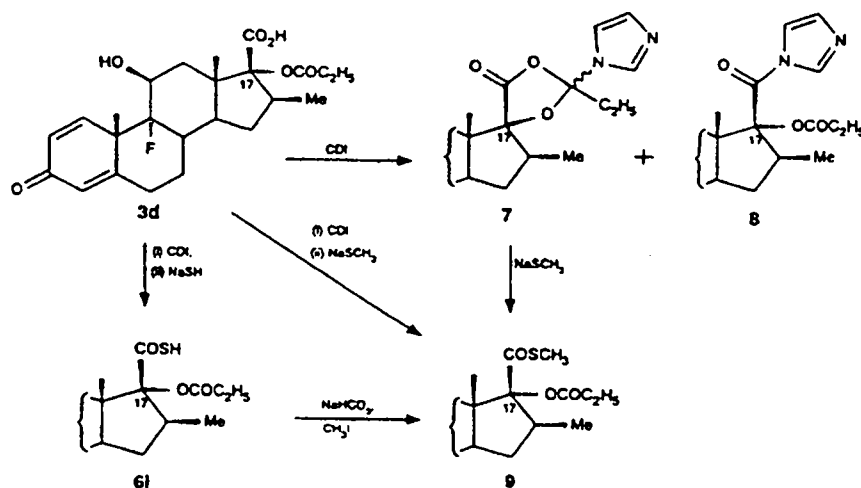
Scheme 1



Scheme 2



Scheme 3

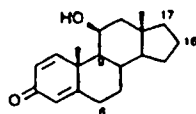


analogue 4ca (see Scheme 2, also Table 1 for the definition of these compound letters).

Gais¹² reported that carboxylic acid imidazolides are accessible in almost quantitative yields from carboxylic acids and 1,1'-carbonyldiimidazole (CDI) and that they react rapidly with aliphatic and aromatic thiols to give thioesters in high yields. Kertesz and Marx¹¹ applied this method to the synthesis of alkyl androstane-17 β -carbothioates. We found that the imidazolides from 17 α -hydroxy 17 β -carboxylic acids also react with hydrogen sulfide to give 17 α -hydroxy 17 β -carbothioic acids 5. Like the corresponding carboxylic acids, these were readily and selectively 17 α -acylated without concomitant 11 β -acylation (Scheme 2).

Kertesz and Marx¹¹ reported that CDI failed to activate 17 α -acyloxy 17 β -carboxylic acids, but we found that CDI in dimethylformamide at 22 °C activated the

17-propionate acid 3d to reaction with NaSH (to give 6i) or NaSMe (to give 9) but not to reaction with H₂S. The reaction of H₂S with other carboxyl-activated species is known to be base-catalyzed.¹³ The known thioester 9¹¹ could also be prepared by methylation of 6i. The nature of the activated species was studied by partitioning the reaction mixture between water (not acid) and ethyl acetate (Scheme 3). The two major components isolated by preparative TLC were the diastereoisomeric 17-spiro-2'-(1-imidazolyl)-1',3'-dioxolan-4'-ones 7. The structures of each were indicated by their characteristic IR absorption (1810 cm⁻¹) for the spirocyclic carbonyl and by their ¹³C NMR spectra, where the spirocyclic ring carbon atoms were readily assigned. In particular the 2'-carbon resonances (112.1 and 112.0 ppm) in the two isomers showed no C-H coupling in the off-resonance spectra. These and the

Table 1. Physical Properties of Intermediates^a

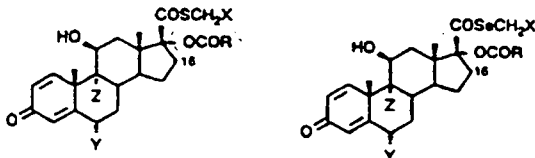
no.	6a	9a	16	17a	17b	mp, °C	[α] _D deg (dioxane)	formula	anal. ^b	UV, λ _{max} (EtOH) nm (ε × 10 ⁻³)
2a	F	H	H	OH	CO ₂ H	241–248	+54	C ₂₆ H ₂₅ FO ₅	C.H	242 (15.3)
2b	H	F	H	OH	CO ₂ H	289–293	+66 ^c	C ₂₆ H ₂₅ FO ₅	C.H	239.5 (14.5)
2c	F	F	—CH ₂ —	OH	CO ₂ H	248–252 ^c	–24	C ₂₇ H ₂₄ F ₂ O ₅	C.H	238 (16.0)
3a	F	H	H	OCOC ₂ H ₅	CO ₂ H	224–227	+3	C ₂₈ H ₂₆ FO ₆	C.H	242 (14.3)
4ba	H	F	α-CH ₃	OCOC ₂ H ₅	COSCONMe ₂	191–193	+82	C ₂₇ H ₃₆ FNO ₆ S	C.H,N,S	239 (18.7)
4bb	H	F	β-CH ₃	OCOC ₂ H ₅	COSCONMe ₂	foam	+172	C ₂₆ H ₃₄ FNO ₆ S	C.H,N,S ^c	238 (19.6)
4bc	H	F	β-CH ₃	OCOC ₂ H ₅	COSCONMe ₂	167–170	+185	C ₂₇ H ₃₄ FNO ₆ S	C.H,N	237.5 (19.8)
	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCONMe ₂	189–192	+6	C ₂₇ H ₃₄ FNO ₆ S	C.H,N,S ^c	236.5 (19.2)
	H	F	β-CH ₃	OCOC ₂ H ₅	CO ₂ CONMe ₂	200–203	+74	C ₂₇ H ₃₆ FNO ₇	C.H,N	238 (15.9)
5a	H	F	H	OH	COSH	222–225	+116	C ₂₆ H ₂₆ FO ₄ S	C.H	244 (19.3)
5b	H	F	α-CH ₃	OH	COSH	209–214	+104	C ₂₇ H ₂₇ FO ₄ S	C.H,S ^c	245 (17.6)
5c	F	F	α-CH ₃	OH	COSH	230–232	+94	C ₂₇ H ₂₆ F ₂ O ₄ S	C.H,S	243 (21.0)
5d	H	F	β-CH ₃	OH	COSH	198–201 ^c	+189	C ₂₇ H ₂₇ FO ₄ S	C.H,S ^a	243 (19.5)
	F	F	—CH ₂ —	OH	COSH	251–256 ^c	+58	C ₂₇ H ₂₄ F ₂ O ₄ S	C.H,S	242 (20.5)
	F	H	H	OCOC ₂ H ₅	COSH	189–193	+72	C ₂₈ H ₂₈ FO ₆ S	C.H,S	247 (18.1)
6b	H	F	H	OCOC ₂ H ₅	COSH	136–138	+75	C ₂₈ H ₂₈ FO ₆ S	C.H,S	245 (18.4)
6c	H	F	α-CH ₃	OCOC ₂ H ₅	COSH	141–143	+30	C ₂₄ H ₃₁ FO ₄ S	C.H	243 (16.3)
6d	F	F	α-CH ₃	OCOC ₂ H ₅	COSH	175–177	–10	C ₂₈ H ₂₈ F ₂ O ₆ S	C.H,S	242.5 (18.0)
6e	F	F	α-CH ₃	OCOC ₂ H ₅	COSH	161–164	–27	C ₂₄ H ₃₀ F ₂ O ₆ S	C.H,S	243 (18.9)
6f	F	F	α-CH ₃	OCOC ₂ H ₅	COSH	155–157	+21	C ₂₈ H ₃₂ F ₂ O ₆ S	C.H,S	242.5 (18.4)
6g	H	H	β-CH ₃	OCOC ₂ H ₅	COSH	159–163	+113	C ₂₄ H ₃₂ O ₆ S	C.H,S	247 (17.8)
6h	H	F	β-CH ₃	OCOC ₂ H ₅	COSH	178.5–179	+98	C ₂₄ H ₂₈ FO ₄ S	C.H,S ^a	242 (17.8)
6i	H	F	β-CH ₃	OCOC ₂ H ₅	COSH	177–179	+110	C ₂₄ H ₃₁ FO ₄ S	C.H,S	242 (18.3)
6j	H	F	β-CH ₃	OCOC ₂ H ₅	COSH	175–176	+107	C ₂₈ H ₃₃ FO ₆ S	C.H,S ^a	244 (18.1)
6k	H	F	—CH ₂ —	OCOC ₂ H ₅	COSH	236–239	–71	C ₂₄ H ₂₈ FO ₄ S	C.H,S ^c	242 (17.7)
7a	H	F	β-CH ₃	spiro(C ₆ H ₉ N ₃ O ₃) ^d		193–195	+96	C ₂₇ H ₃₃ FN ₂ O ₅	C.H,N ^e	240 (14.3)
7b	H	F	β-CH ₃	spiro(C ₆ H ₉ N ₃ O ₃) ^d		168–176	–8	C ₂₇ H ₃₃ FN ₂ O ₅	C.H,N ^e	240 (14.5)
8	H	F	β-CH ₃	OCOC ₂ H ₅	CO(C ₃ H ₇ N ₂)	190–203	+52	C ₂₇ H ₃₃ FN ₂ O ₅	C.H,N ^m	240 (17.3)
10i	F	H	H	OCOC ₂ H ₅	COSCH ₂ Cl	188–191	+48	C ₂₄ H ₃₀ ClFO ₄ S	C.H,Cl,S ^a	240 (18.7)
10j	H	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	247–250	+50.5	C ₂₈ H ₃₂ ClFO ₆ S	C.H,Cl,S	238 (19.0)
10k	F	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	280–283	+45	C ₂₄ H ₂₉ ClF ₂ O ₅ S	C.H,Cl,S	238.5 (19.8)
10l	F	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	235–238	+49	C ₂₆ H ₃₃ ClF ₂ O ₆ S	C.H,Cl,S	238.5 (19.9)
11b	F	H	H	OCOC ₂ H ₅	COSCH ₂ Cl	195–197	+18	C ₂₄ H ₃₀ FIO ₄ S	C.H,I,S	243.5 (20.7)
11c	H	F	H	OCOC ₂ H ₅	COSCH ₂ Cl	175–178	+4	C ₂₄ H ₃₀ FIO ₄ S	C.H,I ^c	242 (17.9)
11d	F	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	241–243	+78	C ₂₄ H ₂₉ F ₂ IO ₄ S	C.H,I,S	240 (20.2)
11e	F	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	233–236 ^c	+87	C ₂₈ H ₃₁ F ₂ IO ₄ S	C.H,I,S	241 (20.6)
1	F	F	α-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	210–212	+89	C ₂₆ H ₃₃ F ₂ IO ₄ S	C.H,I,S ^m	241 (20.7)
1	H	F	β-CH ₃	OCOC ₂ H ₅	COSCH ₂ Cl	204 ^c –205	–29	C ₂₄ H ₃₀ FIO ₄ S	C.H,I,S	241 (20.6)
11h	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCH ₂ Cl	191–199	–31	C ₂₅ H ₃₀ FIO ₄ S	C.H,I,S	241 (19.8)
16	H	F	β-CH ₃	epoxide	COSCH ₂ Cl	246–251	+131	C ₂₂ H ₂₆ ClFO ₄ S	C.H,Cl	239 (20.5)
	H	F	—CH ₂ —	OH	COSCH ₂ Cl	242–243	+36	C ₂₂ H ₂₆ ClFO ₄ S	C.H	239.5 (19.4)
a	H	F	β-CH ₃	epoxide	COSCH ₂ Cl	297–299	+156	C ₂₂ H ₂₇ FO ₄ Se	C.H,Se	239 (16.3)
16b	H	F	β-CH ₃	epoxide	COSCH ₂ Cl	229–232 ^c	+111	C ₂₂ H ₂₆ ClFO ₄ Se	C.H,Cl ^b	237.5 (16.5)
19a	H	F	—CH ₂ —	OH	COSCH ₂ Cl	248–254 ^c	+82.5	C ₂₂ H ₂₇ FO ₄ Se	C.H,Se	240.5 (15.9)
19b	H	F	—CH ₂ —	OH	COSCH ₂ Cl	237–239	+45.5	C ₂₂ H ₂₆ ClFO ₄ Se	C.H,Cl,Se	240.5 (16.3)
20a ^d	H	F	—CH ₂ —	OH	COSCH ₂ Cl	225–235 ^c	+124	C ₂₂ H ₂₆ FO ₄ Se	C.H	238 (15.7)
20b ^d	H	F	—CH ₂ —	OH	COSCH ₂ Cl	209–210	+142	C ₂₂ H ₂₄ ClFO ₄ Se	C.H	237 (16.1)
21a ^d	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCH ₂ Cl	209–211	–9	C ₂₅ H ₂₉ FO ₄ Se	C.H,Se	237 (16.0)
21b ^d	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCH ₂ Cl	156–158	–8	C ₂₅ H ₂₈ ClFO ₄ Se	C.H	237 (16.1)
22c	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCH ₂ Cl	174–175	–70	C ₂₅ H ₃₀ FIO ₄ Se	C.H,Se	238 (16.7)
22d	H	F	—CH ₂ —	OCOC ₂ H ₅	COSCH ₂ F	216–218	–43.5	C ₂₅ H ₃₀ F ₂ O ₅ Se	C.H	239.5 (16.8)
24	H	F	β-CH ₃	OCOC ₂ H ₅	COS ₂ ^p	234–235	+107	C ₄₈ H ₆₀ F ₂ O ₁₀ S ₂	C.H,S ^m	238 (37.1)

^a ¹H NMR and infrared spectra were obtained for all compounds, and data are in the Experimental Section for selected compounds. ^b Persistent solvation was confirmed spectroscopically. ^c Decomposition. ^d 11-Ketones. ^e Solvate (0.5EtOAc). ^f Solvate (0.25Me₂CO). ^g Solvate (1.0H₂O). ^h Solvate (0.25H₂O). ⁱ Isomer A. ^j Isomer B. ^k Solvate (0.16EtOAc). ^l Solvate (0.2EtOAc). ^m Solvate (0.5H₂O). ⁿ Solvate (0.33H₂O). ^o Solvate (0.6MeOH). ^p Disulfide.

C-17 resonances (92.1 and 91.1 ppm) were structurally characteristic, and the ¹H NMR confirmed that the ethyl groups in each isomer were no longer part of an ester function; the configurations of the two isomers were not established. From a further experiment, in which the reaction mixture was treated with dimethylamine, the same dioxolanones 7 were isolated together with a minor third component of intermediate polarity, identified as the imidazolidine 8, ν_{max} 1742 cm⁻¹. The dioxol-

anones 7 each reacted with NaSMc to give 9, but not with NaSH. There was insufficient 8 to test its reactivity.

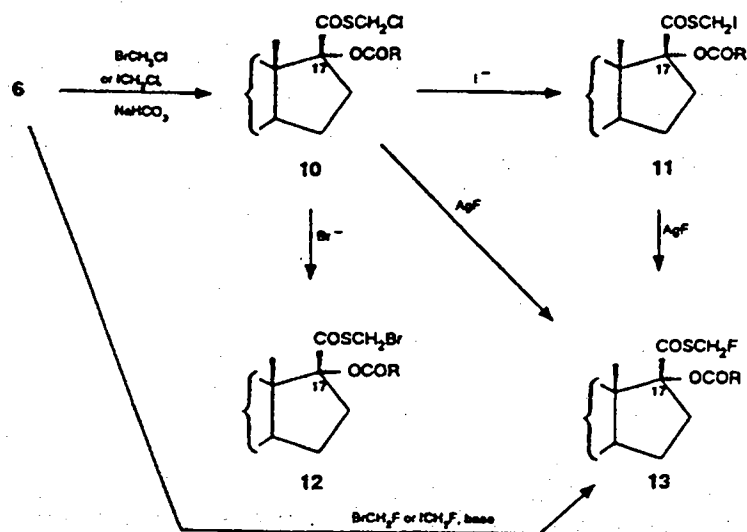
Chloromethyl carbothioates 10 were prepared from carbothioate salts by alkylation with bromochloromethane, or chloriodomethane, in dimethylacetamide. The chloromethyl thioesters 10 reacted with sodium iodide to give iodomethyl thioesters 11, which in turn reacted with sodium bromide or silver fluoride

Table 2. Biologically-Assayed Halomethyl Androstane-17 β -carbothioates and -17 β -carboselenoates (Physical Properties^a)


no.	Z	Y	X	R	16	mp, °C	[α] _D , detg (dioxane)	formula	anal.	UV, λ _{max} (EtOH) nm (ε × 10 ⁻³)
13a	H	F	F	C ₂ H ₅	H	224–225	+70	C ₂₄ H ₃₀ F ₂ O ₆ S	C,H,F,S	238.5 (17.4)
10a	F	H	Cl	C ₂ H ₅	H	196–199	+38	C ₂₄ H ₃₀ ClFO ₆ S	C,H,S	238 (16.9)
13b	F	H	F	C ₂ H ₅	H	207–211	+70	C ₂₄ H ₃₀ F ₂ O ₆ S	C,H,F,S	237 (17.1)
13c	F	H	F	C ₂ H ₅	α-CH ₃	242–243	+37	C ₂₅ H ₃₂ F ₂ O ₆ S	C,H,S	237 (18.0)
10b	F	F	Cl	C ₂ H ₅	α-CH ₃	272–275	+49	C ₂₅ H ₃₁ ClF ₂ O ₆ S	C,H	238 (20.0)
	F	F	F	CH ₃	α-CH ₃	308–310	+29	C ₂₄ H ₂₈ F ₃ O ₆ S	C,H,S	236 (19.0)
	F	F	F	C ₂ H ₅	α-CH ₃	274–275	+32	C ₂₅ H ₃₁ F ₃ O ₆ S	C,H,F,S	236.5 (18.6)
13f	F	F	F	C ₃ H ₇	α-CH ₃	249–252	+32	C ₂₆ H ₃₃ F ₃ O ₆ S	C,H,F,S	237 (19.1)
10c	H	H	Cl	C ₂ H ₅	β-CH ₃	192–193	+65	C ₂₄ H ₃₂ ClO ₆ S	C,H,Cl,S	241 (17.8)
13g	H	H	F	C ₂ H ₅	β-CH ₃	223–225	+103	C ₂₅ H ₃₃ FO ₆ S	C,H,S	240 (16.3)
10d	F	H	Cl	CH ₃	β-CH ₃	220–223	+39.5	C ₂₄ H ₃₀ ClFO ₆ S	C,H,Cl,S	238 (18.4)
10e	F	H	Cl	C ₂ H ₅	β-CH ₃	212–214	+44	C ₂₅ H ₃₂ ClFO ₆ S	C,H,Cl,S	237 (17.7)
12 ^c	F	H	Br	C ₂ H ₅	β-CH ₃	186.5–187	+2	C ₂₅ H ₃₂ BrFO ₆ S	C,H,Br,S	241 (19.9)
11a ^c	F	H	I	C ₂ H ₅	β-CH ₃	196–197	-32	C ₂₅ H ₃₂ IO ₆ S	C,H,I,S	242 (20.2)
13i	F	H	F	C ₂ H ₅	β-CH ₃	237–241	+98	C ₂₅ H ₃₂ F ₂ O ₆ S	C,H,F,S	237 (17.4)
10f	F	H	Cl	C ₃ H ₇	β-CH ₃	172–175	+46	C ₂₆ H ₃₄ ClFO ₆ S	C,H,Cl,S	239 (18.7)
10g	F	H	Cl	C ₂ H ₅	-CH ₂	212–221	-56	C ₂₅ H ₃₀ ClFO ₆ S	C,H,Cl,S	239 (19.5)
13j	F	H	F	C ₂ H ₅	-CH ₂	205–215	-58	C ₂₅ H ₃₀ F ₂ O ₆ S	C,H,F,S	237 (18.1)
10h	F	F	Cl	C ₂ H ₅	-CH ₂	242–245	-56	C ₂₅ H ₂₈ ClF ₂ O ₆ S	C,H,Cl,S	238.5 (19.9)
13k	F	F	F	C ₂ H ₅	-CH ₂	251–255 ^d	-56	C ₂₆ H ₃₀ F ₃ O ₆ S	C,H,S	236.5 (19.1)
22a	F	H	H	C ₂ H ₅	-CH ₂	225–227	-37	C ₂₅ H ₃₁ FO ₆ Se	C,H,Se	239.5 (16.3)
22b	F	H	Cl	C ₂ H ₅	-CH ₂	212–214	-48	C ₂₅ H ₃₀ ClFO ₆ Se	C,H,Cl,Se	240.5 (16.6)

^a ¹H NMR and infrared spectra were obtained for all compounds, and data are in the Experimental Section for selected compounds.^b Solvated with 0.5 mol of H₂O. ^c Solvated with 0.33 mol of H₂O. ^d Decomposition.

Scheme 4



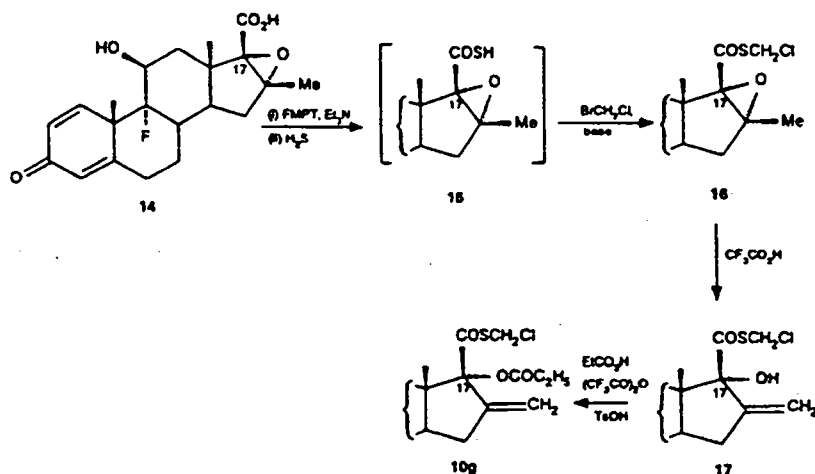
to give the bromomethyl and fluoromethyl thioesters 12 and 13, respectively. The fluoromethyl thioester 13e was also prepared directly from the potassium salt of the carbothioic acid 6e, using fluoroiodomethane¹⁴ or bromofluoromethane¹⁵ (Scheme 4).

Kertesz and Marx¹¹ reported that 2-fluoro-*N*-methylpyridinium tosylate (FMPT) could be used for the activation of 17 β -carboxylic acids in the presence of a 16 α ,17 α -acetone but that neighboring group participation dominated the chemistry of 17 α -hydroxy or 17 α -acyloxy compounds. FMPT also activated the 16 α ,17 α -

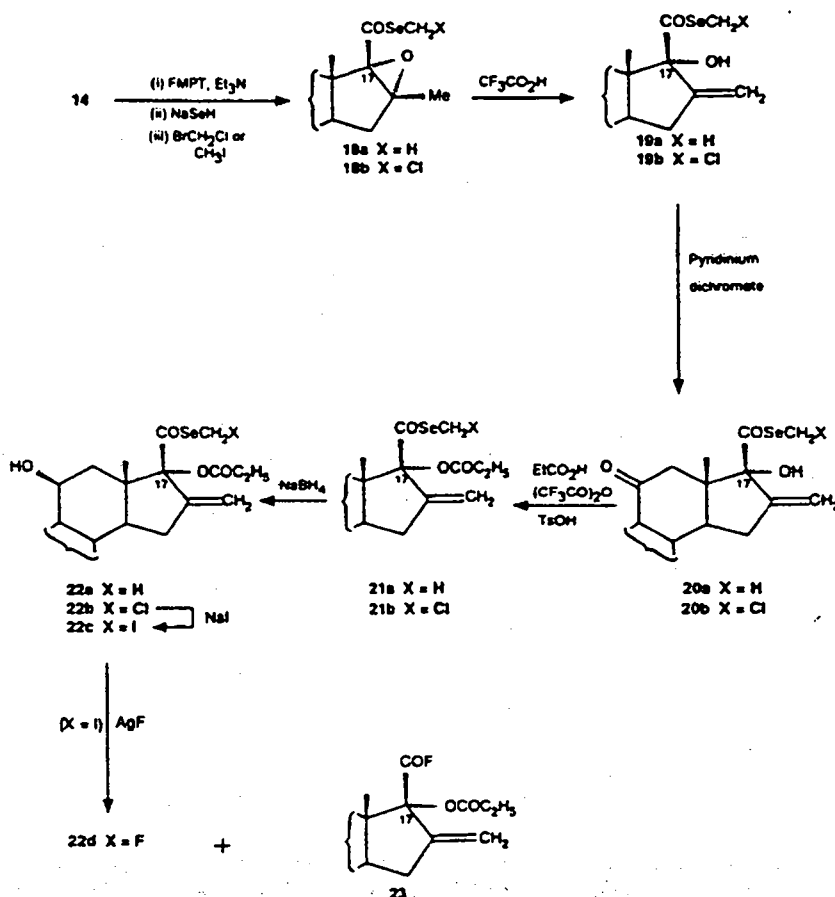
epoxy-16 β -methyl 17 β -carboxylic acids 14 to reaction with H₂S. The resulting carbothioic acid 15 was unstable but treatment with bromochloromethane *in situ* gave the chloromethyl carbothioate 16. This could be rearranged with trifluoroacetic acid to the 16-methylene 17 α -ol 17 which on propionylation in the presence of acid gave a mixture of the 17 α -ester 10g and the isomeric 11 β -monoester (Scheme 5).

Activation of 14 with FMPT and reaction with NaSeH¹⁶ gave the corresponding carboselenoic acid, which could be alkylated *in situ* to the methyl or

Scheme 5



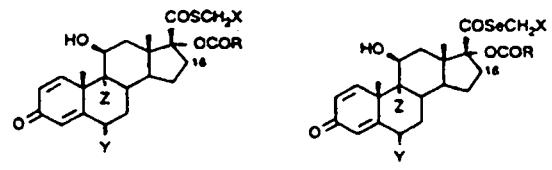
Scheme 6



chloromethyl carboselenoates **18a,b**. Epoxide rearrangement ($\text{CF}_3\text{CO}_2\text{H}$) then gave the corresponding 11β - 17α -diols **19a,b**. In this series, oxidation of **19a,b** to the 11 -ketones **20a,b** prior to 17α -propionylation followed by selective reduction of 11 -oxo esters **21a,b** to the 11β -alcohols **22a,b** avoided unwanted 11β -esterification (Scheme 6).

Reaction of the iodomethyl selenoester **22c** with silver fluoride in acetonitrile gave the corresponding fluoro-methyl selenoester **22d** as a minor product (3%), but the major product (29%) was the 17β -acyl fluoride **23**,

presumably formed by silver ion-assisted displacement of the selenide group by fluoride ion. While **23** was not analytically pure, the structure of the major component (83% by HPLC) was clearly revealed by its highly characteristic ^1H , ^{13}C , and ^{19}F NMR, infrared, and mass spectra. The same main fragment ions were observed in the chemical ionisation mass spectra of both **22d** and **23**, the initial losses being those of HSeCH_2F and HF , respectively, from the major MH^+ molecular ions. The MH^+ peaks were confirmed by HRMS accurate mass measurements.

Table 3. Biological Activities of Halomethyl Androstane-17 β -carbothioates and -17 β -carboselenoates


no.	Z	Y	X	R	16	human V ^a	mouse		rat	
							AIT ^b	HPA ^c	AIT ^b	HPA ^c
13a	H	F	F	C ₂ H ₅	H	697 (230–2438)	56 (36–86)	>200 (G)	97 (62–156)	–
10a	F	H	Cl	C ₂ H ₅	H	916 (471–1874)	20 (14–29)	100 (G)	–	–
13b	F	H	F	C ₂ H ₅	H	1984 (1023–4013)	63 (39–105)	149 (103–219)	39 (27–56)	1.5 (G)
13c	F	H	F	C ₂ H ₅	α-CH ₃	653 (311–1395)	–	–	–	–
10b	F	F	Cl	C ₂ H ₅	α-CH ₃	124 (63–231)	56 (37–86)	0.04 (0.01–0.09)	29 (25–32)	<0.02 (G)
13d	F	F	F	CH ₃	α-CH ₃	392 (159–959)	76 ^d	2.9 (1.4–5.2)	88 ^e	3 (G)
13e	F	F	F	C ₂ H ₅	α-CH ₃	945 (551–1655)	113 ^f	1.0 (0.5–2.1)	85 ^g	1.5 (0.8–2.2)
13f	F	F	F	C ₃ H ₇	α-CH ₃	299 (98–953)	55 (34–87)	0.7 (G)	55 (35–86)	–
10c	H	H	Cl	C ₂ H ₅	β-CH ₃	295 (72–1148)	27 (17–44)	–	29 (19–44)	1.4 (0.5–3.2)
13g	H	H	F	C ₂ H ₅	β-CH ₃	800 (231–2773)	50 (35–71)	–	44 (30–63)	5.1 (1.8–11.8)
10d	F	H	Cl	CH ₃	β-CH ₃	544 (154–2047)	59 (33–103)	14.7 (8.8–24.6)	24 (G)	0.5 (G)
13h	F	H	F	CH ₃	β-CH ₃	1388 (374–5370)	67 (47–95)	–	40 (25–64)	13.5 (G)
10e	F	H	Cl	C ₂ H ₅	β-CH ₃	1469 (858–2541)	41 (27–64)	44 (G)	36 (24–53)	0.9 (0.5–1.7)
12	F	H	Br	C ₂ H ₅	β-CH ₃	254 (G)	–	–	–	–
11a	F	H	I	C ₂ H ₅	β-CH ₃	41 (G)	–	–	–	–
13i	F	H	F	C ₂ H ₅	β-CH ₃	1262 (597–2669)	89 (45–169)	450 ^h	39 (30–52)	13 (8–24)
10f	F	H	Cl	C ₃ H ₇	β-CH ₃	143 (41–435)	–	–	–	–
10g	F	H	Cl	C ₂ H ₅	–CH ₂	365 (198–665)	42 (28–64)	2 (1–3)	12 (9–17)	0.8 (G)
13j	F	H	F	C ₂ H ₅	–CH ₂	1497 (575–4085)	41 (28–64)	44 (27–76)	20 (14–26)	2.5 (G)
10h	F	F	Cl	C ₂ H ₅	–CH ₂	170 (G)	108 (70–171)	>100 (G)	–	–
13k	F	F	F	C ₂ H ₅	–CH ₂	1048 (G)	197 (G)	>100 (G)	–	–
22a	F	H	H	C ₂ H ₅	–CH ₂	187 (85–415)	27 (16–44)	–	19 (12–29)	<0.2
22b	F	H	Cl	C ₂ H ₅	–CH ₂	200 (103–388)	40 (27–61)	2 (G)	16 (9–26)	–
(fluocinolone acetonide) ^y						100	100	100	100	100

^a Human vasoconstrictor activity relative to fluocinolone acetonide (100). Numbers in parentheses are 95% confidence level intervals or G represents a graphical estimate. ^b Topical antiinflammatory activity relative to fluocinolone acetonide (100). Parentheses as for a. ^c Systemic corticosteroid activity after topical application relative to fluocinolone acetonide (100). Parentheses as for a. ^d Mean of two results: 35 (21–58) and 117 (81–167). ^e Mean of three results: 103 (60–176), 84 (47–158), and 76 (37–156). ^f Mean of two results: 134 (85–212) and 86 (46–150). ^g Mean of two results: 72 (57–90) and 97 (70–136). ^h Mean of two results: 530 (G) and 370 (G). ⁱ Standard.

The ¹H NMR spectra of carbothioic acids were best measured in deuteriochloroform if solubility was sufficient, as in Me₂SO-*d*₆ impurity signals gradually appeared due to oxidation to the neutral disulfide (e.g., with 6i), a process complete in a longer time or at elevated temperature.

In each series of halomethyl 17 α -acyloxy 17 β -carbothioates the ultraviolet extinction coefficients increased from ca. 16 000 to ca. 20 000, and the positions of the maxima moved slightly to higher wavelength (ca. 239 to 244 nm) on progressing from fluoromethyl through to iodomethyl thioesters. Gradations of optical rotation at 589 nm were also noted, increasing when a 16 α -methyl substituent was present but decreasing when a 16 β -methyl or no substituent was present. Presumably the contribution due to the carbothioate chromophore is considerably influenced by its conformation, and this in turn depends on the nature of ring D and its substituents.

Biological Results and Discussion

Topical activity in humans was measured by the vasoconstriction assay according to the method of McKenzie and Atkinson.¹⁷ Topical antiinflammatory activity was measured in rats and mice by modifications of the croton oil ear assay of Tonelli et al.¹⁸ The undesired hypothalamic–pituitary–adrenal (HPA) function suppression was assessed in rats and mice by measuring reductions of levels of circulating corticosterone in response to ether

stress, using the procedure of Zenker and Bernstein.¹⁹ The results are shown in Table 3.

In the vasoconstriction assay, fluoromethyl carbothioates 13 were in general more active than their chloromethyl analogues 10 (13h, 10d; 13g, 10c; 13e, 10b; 13b, 10a; 13j, 10g; 13k, 10h; six pairs); however, for another pair (13i, 10e) the chloro analogue had the slightly greater potency. The bromomethyl and iodomethyl carbothioates 12 and 11a were less active than the chloromethyl analogue 10e. 17-Propionates 10e, 13e were better than the acetate (10d, 13d) and butyrate (10f, 13f) analogues, although the potency of the propionate (13i) was marginally less than that of the acetate (13h). A similar pattern was found in the mouse and rat antiinflammatory activities. A different pattern was found for HPA suppression where the 16 α -methyl compounds 10b, 13d, and 13e showed little effect in both mouse and rat. The most active of these in the vasoconstriction and antiinflammatory tests was 13e (fluticasone propionate, FP), so this was chosen for more detailed examination. The carboselenoates 22a,b showed moderate activity but were not examined further as it was considered unlikely that drugs containing selenium would be acceptable.

The fluoromethyl and chloromethyl carbothioates 13i and 10e were, respectively, more than 3.5 and 1.5 times as active than their oxygen analogues¹ in the vasoconstriction test, while the methyl carbothioate analogue of FP (13e) has been reported¹¹ to show topical activity

in the vasoconstriction test only in the order of that of the standard, fluocinolone acetonide.

FP did cause HPA suppression if given as a suspension in saline by the subcutaneous route in rats [1.2 (0.8–1.7)] and mice [0.7 (G)], compared with betamethasone (1.0); in rats the suppression was measured by weighing the adrenals. Given orally, however, it showed only weak adrenolytic activity in rats [0.13 (0.08–0.21)] and depression of corticosterone levels in mice [0.01 (0.004–0.03)] compared with betamethasone (1.0). Weak glucocorticoid activity after oral administration is particularly of value in the treatment of airway conditions where a high proportion of the dose is swallowed.²⁰

FP has been reported⁵ to be rapidly converted by liver homogenates (from mouse, rat, or dog) into the known xylic acid 3f.¹¹ This acid has since been confirmed as the principal metabolite in a study²⁰ of the human pharmacology of FP, arising from orally administered drug by first-pass conversion in the liver. 3f showed negligible HPA suppression as measured by its adrenolytic activity in rats [<0.01 (G)] and by depression of corticosterone levels in mice [<0.001 (G)] compared with betamethasone (1.0) by the subcutaneous route. Formulations of FP have now received approval for the treatment of rhinitis (Flixonase²¹), asthma (in UK, Flixotide²¹), and steroid-responsive dermatoses (in USA, Cutivate²¹).

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined in dioxane at 20–22 °C; ¹H NMR spectra were determined in Me₂SO-*d*₆ (unless stated otherwise) at 60, 90, or 100 MHz on Perkin-Elmer R24B, R32, or JEOL MH100 spectrometers, respectively. The R32 instrument was also used at 84.68 MHz for ¹⁹F NMR. A JEOL FX100 Fourier-transform spectrometer was used at 25.05 MHz for ¹³C NMR or at 100 MHz for ¹H NMR. Chemical shifts are relative to Me₃Si(CH₃)₂SO₃Na in Me₂SO-*d*₆ and SiMe₄ in CHCl₃-*d* for ¹H and ¹³C NMR and to CFCl₃ for ¹⁹F NMR, as internal standards. IR spectra were recorded in Nujol mulls, or in CHBr₃, where so indicated. Mass spectra were determined on a Finnigan MAT 4600 spectrometer using positive-ion chemical ionization with ammonia as the reagent gas. Accurate mass measurements were made on a Kratos concept spectrometer by Mrs. V. Boote, Department of Chemistry, University of Manchester. Organic reaction extracts were routinely dried over magnesium sulfate prior to removal of the solvent by rotary evaporation at ca. 20 mmHg at or below 50 °C. Products were dried in vacuo at up to 50 °C. Analytical TLC was conducted on Merck Kieselgel 60 F₂₅₄ plates, developed with chloroform:acetone (e.g., 4:1) for neutral compounds or chloroform:acetone:acetic acid (e.g., 30:8:1) for acidic compounds. Preparative-layer chromatography (PLC) was performed in the same solvent systems on Merck Kieselgel 60 PF₂₅₄ plates. Products were usually detected at 254 nm and eluted with ethyl acetate. Physical properties of intermediates are given in Table 1; those of biologically-assayed compounds are in Table 2. ¹H NMR (in Me₂SO-*d*₆ unless stated otherwise) and infrared spectra (in Nujol unless stated otherwise) were taken for all compounds, and where solvation is tabulated this was confirmed from the spectra.

6 α -Fluoro-11 β ,17 α -dihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic Acid (2a). A solution of 6 α -fluoro-11 β ,17 α ,21-trihydroxypregna-1,4-diene-3,20-dione (1a)²² (4.99 g, 13.2 mmol) in tetrahydrofuran (50 mL) was stirred with a solution of periodic acid (10.0 g, 45 mmol) in water (24 mL) at 22 °C for 50 min. The tetrahydrofuran was removed in vacuo to leave an aqueous suspension which was filtered, and the solid was washed with water and dried to give 2a (4.80 g, 100%). A portion (0.271 g) was crystallized from methanol to give the analytical sample of 2a (0.171 g, 63%).

9 α -Fluoro-11 β ,17 α -dihydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylic Acid (2b). A stirred suspension of 9 α -fluoro-11 β ,17 α ,21-trihydroxypregna-1,4-diene-3,20-dione (1b)²² (10.0 g, 26.4 mmol) in tetrahydrofuran (55 mL) was stirred at 22 °C for 2 h with a solution of periodic acid (9.0 g, 39.5 mmol) in water (90 mL) and then poured into water (150 mL) and crushed ice (250 mL). Filtration gave 2b (9.42 g, 98%), a portion (0.100 g) of which was recrystallized from ethanol to give the analytical sample of 2b (0.060 g, 59%).

6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carboxylic Acid (2c). 6 α ,9 α -Difluoro-11 β ,17 α ,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione (1c)²⁴ (3.6 g) was oxidized as in the preceding experiment to give 2c (3.40 g, 98%). A portion (0.250 g) crystallized from aqueous methanol gave the analytical sample of 2c (0.162 g, 64%).

6 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic Acid (3a). A solution of 2a (4.49 g, 12.3 mmol) and Et₃N (4.46 mL, 31.6 mmol) in CH₂Cl₂ (160 mL) at –5 °C was treated dropwise with stirring with propionyl chloride (2.80 mL, 32 mmol) in CH₂Cl₂ (5 mL) during 5 min. After 20 min the reaction mixture was diluted with CH₂Cl₂, washed with aqueous NaHCO₃ and then H₂O, dried, and evaporated to give the intermediate mixed anhydride as a solid (5.70 g). This was stirred in acetone (30 mL) with Et₃NH (4.6 mL, 44.3 mmol) for 30 min to give a clear yellow solution which was concentrated, diluted with water (150 mL), and washed with EtOAc. The aqueous phase was acidified to pH 2 with 2 N HCl (50 mL) and extracted with EtOAc. The extract was washed with water and evaporated to give a foam (5.82 g), a portion of which (0.304 g) was crystallized from EtOAc to give the analytical sample of 3a (0.144 g, 47%) as plates.

Formation of 17 β -(*N,N*-dimethylcarbamoyl)thio]carbonyl Compounds 4b. General Method A. The steroid 17 β -carboxylic acid 3 (1 equiv) stirred in CH₂Cl₂ (ca. 15 mL/g of 3) was treated successively with Et₃N (1 equiv) and *N,N*-dimethylthiocarbamoyl chloride (2 equiv) under N₂ at 20 °C, the reaction being monitored by TLC until no further consumption of starting material was observed (usually 6–30 h). The reaction mixture was diluted with EtOAc (ca. 50 mL/g of 3), washed with 1N HCl, 5% NaHCO₃, and water, dried, and evaporated to give the crude anhydride 4b, purified by crystallization or by PLC then crystallization.

17 β -(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -(propionyloxy)androsta-1,4-dien-3-one (4ba). 9 α -Fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3b)²⁵ was treated by general method A, but with the addition of NaI (1 equiv) to the reaction mixture, to give crystalline 4ba (63%) recrystallized twice from acetone to give the analytical sample: IR (CHBr₃) 3610 (OH), 1740, 1710 (w) (COSCON, propionate), 1670, 1632, 1618 ($\Delta^{1,4}$ -3-one) cm⁻¹.

17 α -Acetoxy-17 β -(*N,N*-dimethylcarbamoyl)thio]carbonyl]-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-dien-3-one (4bb). 17 α -Acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-diene-17 β -carboxylic acid (3c)¹¹ treated by general method A gave crude anhydride (87%, ca. 90% pure by TLC), purified by PLC to give the analytical sample of 4bb as a foam: IR (CHBr₃) 3590 (OH), 1735 (COSCON, propionate), 1665, 1630, 1612 ($\Delta^{1,4}$ -3-one) cm⁻¹.

17 β -(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9 α -fluoro-11 β -hydroxy-16 β -methyl-17 α -(propionyloxy)androsta-1,4-dien-3-one (4bc). 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3d),¹¹ solvated with 0.75 mol of EtOAc (4.99 g, 9.96 mmol) in pyridine (20 mL), was treated with dimethylthiocarbamoyl chloride (2.69 g, 21.8 mmol) for 19 h at room temperature. TLC indicated that only half of the starting material had been consumed. Isolations in general method A gave the crude anhydride (2.10 g, 40.5%), part of which was purified by PLC and crystallization from ether to give the analytical sample of 4bc: IR (CHBr₃) 3670 (OH), 1740 (COSCON, propionate), 1670, 1636, 1618 ($\Delta^{1,4}$ -3-one) cm⁻¹; ¹H NMR (90 MHz) 0.99 (13-CH₃, s) 1.07 (propionate CH₃, t, *J* = 7 Hz), 1.29 (16 β -CH₃, d, *J*

= 6 Hz), 2.39 (propionate CH_2 , q, $J = 7$ Hz), 2.99, 3.04 (NMe_2 , singlets), 7.32 (1-H, d, $J = 10$ Hz).

In a second method, 9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic acid, 6i, solvated with 0.75 mol of EtOAc (517 mg, 1.0 mmol) and Et_3N (0.49 mL, 3.5 mmol) in CH_2Cl_2 (10 mL), was treated with *N,N*-dimethylcarbamoyl chloride (0.37 mL, 4 mmol) and stirred under nitrogen at room temperature for 24 h. The mixture was diluted with EtOAc, washed successively with 1 N HCl, aqueous NaHCO_3 , and H_2O , dried, and evaporated to a foam (674 mg). PLC gave solvated 4bc as a solid (249 mg, 44%): $[\alpha]_D^{25} + 168^\circ$ (c 1.05); MS m/e 522 (MH^+), 417 ($\text{MH}^+ - \text{Me}_2\text{NCOSH}$), with mass, IR, and ^1H NMR spectra closely similar to those of the above. Anal. ($\text{C}_{27}\text{H}_{36}\text{FNO}_6 \cdot 0.5\text{EtOAc}$) C, H, N, S.

17 β -[(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9 α -fluoro-11 β -hydroxy-16-methylene-17 α -(propionyloxy)androsta-1,4-dien-3-one (4bd). 9 α -Fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3e)²⁵ treated by general method A gave the crude anhydride (86%), a portion of which was purified by PLC and crystallization from acetone to give the analytical sample 4bd (43%): IR (CHBr_3) 3620 (OH), 1740, 1710 (COSCON, propionate), 1665, 1630, 1612 ($\Delta^{14,3}$ -one) cm^{-1} .

17 β -[(*N,N*-Dimethylcarbamoyl)oxy]carbonyl]-9 α -fluoro-11 β -hydroxy-16 β -methyl-17 α -(propionyloxy)androsta-1,4-dien-3-one (4ca). 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3d),¹¹ solvated with 0.75 mol of EtOAc (491 mg, 0.98 mmol) in pyridine (2 mL), was treated with dimethylcarbamoyl chloride (208 mg, 1.94 mmol) at room temperature for 2 h. Isolation as in general method A gave the crude anhydride (489 mg), which was purified by two recrystallizations from acetone to give the analytical sample of 4ca (73%): IR (CHBr_3) 3625 (OH), 1783 (COOCON), 1740, 740 (propionate), 1673, 1634, 1618 ($\Delta^{14,3}$ -one) cm^{-1} .

Formation of 17 α -Hydroxy 17 β -Carbothioic Acids 5. **General Method B.** A solution of the 17 α -hydroxy 17 β -carboxylic acid 2 (1 equiv) in DMF (ca. 20 mL/g of 2) was treated with 1,1'-carbonyldiimidazole (2 equiv), and the mixture was stirred under nitrogen at room temperature for ca. 4 h. Hydrogen sulfide was bubbled into the reaction for 15–30 min. After 0.5–4 h the reaction mixture was poured into 2 N HCl and ice, and the precipitated acid 5 was collected by filtration.

9 α -Fluoro-11 β ,17 α -dihydroxy-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (5a). The carboxylic acid 2b treated by general method B gave 5a (97%), mp 219–222 °C. A portion (0.12 g) crystallized from ethanol gave the analytical sample 5a (0.07 g, 57%).

9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (5b). 9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (2d)⁸ by general method B gave the analytical sample of 5b (97%).

6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (5c). 6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (2e)¹¹ by general method B gave the analytical sample of 5c (92%): ^1H NMR (100 MHz) 0.85, (16 α - CH_3 , d, $J = 6$ Hz), 0.97 (13- CH_3 , s), 1.50 (10- CH_3 , s), 4.20 (11 α -H, m), 5.35 (11 β -OH, m), 6.10 (4-H, m), 6.26 (2-H, dd, $J = 10$, 2 Hz), 7.26 (1-H, broad d, $J = 10$ Hz).

9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (5d). 9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (2f)¹¹ by general method B, except that the first stage was carried out at –5 °C for 18 h and the product was isolated by extraction with EtOAc and crystallized twice from EtOAc to give 5d (60%): ^1H NMR (90 MHz) 1.02 (13- CH_3 , s), 1.10 (16 β - CH_3 , d, $J = 6$ Hz), 1.56 (10- CH_3 , s), 4.22 (11 α -H, m), 4.09 (4-H, m), 6.28 (2-H, dd, $J = 10$, 2 Hz), 7.37 (1-H, d, $J = 10$ Hz).

6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (5e). The carboxylic acid 2c by general method B gave 5e (89%). A

portion (0.25 g) crystallized from ethyl acetate gave the analytical sample of 5e (0.10 g, 36%).

Formation of 17 α -Acyloxy 17 β -Carbothioic Acids 6.

General Method C. The crude 17 β -[(*N,N*-dimethylcarbamoyl)thio]carbonyl compound 4b prepared by general method A was refluxed under nitrogen in Et_3NH (5–20 mL/g) for 3.5–6 h. The cooled reaction mixture was poured into 6 N HCl (ca. 60 mL/g) and ice (ca. 60 mL/g). The product was extracted into EtOAc, and the extract was washed with water before back-extraction into 5% Na_2CO_3 (ca. 120 mL/g). The aqueous layer was acidified with HCl to pH 1 and the product extracted into EtOAc, washed with water, dried, and evaporated to give 6.

General Method D. The crude 17 α -hydroxy 17 β -carbothioic acid (5), prepared by general method B, with Et_3N (ca. 3.5 equiv) in CH_2Cl_2 (ca. 25 mL/g) at ca. 0 °C was treated dropwise with an acyl chloride (ca. 4.5 equiv) and then stirred for ca. 45 min. The solution was washed with 2 N Na_2CO_3 , water, 2 N HCl, water, and brine, dried, and evaporated to leave a residue of the intermediate anhydride. This was dissolved in acetone (ca. 25 mL/g) and treated with Et_3NH (ca. 10 equiv) for ca. 1 h and then poured into 2 N HCl (ca. 40 mL/g) and ice (ca. 40 mL/g) to precipitate the carbothioic acid 5.

6 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6a). The 17 β -carboxylic acid 3a was converted by general methods A and then C and the product crystallized from a mixture of acetone and petrol (bp 60–80 °C) to give 6a (46%).

9 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6b). The 17 β -carboxylic acid 2b was converted by general methods B then D (using propionyl chloride) to give crude 6b (93%), mp 118–120 °C. A portion (0.35 g) crystallized from EtOAc gave the analytical sample of 6b (0.16 g, 44%).

9 α -Fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6c). 9 α -Fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3b)²⁵ was converted by general methods A then C, and the product was crystallized twice from acetone to give 6c (29%). The 17 α -hydroxy compound 5b also gave 6c (90%), mp 134–137 °C, by general method D, using propionyl chloride.

17 α -Acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (6d). The 17 α -hydroxy compound 5c was converted by general method D using acetyl chloride to give 6d (94%). Crystallization of a portion (0.40 g) from EtOAc gave the analytical sample of 6d (0.28 g, 64%).

6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6e). The 17 α -hydroxy compound 5c was converted by general method D using propionyl chloride to give 6e (91%). Crystallization of a portion (0.40 g) from EtOAc gave the analytical sample of 6e (0.29 g, 54%): ^1H NMR (90 MHz, in CHCl_3 -d) 0.99 (16 α - CH_3 , d, $J = 7$ Hz), 1.15 (propionate CH_3 , t, $J = 7$ Hz), 1.16 (13- CH_3 , s), 1.54 (10- CH_3 , s), 2.40 (propionate CH_2 , q, $J = 7$ Hz), 4.46 (11 α -H, broad m), 5.46 (6-H, broad dm, ca. $J = 50$ Hz), 6.40 (2-H, broad d, $J = 10$ Hz), 6.46 (4-H, m), 7.18 (1-H, d, $J = 10$ Hz). 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboxylic acid (3f)¹¹ also gave 6e (25%) using general methods A then C.

17 α -(Butyryloxy)-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (6f). The 17 α -hydroxy compound 5c was converted by general method D using butyryl chloride to give 6f (89%). Crystallization of a portion (0.40 g) from EtOAc gave the analytical sample of 6f (0.27 g, 60%).

11 β -Hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6g). 11 β -Hydroxy-16 β -methyl-17 β -(propionyloxy)-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (3g)⁸ was converted by general methods A then C and crystallized from ethyl acetate to give 6g (24%).

17 α -Acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (6h). Crude 4bb was converted by general method C to give 6h (51%): A

portion (0.150 g) crystallized twice from EtOAc gave the analytical sample of 6h (0.127 g, 43%).

9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6i). Crude 4bc was converted by general method C and crystallization to give 6i (42%), mp 172–173 °C; a portion was recrystallized twice from acetone to give the analytical sample of 6i: ¹H NMR (90 MHz) 1.00 (13-CH₃, s), 1.07 (propionate CH₃, t, *J* = 7 Hz), 1.29 (16 β -CH₃, d, *J* = 6 Hz), 1.54 (10-CH₃, s), 2.37 (propionate CH₂, q, *J* = 7 Hz), 4.30 (11 α -H, broad m), 5.45 (11 β -OH, m), 6.07 (4-H, m), 6.27 (2-H, d, *J* = 10 Hz), 7.32 (1-H, d, *J* = 10 Hz) with signals for the disulphide developing with time; ¹H NMR (90 MHz in CHCl₃-d) 1.07 (13-CH₃, s), 1.17 (propionate CH₃, t, *J* = 7 Hz), 1.37 (16 β -CH₃, d, *J* = 6 Hz), 1.57 (10-CH₃, s), 2.38 (propionate CH₂, q, *J* = 7 Hz), 4.46 (11 α -H, broad m), 6.17 (4-H, m), 6.37 (2-H, d, *J* = 10 Hz), 7.27 (1-H, d, *J* = 10 Hz).

he 17 α -hydroxy compound 5d was also converted into 6i (33%), mp 174–179 °C from EtOAc, using general method D with propionyl chloride. In a third method, the carboxylic acid 3d¹¹ (0.70 g, 1.40 mmol) and CDI (0.473 g, 2.9 mmol) in DMF (26 mL) were stirred at 22 °C under N₂ for 19.5 h. A dark-brown solution, prepared by passing H₂S through sodium hydride (60% in oil, 0.235 g) in DMF (10 mL), was added, and stirring was continued for 5.5 h. The mixture was diluted with EtOAc (100 mL), washed with 2N HCl, water, and brine, dried, and evaporated *in vacuo* to give 6i (0.186 g, 26%).

17 α -(Butyryloxy)-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioic Acid (6j). 17 α -(Butyryloxy)-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic acid (3h)⁸ was converted by general methods A then C and crystallization from EtOAc to give 6j (34%).

9 α -Fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (6k). Crude 4bd was converted by general method C to give crude 6k (44%), purified by crystallization of a portion (0.20 g) from EtOAc to give the analytical sample of 6k (0.137 g, 30%).

9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17(R)-spiro-5'-[2 β -ethyl-2'-f-(imidazol-1-yl)-1'-3'-dioxolan-4'-one], Isomers 7a and 7b. A solution of 3d (1.337 g, 2.67 mmol) in DMF (40 mL) was stirred under N₂ and treated with CDI (0.910 g, 5.6 mmol). After 5 h at 22 °C the reaction mixture was poured into water (250 mL) and extracted with EtOAc. The extract was washed with water, 3% Na₂CO₃, water, and brine, dried, and evaporated *in vacuo*. PLC gave the more-polar isomer 7a (0.41 g, 32%), crystallized from EtOAc: IR 1810 (4'-one), 1660, 1620, 1604 ($\Delta^{1,4}$ -3-one) cm⁻¹;

¹H NMR (90 MHz) 0.85 (ethyl CH₃, t, *J* = 8 Hz), 1.14 (13-CH₃, s), 1.17 (16 β -CH₃, d, *J* = 7 Hz), 1.47 (10-CH₃, s), 2.31 (ethyl CH₂, q, *J* = 8 Hz), 7.02, 7.27, 7.81 (imidazole protons); ¹³C NMR 8.6, 34.8 (ethyl), 17.1 (C18), 24.4 (C19), 71.4 (C11), 92.1 (C17), 102.1 (C9), 112.1 (C2'), 117.7, 130.8, 135.3 (imidazole), 153.8 (C1), 170.2 (C4'). The less-polar isomer 7b (0.218 g, 17%) crystallized from EtOAc: IR 1810 (4'-one), 1667, 1629, 1604 ($\Delta^{1,4}$ -3-one) cm⁻¹; ¹H NMR (90 MHz) 0.82 (ethyl CH₃, t, *J* = 8 Hz), 0.85 (16 β -CH₃, d, *J* = 7 Hz), 1.25 (13-CH₃, s), 1.56 (10-CH₃, s), 2.27 (ethyl CH₂, q, *J* = 8 Hz), 7.02, 7.37, 7.87 (imidazole protons); ¹³C NMR 8.6, 34.0 (ethyl), 17.2 (C18), 24.5 (C19), 71.6 (C11), 91.1 (C17), 102.4 (C9), 112.0 (C2'), 118.0, 131.0, 136.0 (imidazole), 154.0 (C1), 170.7 (C4'). In a repeat experiment on (0.455 g, 1.05 mmol) in which dimethylamine (1 mL) in DMF (9 mL) was added after 4 h, and stirring continued for 24 h, the isomers 7a and 7b were accompanied by a compound of intermediate polarity which crystallized from EtOAc–petroleum ether (bp 60–90 °C) to give 1-[(9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -propionyloxy)androsta-1,4-dien-17 β -yl]carbonyl]imidazole (8, 0.039 g, 4%): IR 1742 (imidazole C=O and ester), 1669, 1625, 1605 ($\Delta^{1,4}$ -3-one) cm⁻¹; ¹H NMR (90 MHz) 0.94 (propionate CH₃, t, *J* = 7 Hz), 1.08 (13-CH₃, s), 1.35 (16 β -CH₃, d, *J* = 7 Hz), 1.54 (10-CH₃, s), 2.43 (propionate CH₂, q, *J* = 7 Hz), 7.08, 7.69, 8.31 (imidazole protons).

S-Methyl 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioic Acid (9). A mixture of 6i (0.277 g, 0.61 mmol) and NaHCO₃

(0.167 g, 1.99 mmol) in CH₃I (0.3 mL, 4.8 mmol) and dimethylacetamide (2 mL) was stirred at room temperature for 3 h, diluted with EtOAc (150 mL), washed with 10% sodium thiosulfate (50 mL), water, 1 N HCl, water, 5% NaHCO₃, and water, dried, and evaporated *in vacuo* to give a foam (0.221 g) which was crystallized twice from methanol to give 9 (0.191 g, 67%): mp 235–237 °C; λ_{max} (EtOH) 239 nm (ϵ 18 995) [lit.¹¹ mp 223–224 °C; λ_{max} (MeOH) 239 nm (ϵ 18 890)]. Alternatively, 3d (0.681 g, 1.36 mmol) and CDI (0.456 g, 2.8 mmol) were stirred under N₂ at 22 °C in DMF (26 mL) for 19.5 h. A solution made from NaH (60% in oil, 0.285 g) in DMF (10 mL) saturated with MeSH was added, and after 5.5 h EtOAc (100 mL) was added and the solution was washed with 2 N–HCl, water, 2 N–Na₂CO₃, H₂O, and brine, dried, and evaporated *in vacuo* to give 9 (0.306 g, 45%). Similarly, 7a (0.131 g) with MeSNa in DMF for 1 h gave crude 9 as a foam (0.103 g, 81%) and 7b (0.042 g) gave crude 9 (0.041 g, 104%).

Formation of S-Chloromethyl 17 β -Carbothioates 10. General Method E. A solution of the carbothioic acid 6 (1 equiv) in dimethylacetamide (3.5–10 mL/g) was stirred with NaHCO₃ (2 equiv) and bromochloromethane (2–5 equiv) for 1–2 h, diluted with EtOAc (ca 200 mL/g), washed with 5% NaHCO₃ and water, dried, and evaporated *in vacuo* to give crude 10.

S-Chloromethyl 9 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10a). General method E on 6a and two crystallizations from methanol gave 10a (52%).

S-Chloromethyl 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10b). General method E on 6e and crystallization from EtOAc gave 10b (67%): ¹H NMR (90 MHz) 0.94 (16 α -CH₃, d, *J* = 7 Hz), 1.06 (13-CH₃, s), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.54 (10-CH₃, s), 2.40 (propionate CH₂, q, *J* = 7 Hz), 4.29 (11 α -H, broad m), 5.22 (CH₂Cl, s), ca. 5.65 (6-H, broad dm, *J* = 50 Hz), 6.18 (4-H, m), 6.36 (2-H, broad d, *J* = 10 Hz), 7.31 (1-H, broad d, *J* = 10 Hz).

S-Chloromethyl 11 β -Hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10c). General method E on 6g and crystallization from EtOAc gave 10c (76%).

S-Chloromethyl 17 α -Acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (10d). General method E on 6h and two crystallizations from EtOAc gave 10d (76%).

S-Chloromethyl 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10e). General method E on 6i and two crystallizations from methanol gave 10e (36%): ¹H NMR (90 MHz) 0.98 (13-CH₃, s), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.37 (16 β -CH₃, d, *J* = 7 Hz), 1.53 (10-CH₃, s), 2.38 (propionate CH₂, q, *J* = 7 Hz), 4.28 (11 α -H, broad m), 5.11 (CH₂Cl, s), 6.05 (4-H, m), 6.27 (2-H, broad d, *J* = 10 Hz), 7.29 (1-H, d, *J* = 10 Hz). A similar result was obtained with ICH₂Cl in place of BrCH₂Cl.

S-Chloromethyl 17 α -(Butyryloxy)-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (10f). General method E on 6j and crystallization from EtOAc gave 10f (53%).

S-Chloromethyl 9 α -Fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10g). General method E on 6k and PLC followed by two crystallizations from EtOAc gave 10g (50%): ¹H NMR (90 MHz) 1.01 (propionate CH₃, t, *J* = 7 Hz), 1.01 (13-CH₃, s), 1.54 (10-CH₃, s), 2.32 (propionate CH₂, q, *J* = 7 Hz), 4.30 (11 α -H, m), 5.21 (CH₂Cl, s), 5.50–5.71 (16=CH₂ and 11 β -OH, m), 6.08 (4-H, m), 6.29 (2-H, dd, *J* = 10, 2 Hz), 7.32 (1-H, d, *J* = 10 Hz).

S-Chloromethyl 6 α ,9 α -Difluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10h). General methods D then E on 5e, with PLC and crystallization from aqueous methanol, gave 10h (19.7%).

S-Chloromethyl 6 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10i). General method E on 6a and crystallization from acetone and

petroleum ether (bp 60–80 °C) then EtOAc and petroleum ether (bp 60–80 °C) gave 10i (81%).

S-Chloromethyl 9 α -Fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (10j). General method E on 6c and two crystallizations from acetone gave 10j (36%).

S-Chloromethyl 17 α -Acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (10k). General method E on 6d and crystallization from acetone gave 10k (74%).

S-Chloromethyl 17 α -(Butyryloxy)-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (10l). General method E on 6f and two crystallizations from acetone gave 10l (50%).

Formation of S-Iodomethyl 17 β -Carbothioates 11. General Method F. The S-chloromethyl carbothioate 10 (1 equiv) and NaI (ca. 4 g/g, ca. 12 equiv) were refluxed in acetone (10–15 mL/g) for 3–7 h. EtOAc (150 mL/g) was added, and the solution was washed with water, 10% sodium thiosulfate or 5% sodium metabisulfate, 5% NaHCO₃, and water, dried, and evaporated *in vacuo* to give crude 11.

S-Iodomethyl 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (11a). General method F on 10e and PLC and then two crystallizations from acetone gave 11a (41%): ¹H NMR (90 MHz in CHCl₃-d) 4.26 and 4.52 (CH₂I, dd, *J* = 11 Hz).

S-Iodomethyl 6 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (11b). General method F on 10i and two crystallizations from acetone and petroleum ether (bp 60–80 °C) gave 11b (76%).

S-Iodomethyl 9 α -Fluoro-11 β -hydroxy-3-oxo-17 β -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (11c). General method F on 10d and crystallization from methanol gave 11c (81%).

S-Iodomethyl 17 α -Acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (11d). General method F on 10k and crystallization from EtOAc gave 11d (82%).

S-Iodomethyl 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (11e). General method F on 10b and crystallization from EtOAc gave 11e (85%): ¹H NMR (90 MHz) 4.63 (CH₂I, s).

S-Iodomethyl 17 α -(Butyryloxy)-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (11f). General method F on 10l and crystallization from EtOAc gave 11f (85%).

S-Iodomethyl 17 α -Acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (11g). General method F on 10d then PLC and two crystallizations from EtOAc gave 11g (71%).

S-Iodomethyl 9 α -Fluoro-11 β -hydroxy-16-methylene-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (11h). General method F on 10g then PLC and two crystallizations from acetone gave 11h (74%).

S-Bromomethyl 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (12). A solution of 11a (0.660 g, 1.12 mmol) in acetone (20 mL) was stirred with LiBr (0.972 g, 11.2 mmol) at room temperature for 5 d. The reaction mixture was diluted with EtOAc (150 mL), washed with 10% sodium thiosulfate, water, and brine, dried, and evaporated *in vacuo* to give a foam (0.624 g). This crystallized from acetone and petroleum ether (bp 40–60 °C) to give 12 (0.499 g, 82%): ¹H NMR (90 MHz in CHCl₃-d) 4.51 and 4.89 (CH₂Br, dd, *J* = 11 Hz).

Formation of S-Fluoromethyl 17 β -Carbothioates 13. General Method G. The S-iodomethyl carbothioate (11, 1 equiv) and AgF (3–10 equiv) were stirred in the dark at room temperature in CH₃CN (12–75 mL/g) for 1–72 h. The highest reaction rates were achieved with finely pulverized AgF, obtained in granular form (from Ventron). The reaction mixture was diluted with EtOAc (ca. 150 mL/g) and filtered through kieselguhr. The filtrate was washed with water, dried, and evaporated *in vacuo* to give crude 13.

S-Fluoromethyl 6 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (13a). Gen-

eral method G on 11b and two crystallizations from acetone and petroleum ether (bp 60–80 °C) gave 13a (62%).

S-Fluoromethyl 9 α -Fluoro-11 β -hydroxy-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (13b). General method G on 11c and two crystallizations from MeOH gave 13b (58%).

S-Fluoromethyl 9 α -Fluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (13c). General methods F then G on 10j, without purification of the intermediate S-iodomethyl carbothioate, PLC, and two crystallizations from acetone gave 13c (43%).

S-Fluoromethyl 17 α -Acetoxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (13d). General method G on 11d and recrystallization from EtOAc gave 13d (70%).

S-Fluoromethyl 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (13e). Small pieces of AgF (2.46 g, 19.4 mmol) were stirred in CH₃CN (320 mL, dried over molecular sieves) for 17 h. The S-iodomethyl ester 11e (5.9 g, 9.7 mmol) was added, and the reaction mixture was stirred for 2 h. Finely powdered AgF (2.46 g, 19.4 mmol) was added, and after being stirred for a further 2 h the reaction mixture was concentrated to ca. 50 mL *in vacuo* and diluted with EtOAc (800 mL). After filtration through kieselguhr, the filtrate was washed with 2 N HCl (400 mL), water (3 × 400 mL), and brine (400 mL), dried over MgSO₄, and evaporated *in vacuo* to low volume when crystallization occurred. The white crystals (4.2 g, 87%) were collected and recrystallized from acetone to give 13e (3.6 g, 74%): IR 3350 (OH), 1750 (propionate), 1708 (carbothioate), 1668, 1622, 1612 ($\Delta^{1,4}$ -one) cm⁻¹; ¹H NMR (90 MHz) 0.96 (16 α -CH₃, d, *J* = 7 Hz), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.07 (13-CH₃, s), 1.56 (10-CH₃, s), 2.33 (propionate CH₂, q, *J* = 7 Hz), 4.32 (11 α -H, broad m), 5.63 (11-OH, broad d, *J* = 4 Hz), ca. 5.75 (6-H, broad dm, *J* = 50 Hz), 6.00 (SCH₂F, d, *J* = 51 Hz), 6.19 (4-H, m), 6.37 (2-H, dd, *J* = 10, 2 Hz), 7.33 (1-H, d, *J* = 10 Hz).

The fluoromethyl ester 13e was also prepared from the carbothioic acid 6e (0.5 g, 1.07 mmol) in DMF (2.05 mL) by first stirring it at –5 °C under nitrogen for 5 min with K₂CO₃ (0.118 g, 1.18 mmol). Cold (–60 °C) bromofluoromethane (0.138 g, 1.22 mmol) was added, and the mixture was stirred at 0 °C to –5 °C for 1 h and then diluted with EtOAc (6 mL). The mixture was washed with 5% Na₂CO₃, and the aqueous layer was extracted with EtOAc (6 mL). The combined organic extracts were washed with H₂O (4 mL) and concentrated *in vacuo* to ca. 1.5 mL. After the suspension was cooled to 0 °C and stirred for 1 h, the solid was collected by filtration and dried at 40 °C *in vacuo* for 16 h to give 13e (0.370 g, 69.3%), with a second crop (0.050 g, 9.4%) by concentration of the mother liquors.

The fluoromethyl ester 13e was also prepared from the carbothioic acid 6e (47.9 g, 102 mmol) in DMF (190 mL) by first stirring it with KHCO₃ (11.26 g, 112 mmol) at room temperature for 10 min under N₂. Fluoriodomethane (17.2 g, 107 mmol) was added over 3–4 min with cooling to keep the temperature at 22–25 °C. Isolation after 0.25 h as in the preceding experiment gave 13e (67.1%), mp 184–185 °C, with IR and ¹H NMR spectra resembling those detailed above. The latter showed solvation with DMF (ca. 0.05 mol).

S-Fluoromethyl 17 α -(Butyryloxy)-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (13f). General method G on 11f and crystallization from EtOAc gave 13f (76%).

S-Fluoromethyl 11 β -Hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carbothioate (13g). General methods F then G on 10c, without purification of the intermediate S-iodomethyl carbothioate, and crystallization from EtOAc gave 13g (23%).

S-Fluoromethyl 17 α -Acetoxy-9 α -fluoro-11 β -hydroxy-16 β -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate (13h). General method G on 11g and two crystallizations from acetone gave 13h (35%).

S-Fluoromethyl 9 α -Fluoro-11 β -hydroxy-16 β -methyl-3-oxo-17 α -(propionyloxy)androsta-1,4-diene-17 β -carboth-

ioate (13i). General method G on 11a with PLC and crystallization from MeOH then MeOH and Et₂O gave 13i (33%).

The fluoromethyl ester 13i was also prepared from the chloromethyl ester 10e (0.377 g, 0.760 mmol) with AgF (0.669 g, 5.3 mmol) in CH₃CN (6 mL) in the dark for 38 days. Isolation as in general method G gave 13i (0.070 g, 19.2%): ¹H NMR (90 MHz) 0.94 (13-CH₃, s), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.35 (16β-CH₃, d, *J* = 7 Hz), 1.52 (10-CH₃, s), 2.38 (propionate CH₂, q, *J* = 7 Hz), 4.27 (11α-H, m), 5.84 (CH₂F, d, *J* = 51 Hz), 6.04 (4-H, m), 6.24 (2-H, dd, *J* = 10, 2 Hz), 7.29 (1-H, d, *J* = 10 Hz); ¹⁹F NMR (84.68 MHz) -187.5 (CH₂F, t, *J* = 51 Hz), -162 (9α-F, broad dd).

S-Fluoromethyl 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (13j). General method G on 11h with PLC and two crystallizations from acetone gave 13j (22%).

Fluoromethyl 6α,9α-Difluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (13k). General methods F then G on 10h, without purification of the intermediate *S*-iodomethyl carthioate, PLC, and crystallization from aqueous acetone gave 13k (79%): ¹H NMR 0.98 (13-CH₃, s), 1.03 (propionate CH₃, t, *J* = 7 Hz), 1.55 (10-CH₃, s), 2.34 (propionate CH₂, q, *J* = 7 Hz), 4.32 (11α-H, m), 5.63 (16=CH₂, broad m), ca. 5.7 (6-H, broad dm, *J* = 50 Hz), 5.95 (SCH₂F, d, *J* = 51 Hz), 6.18 (4-H, m), 6.35 (2-H, dd, *J* = 10, 2 Hz), 7.30 (1-H, broad d, *J* = 10 Hz).

S-Chloromethyl 16α,17α-Epoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate (16). A suspension of 16α,17α-epoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (14)²⁶ (0.753 g, 2.0 mmol) and FMPT (0.680 g, 2.4 mmol) in CH₂Cl₂ (7 mL) was treated dropwise at 0 °C with Et₃N (1.39 mL, 10 mmol) and then stirred at 0 °C for 1 h. H₂S was passed through the mixture for 15 min, and the resultant solution was stirred at 0 °C for 1 h. After addition of BrCH₂Cl (0.26 mL, 4 mmol) the mixture was stirred for 1.5 h at room temperature, diluted with EtOAc (250 mL), washed with 2 N HCl, 5% NaHCO₃, and water, dried, and evaporated *in vacuo* to give a yellow solid (0.818 g). This on PLC and then crystallization from acetone gave 16 (51%).

S-Chloromethyl 9α-Fluoro-11β,17α-dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17β-carbothioate (17). A solution of 16 (0.400 g, 0.91 mmol) in CF₃CO₂H (16 mL) was stirred for 5.5 h at room temperature, evaporated to near dryness *in vacuo*, and dissolved in EtOAc (100 mL). The solution was washed with 5% NaHCO₃ and water, dried, and evaporated *in vacuo* to give a foam (0.466 g), part of which on PLC and two crystallizations from acetone gave 17 (70%).

The 11β,17α-diol 17 (0.227 g, 0.52 mmol) in propionic acid (2.2 mL) and (CF₃CO₂)₂O (0.7 mL) was treated with a dry solution of *p*-toluenesulfonic acid in CHCl₃ (0.044 mL, containing ca. 0.08 g/mL) and then stirred at room temperature for 6 h and at 3 °C for 16.5 h. The reaction mixture was diluted with EtOAc, washed with 5% NaHCO₃, H₂O, and brine, dried, and evaporated *in vacuo* to give a mixture of 11β- and 17α-monopropionates. Purification by PLC gave sample of 10g (48%) containing ca. 7% of the 11β-monopropionate.

Se-Methyl 16α,17α-Epoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboselenoate (18a). The 17β-carboxylic acid 14 (0.376 g, 1.0 mmol) and FMPT (0.340 g, 1.2 mmol) were stirred under N₂ at 0 °C, and Et₃N (0.70 mL, 5.0 mmol) was added dropwise. After 70 min a solution of NaSeH [prepared under N₂ by the addition of EtOH (3 mL) to a mixture of NaBH₄ (0.063 g, 1.66 mmol) and powdered Se (0.118 g, 1.5 mmol) at 0 °C followed by stirring for 20 min] was added, and the brown solution was stirred at 0 °C for 1.25 h. MeI (0.12 mL, 2.0 mmol) was added under N₂, and the yellow solution was stirred for 3.75 h at room temperature. The reaction mixture was diluted with EtOAc (200 mL), washed with 2 N HCl, 5% NaHCO₃, and water, dried, and evaporated *in vacuo* to give a solid (0.390 g). PLC and two crystallizations from acetone gave 18a (0.174 g, 38.4%): IR (in CHBr₃) 1680 (carboselenoate) cm⁻¹; ¹H NMR

(90 MHz) 1.38 (13-CH₃, s), 1.54 and 1.58 (16β-CH₃ and 10-CH₃, singlets), 2.22 (SeCH₃, s).

Se-Chloromethyl 16α,17α-Epoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carboselenoate (18b). The carboxylic acid 14 (0.376 g, 1.0 mmol) reacted as in the preceding experiment, using FMPT-NEt₃, NaSeH [from Se (2.0 mmol)] and BrCH₂Cl (0.130 mL, 2.0 mmol) in place of MeI, to give, after crystallization from acetone, 18b (29.5%): IR 1710 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 1.41 (13-CH₃, s), 1.54 and 1.58 (16β-CH₃ and 10-CH₃, singlets), 5.06 (SeCH₂Cl, s).

Se-Methyl 9α-Fluoro-11β,17α-dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17β-carboselenoate (19a). The epoxide 18a (0.574 g, 1.27 mmol) in CF₃CO₂H (25 mL) was stirred at room temperature for 2.5 h and then diluted with 5% NaHCO₃ (550 mL). The product was extracted into EtOAc, and the extract was washed with water, dried, and evaporated *in vacuo* to give a yellow foam (0.561 g). PLC and two crystallizations from acetone gave 19a (0.326 g, 56.8%): IR 1700 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 0.91 (13-CH₃, s), 1.53 (10-CH₃, s), 2.06 (SeCH₃, s), 4.97 and 5.22 (16=CH₂, broad singlets), 6.38 (17α-OH, s).

Se-Chloromethyl 9α-Fluoro-11β,17α-dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17β-carboselenoate (19b). The epoxide 18b (1.332 g), in a manner similar to the preceding experiment, gave crystalline 19b (0.276 g, 20.7%): IR 1720 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 0.96 (13-CH₃, s), 1.53 (10-CH₃, s), 5.01 (SeCH₂Cl, s), 5.00 and 5.25 (16=CH₂, broad singlets), 6.71 (17α-OH, s).

Se-Methyl 9α-Fluoro-17α-hydroxy-16-methylene-3,11-dioxoandrosta-1,4-diene-17β-carboselenoate (20a). Pyridinium dichromate²⁷ (0.130 g, 0.345 mmol) was added to a solution of 19a (0.125 g, 0.246 mmol) in DMF (1.4 mL), and the mixture was stirred at 0 °C for 6 h. More pyridinium dichromate (0.130 g, 0.345 mmol) was added, and stirring continued for 24 h at 3–4 °C. The mixture was diluted with water (20 mL), and the product was extracted into EtOAc. The extract was washed with water, dried, and evaporated *in vacuo* to a yellow gum (0.116 g) which, on PLC and two crystallizations from acetone, gave 20a (0.050 g, 45.0%): IR 3390 (OH), 1718 (11-one), 1689 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 0.66 (13-CH₃, s), 1.53 (10-CH₃, s), 2.09 (SeCH₃, s), 5.04 and 5.29 (16=CH₂, broad singlets), 6.92 (17α-OH, s).

Se-Chloromethyl 9α-Fluoro-17α-hydroxy-16-methylene-3,11-dioxoandrosta-1,4-diene-17β-carboselenoate (20b). Pyridinium dichromate (7.825 g, 20.8 mmol) was added to a stirred solution of 19b (4.155 g, 8.32 mmol) in DMF (46 mL), and after 3.25 h the product was isolated as in the preceding experiment to give crude 20b (3.00 g, 74.2%). Two crystallizations of a portion (0.150 g) from acetone gave the analytical sample of 20b (0.056 g): IR 3350 (broad, OH), 1720 (11-one), 1709 (carboselenoate); ¹H NMR (90 MHz) 0.83 (13-CH₃, s), 1.54 (10-CH₃, s), 5.06 (SeCH₂Cl, s), 5.06 and 5.34 (16=CH₂, broad singlets), 7.26 (17α-OH, s).

Se-Methyl 9α-Fluoro-16-methylene-3,11-dioxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (21a). A solution of 20a (1.451 g, 3.214 mmol) in propionic acid (14.5 mL) and (CF₃CO₂)₂O (5.8 mL) was stirred and treated with a solution of *p*-toluenesulfonic acid (0.016 g) in CHCl₃ (0.20 mL) for 38 h at room temperature. The mixture was poured into 5% NaHCO₃ (400 mL), and the product was extracted into EtOAc (300 mL). The extract was washed with water, dried, evaporated *in vacuo*, and purified by PLC to give 21a (1.095 g, 67%). A portion of (0.250 g) recrystallized twice from acetone gave the analytical sample of 21a (0.198 g): IR 1740 (propionate), 1722 (11-one), 1678 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 0.71 (13-CH₃, s), 1.05 (propionate CH₃, t, *J* = 7 Hz), 1.55 (10-CH₃, s), 2.23 (SeCH₃, s), 2.39 (propionate CH₂, q, *J* = 7 Hz), 5.64 and 5.70 (16=CH₂, broad singlets).

Se-Chloromethyl 9α-Fluoro-16-methylene-3,11-dioxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (21b). Propionylation of 20b (2.850 g, 5.87 mmol) as in the preceding experiment but for 6 days gave 21b (2.380 g, 75%). A portion (0.150 g) crystallized twice from acetone gave the analytical sample of 21b (0.070 g): IR 1744 (propionate), 1718 (11-one), 1688 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz)

0.77 (13-CH₃, s), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.55 (10-CH₃, s), 2.42 (propionate CH₂, q, *J* = 7 Hz), 5.21 (SeCH₂Cl, s), 4.30 (16=CH₂, broad).

Se-Methyl 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (22a). A suspension of 21a (0.841 g, 1.66 mmol) and NaBH₄ (0.069 g, 1.82 mmol) in EtOH (12 mL) was stirred at room temperature for 1.3 h, treated with acetone (3.5 mL), and concentrated to near dryness *in vacuo*. EtOAc (100 mL) was added, and the solution was washed with 1N HCl and water, dried, and evaporated *in vacuo* to give a white foam. Two crystallizations from acetone gave 22a (0.657 g, 77.7%): IR 3340 (broad, OH), 1744, 1735 (propionate), 1718 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 0.96 (13-CH₃, s), 1.02 (propionate CH₃, t, *J* = 7 Hz), 1.54 (10-CH₃, s), 2.20 (SeCH₃, s), 2.32 (propionate CH₂, q, *J* = 7 Hz), 5.61 and 5.66 (16=CH₂, broad singlets).

Chloromethyl 9α-Fluoro-11β-hydroxy-16-methylene-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (22b). The 11-ketone 21b (2.656 g, 4.90 mmol) was reduced as in the preceding experiment to give 22b as a white foam (1.802 g, 67.7%). A portion (0.500 g) was recrystallized from EtOAc to give the analytical sample of 22b (0.297 g, 100%): IR 3310 (broad, OH), 1740 (propionate), 1724 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 1.01 (13-CH₃, s), 1.01 (propionate CH₃, t, *J* = 8 Hz), 1.55 (10-CH₃, s), 2.33 (propionate CH₂, q, *J* = 8 Hz), 4.29 (11α-H, m), 5.19 (SeCH₂Cl, s), 5.60 (11β-OH, m), 5.62 (16=CH₂, broad).

Se-Iodomethyl 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (22c). A mixture of the Se-chloromethyl selenoester 22b (1.291 g, 2.37 mmol) and NaI (4.447 g, 29.7 mmol) in acetone (40 mL) was heated under reflux for 24 h. The mixture was cooled, diluted with EtOAc (200 mL), washed with water (60 mL), 10% sodium thiosulfate (2 × 60 mL), 5% NaHCO₃ (60 mL), and water (2 × 60 mL), dried, and evaporated to a foam (1.392 g). PLC gave colorless crystals (1.225 g, 81%), a portion (0.225 g) of which was recrystallized twice from acetone to give 22c (0.201 g, 72%): IR 1744 (propionate), 1728 (carboselenoate) cm⁻¹; ¹H NMR (90 MHz) 1.00 (propionate CH₃, t, *J* = 8 Hz), 1.02 (13-CH₃, s), 1.53 (10-CH₃, s), 1.00 (propionate CH₃, t, *J* = 8 Hz), 1.02 (13-CH₃, s), 1.53 (10-CH₃, s), 2.31 (propionate CH₂, q, *J* = 8 Hz), 4.43 (SeCH₂I, s), 5.53–5.71 (16=CH₂, 11-OH, broad).

Reaction of 22c with Silver Fluoride. 22c (1.0 g) and Ag₂SO₄ (2.0 g, 10 equiv) in CH₃CN (16 mL) were stirred at ambient temperature in the dark for 24 h. The reaction mixture was diluted with EtOAc (300 mL), solid material was removed by filtration, and the filtrate was washed with water, dried, and concentrated to a foam (0.690 g). Silica gel chromatography eluting with CHCl₃ gave a white solid (0.027 g, 3%, mechanical loss) which was recrystallized from EtOAc–petroleum ether (bp 40–60 °C) to give colorless crystals (0.008 g) of Se-fluoromethyl 9α-fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboselenoate (22d): IR 3600–3000 (OH), 1738, 1708, 1695, (shoulder) cm⁻¹; ¹H NMR (100 MHz) δ 0.96 (13-CH₃, s), 1.00 (propionate CH₃, t, *J* = 7 Hz), 1.51 (10-CH₃, s), 2.32 (propionate CH₂, q, *J* = 7 Hz), 5.5–5.6 (16=CH₂, 11-OH, broad), 6.22 (SeCH₂F, d, *J* = 50 Hz); MS *m/e* (rel intensity) Se cluster MH⁺ 531 (23.0), 529 (100), 527 (52), 526 (19.4), 525 (19.9), 523 (3.0), fragments 415 (14.7); MH⁺ – SeCH₂F, 359 (12.4), 313 (35.1), 293 (24.2). The MH⁺ ion-cluster had relative peak intensities close to the calculated values for the seven Se isotopes, HRMS *m/e* calcd for C₂₈H₃₁F₂O₅Se (MH⁺) 529.1304, found 529.1269. Further elution gave a white foam (0.543 g, 80%), which was recrystallized twice from acetone to give colorless crystals (0.196 g, 29%) of 9α-fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbonyl fluoride 23: 83% pure by HPLC; mp 193–195 °C; [α]_D²⁰ –82° (c 0.93); λ_{max} 239 nm (E_{1cm}^{1%} 346); IR (CHBr₃) 3605 (OH), 1842 (COF), 1738 and 1262 (propionate), 1668, 1630, and 1612 (Δ^{14,3}-one) cm⁻¹; ¹H NMR (90 MHz) 1.01 (propionate, t, *J* = 8 Hz), 1.10 (13-CH₃, s), 1.54 (10-CH₃, s), 2.38 (propionate, q, *J* = 8 Hz), 6.55 and 6.65 (16=CH₂, 11-OH, broad); ¹⁹F NMR (84.68 MHz) +29 (COF, s), –161.7 (9α-F, m); ¹³C NMR (25.05 MHz) 174.3

(s, propionate C=O), 159.3 (d, ¹J_{CF} = 365 Hz, COF), 145.4 (s, C16), 120.9 (s, 16=CH₂; off-resonance t), 87.8 (d, ²J_{CF} = 50 Hz, C17), 10.1 (s, propionate CH₃, off-resonance q); MS *m/e* (rel intensity) 435 (98.7, MH⁺), 415 (100, MH⁺ – HF), 359 (35.7), 313 (16.7), 293 (15.8); HRMS *m/e* calcd for C₂₈H₂₉F₂O₅ (MH⁺) 435.1983, found 435.1982. Anal. (C₂₈H₂₉F₂O₅) H, F, C calcd, 66.3; found, 65.3.

Bis[9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-dien-17β-yl]carbonyl] Disulfide. The carbothioic acid 6i (0.104 g, 0.230 mmol) in DMSO (1 mL) was stirred and heated at 85 °C for 1.5 h. The solution was diluted with EtOAc (100 mL), washed with 5% NaHCO₃ and water, dried, and evaporated *in vacuo* to a solid (0.108 g). PLC and two crystallizations from acetone gave the title disulfide (0.068 g, 65.6%): ¹H NMR (90 MHz) 0.99 (13-CH₃, s), 1.06 (propionate CH₃, t, *J* = 7 Hz), 1.32 (16β-CH₃, d, *J* = 6 Hz), 1.52 (10-CH₃, s), 2.42 (propionate CH₂, q, *J* = 7 Hz), 4.33 (11α-H, m), 5.72 (11β-OH, m), 6.08 (4-H, s), 6.29 (2-H, d, *J* = 10 Hz), 7.36 (1-H, d, *J* = 10 Hz). Anal. (C₄₈H₆₀F₂O₁₀S₂·0.5H₂O) C, H, S.

Test Methods. Human Vasoconstrictor Activity. The method used was a modification of that described by McKenzie and Atkinson.¹⁷ Six male and six female subjects with six marked sites on the flexor surface of each forearm were treated with 12 test solutions, allocated by means of a 12 × 12 latin square. The test solutions (0.02 mL) were four graded doses of the standard fluocinolone acetonide (3, 12.5, 50, 200 ng) and of two test steroids in ethanol. They were pipetted on to the marked circular areas (ca. 2.25 cm²) and spread as evenly as possible. The solvent was allowed to evaporate, and the forearms were enclosed in polythene tubing secured at each end by elastic surgical tape. The tubing was left in place overnight (ca. 16 h), and 1 h after its removal the arms were assessed for areas of vasoconstriction. The areas were scored as either positive or negative, and estimates of relative potency were obtained by analysis of the data using the method of Litchfield and Wilcoxon.²⁸

Topical Antiinflammatory Activity in Rats. The method used was a modification of that described by Tonelli et al.¹⁸ and used 7 groups of 10 rats (54–70 g) in each experiment. Croton oil solution was prepared by mixing croton oil (5 vol), EtOH (20 vol), and Et₂O (75 vol). Graded doses of the standard fluocinolone acetonide and test steroid were dissolved in the croton oil solution such that the doses (standard steroid 0.06, 0.25, and 1 μg) were contained in 0.04 mL. The doses were applied to the inner aspect of both ears, the control group receiving croton oil solution without medication. Six hours later, the rats were sacrificed by CO₂ inhalation and both ears were removed and weighed separately. The metameters used for the analyses of variance and calculation of relative potencies were the logarithm of the applied dose and ear weights.

Topical Antiinflammatory Activity in Mice. The methodology was similar to that for rats except that a mixture of croton oil (2 vol), EtOH (20 vol), and Et₂O (78 vol) was used and the dose volume was 0.02 mL. Nine groups of 10 mice (22–28 g) were used, and doses of the standard fluocinolone acetonide were 0.015, 0.06, 0.25, and 1 μg.

Systemic Corticosteroid Activity after Topical Application to Rats. Seven groups of six rats (170–200 g at the beginning of the experiment) were used. The fur on the dorsal skin was removed by clipping, and a circular area (ca. 2 cm²) was marked using an indelible marker. Graded doses of the standard fluocinolone acetonide and test steroid were dissolved in acetone such that the doses (0.5, 2, 8 μg of standard) were contained in 0.02 mL. The rats were treated once daily for seven consecutive days; one group which received unmedicated vehicle acted as controls. On the day after the final dose, the rats were stressed by exposure to Et₂O vapor for 1 min. Twenty minutes later, the rats were re-anesthetized with intraperitoneal pentobarbitone, and blood was withdrawn by cardiac puncture into heparinized tubes. Plasma corticosterone levels were measured for each blood sample by a modification of the fluorimetric method of Zenker and Bernstein.¹⁹ Alternatively, adrenal glands were removed, blotted, and weighed. The metameters used for the analyses of variance and calculation of relative potencies were the

logarithm of the daily dose and plasma corticosterone concentrations or adrenal weights.

Systemic Corticosteroid Activity after Topical Application to Mice. The methodology was similar to that for rats except that nine groups of 10 mice (25–30 g) were used and that, after stressing, the mice were re-anaesthetised with Et₂O. Daily doses of the standard fluocinolone acetonide were 0.47, 1.9, 7.5, and 30 µg. The blood from two mice was pooled to obtain sufficient for the corticosterone estimation.

Systemic Corticosteroid Activity after Subcutaneous or Oral Administration to Rats and Mice. The methods involved seven daily doses of the standard betamethasone (2.5, 10, and 40 µg to rats and 1.56, 6.25, and 25 µg to mice) and the test steroid given subcutaneously as a suspension in normal saline containing 0.5% Tween 80 by volume (0.2 mL for rats and 0.1 mL for mice). Adrenal weights in rats and corticosterone levels in mice were measured as for topical application above. Oral activities were similarly assessed.

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Supplementary Material Available: ¹H NMR data (5 pages). Ordering information is given on any current masthead page.

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24. Chemistry of Steroid Antagonists

STRUCTURE-ACTIVITY RELATIONSHIPS OF A
SERIES OF NOVEL TOPICAL
CORTICOSTEROIDS*

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Summary—The effect of various heteroaryl groups in the 17-position of topical corticosteroids has been studied. The corticosteroids esterified at C₁₇ were of 9 α ,11 β -dichloro, 9 α -chloro 11 β -hydroxy and 9 α -fluoro 11 β -hydroxy series. Among the 17-acyl groups 2'-furoates were most extensively investigated, although 2'-thenoates, 3'-thenoates and 3'-furoates were also examined. Many of these esters exhibited enhanced topical anti-inflammatory potencies. The most potent compounds investigated were the 21-chloro 17(2'-furoates) either in the 9 α ,11 β -dichloro, or in the 9 α -chloro 11 β -hydroxy series. These compounds were at least 6 times as potent as betamethasone 17-valerate. Among 16-substituents studied 16 α -methyl compounds had the highest potency. Topical anti-inflammatory potencies were determined by using a 5-day modification of the croton oil ear assay in mice. The more potent compounds were also evaluated in the *P. ovale* induced chronic psoriaform lesion in the guinea-pig.

INTRODUCTION

Since the original demonstrations [1,2] of the efficacy of cortisol and cortisol 21-acetate in the treatment of dermatological disorders, extensive research has been carried out towards more effective topical corticosteroid therapy [3]. The more potent analogs of cortisol, i.e. prednisolone, triamcinolone, dexamethasone and betamethasone, were synthesized for treatment of systemic disease, but were useful topically when formulated in appropriate vehicles. Further chemical modifications, as the 16,17-acetonides, 17- and/or 21-esters of anti-inflammatory glucocorticosteroids as triamcinolone and betamethasone led to compounds very widely used in local steroid therapy. Most of the topical corticosteroids in current clinical use belong to these structural categories, although there are important examples of 17-deoxy 21-esters, and 17-oxygenated 21-chloro corticosteroids too.

In this communication we describe a novel series of corticosteroid 17-esters where the 17-acyl functionality is derived from heteroaromatic radicals. We found that esters of furan- and thiophenecarboxylic acids when introduced to the 17-position of a variety of corticosteroids possess very high topical anti-inflammatory potency. The first part of this paper will deal with their synthesis, whereas the structure-activity relationships which have been derived will be discussed in more detail in the second part.

EXPERIMENTAL

Synthesis of corticosteroid 17-heteroarylcarboxylates

In searching for a general process which allows rapid synthesis of a variety of 17-esters we used an

esterification procedure recently published [4] for a specific application. Thus, with the use of the appropriate acid chloride and a nitrogen base, such as 4-dimethylaminopyridine (DMAP) for activation of the acylating agent, a large number of 17-heteroaromatic esters were prepared (Fig. 1):

The acylation reaction of the 17-hydroxy group was preferentially carried out (a) in the 9,11-dichloro series, (b) in the 9(11) series, and (c) in the 11-keto series, substrates having no additional hydroxyl function, in order to avoid unwanted esterification (Fig. 2).

Using the methodology described above we prepared a variety of diesters, with the 17-ester being a heteroarylcarbonyl, in the 9 α ,11 β -dichloro (III), the 9 α -chloro 11 β -hydroxy (V) and the 9 α -fluoro 11 β -hydroxy (VIII) series.

Removal of the 21-ester with selective hydrolysis using HClO₄-MeOH, followed by conversion via the 21-mesylate to the 21-chloro 17-ester in the Δ^4 series (d) or in the 9 α -fluoro 11 β -hydroxy series (e) is shown in Fig. 3.

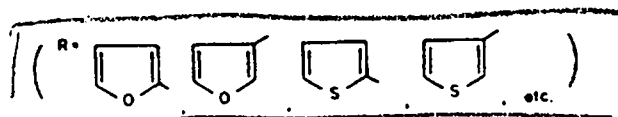
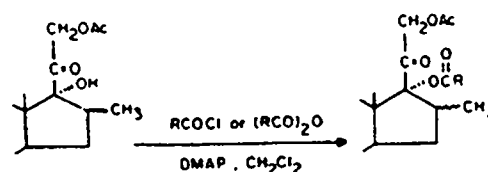
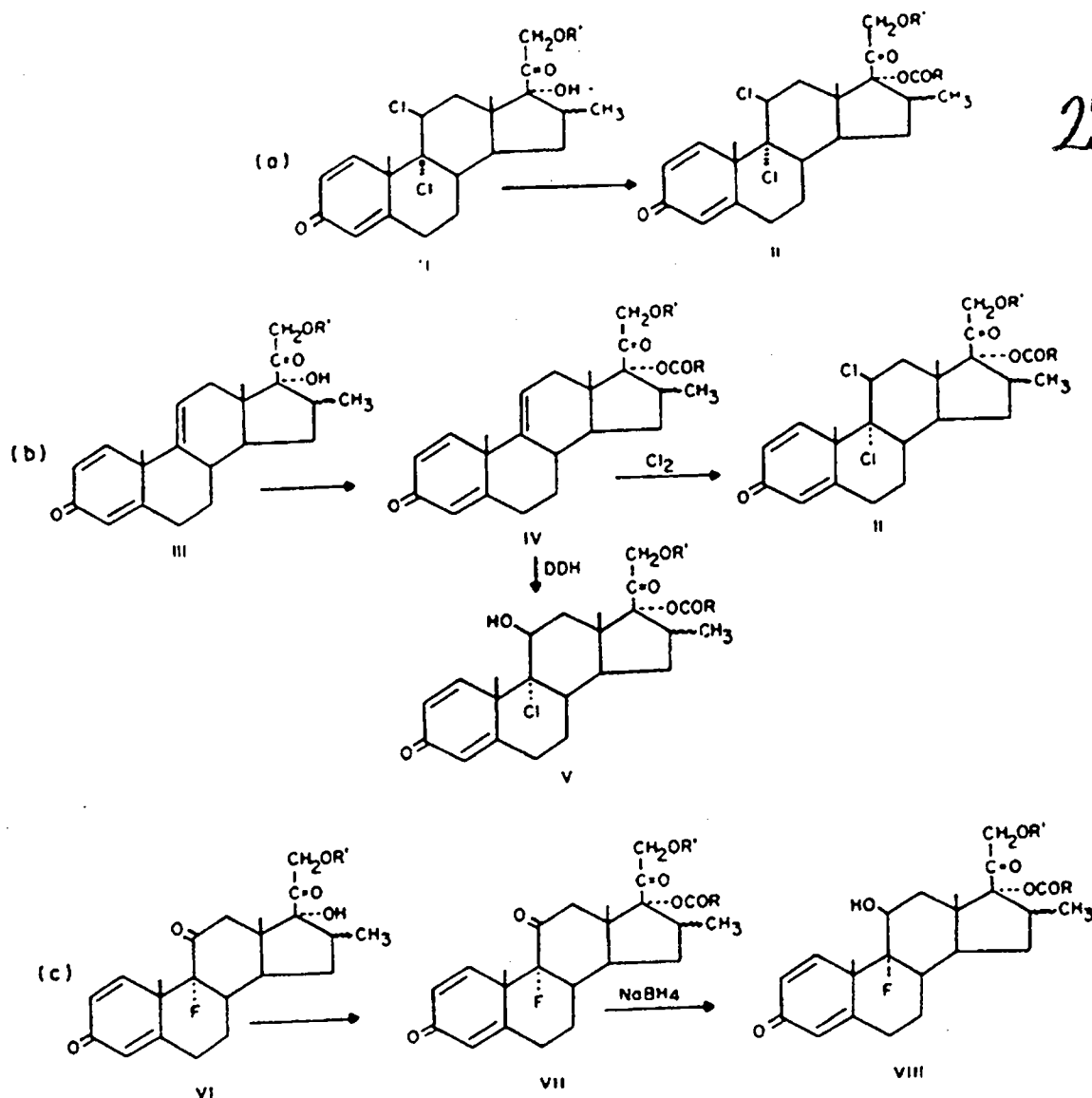


Fig. 1.

*This paper is dedicated to Professor George Büchi for the occasion of his 65th birthday.



(R' = CH₃CO, C₂H₅CO, C₃H₇CO, CH₃OCH₂CO; DDH = 1,3-dichloro-5,5-dimethylhydantoin).

Fig. 2.

RESULTS

Structure-activity relationships of the 17-heteroaryloxy corticosteroids

Croton-oil-induced ear inflammation in mice. Topical anti-inflammatory activity was determined in mice by a modification of the method of Tonelli *et al.* [5]. 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-μl 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. Using the mean of left plus right ear punch weights, potencies were determined relative to betamethasone 17-valerate (compound 38). These values are shown in Table 1 for comparison purposes, relative potencies of betamethasone 17,21-

dipropionate (compound 39) and hydrocortisone (compound 40) are also listed.

***P. ovale*-induced chronic psoriaform lesions in guinea-pigs.** The histopathology of psoriasis is characterized by acanthosis, parakeratosis, abnormalities of cellular differentiations, and infiltration of leukocytes. Effects of corticosteroids on these parameters have been extensively studied in man. Recently, Rosenberg *et al.* [6] reported that topical application of killed *Pityrosporum ovale* (*Malassezia ovalis*) on rabbit skin produced a lesion resembling psoriasis. This supports the suggestion that *P. ovale*, a lipophilic yeast, is associated with several skin disorders in man, including psoriasis [7–10]. We selected the guinea-pig to study a *P. ovale*-induced psoriaform because of the analogous anatomical character and percutaneous absorption patterns between guinea-pig skin and human skin [11–13]. On repeated application of killed *P. ovale* suspensions we are able to induce classic psoriaform lesions in

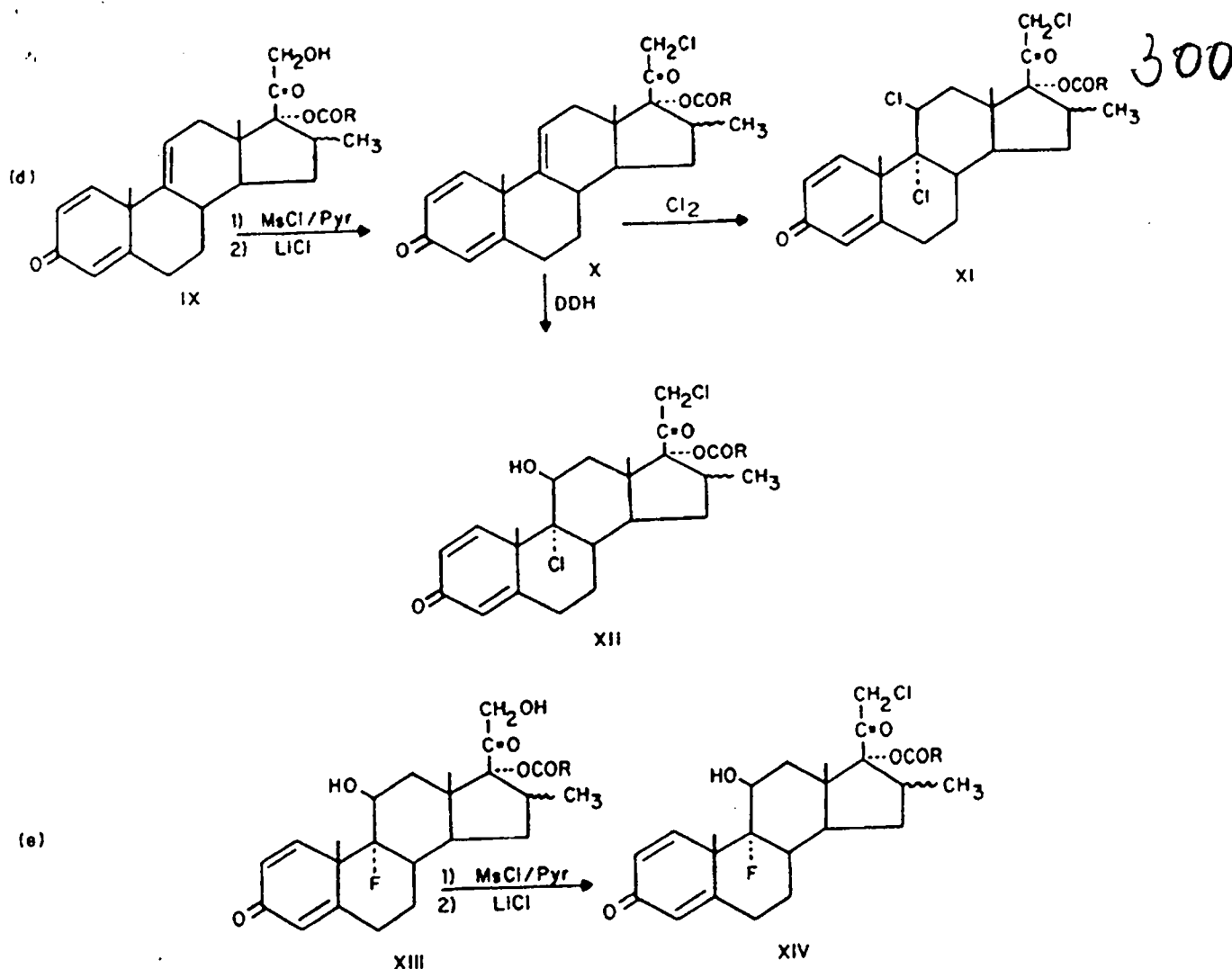


Fig. 3.

guinea-pigs, and these lesions responded to topical corticosteroid therapy.

Psoriaform lesions are induced by 10 repeated daily applications of heat-killed *P. ovale* suspension to the outer surface of the right ear of young male Hartley guinea-pigs. Starting on the eleventh day, a 0.12-ml aliquot of the test steroid in pyridine-water-ether (20:5:75) is applied on the lesioned ear daily for 14 days. Twenty-four hours after the last application of the drug the animals are sacrificed, equal portions of the drug-treated and control ears are excised, fixed, and evaluated histologically for the severity of acanthosis. Potency of the test drugs is determined by comparing the reduction of mean acanthosis to that obtained by betamethasone 17-valerate (Table 2).

DISCUSSION

It is apparent from inspection of Table 1 that introduction of 17-heteroaryl carboxylates affects the topical anti-inflammatory potencies of various series differently.

In the 9,11-dichloro series, the potency of the 17,21-diester with the exception of the 17(2'-thenoate) 21-acetate (compound 4) and 17(2'-

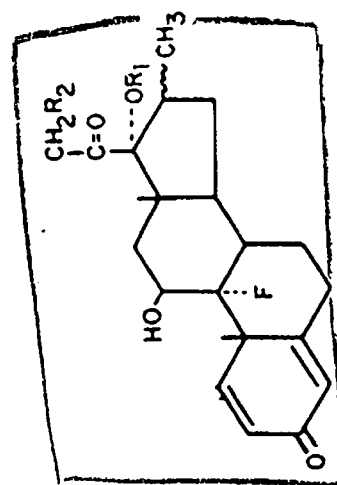
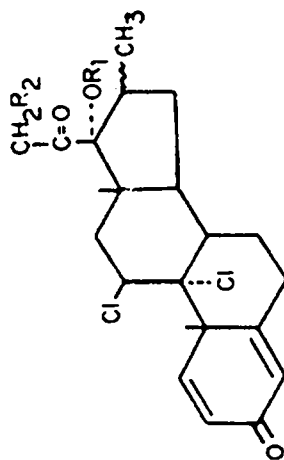
furoate) 21-methoxyacetate (compound 7) did not significantly differ from the standard betamethasone valerate. Replacement of the 21-acyl function with chlorine, and in one case with fluorine, led to significant enhancement in topical anti-inflammatory potency. Thus, the 21-chloro 17(2'-furoate) (compound 8) was 8 times as potent as betamethasone valerate in the croton oil ear assay, and 6 times as potent in the guinea-pig *P. ovale* assay (Table 2). Other 21-halogeno 9,11-dichloro 17-heteroaryl esters with significantly enhanced topical potency were the 21-chloro 17(2'-thenoate) (compound 10), the 21-fluoro 17(2'-furoate) (compound 11) and the 6 α -fluoro compound (compound 14), all at least 3 times as potent as standard.

In the 9 α -fluoro 11 β -hydroxy series, the 17,21-diester showed consistently higher potencies than the standard betamethasone valerate. This is unusual as dexamethasone 17,21-diester, to which the above compounds belong, have been rarely reported to possess significant topical potencies, and no such compound has been clinically introduced [3]. The most potent compound in the series was the 17(2'-furoate) 21-propionate (compound 19) which was 6 times as potent as standard. Other compounds in the series with high potency were the 17(2'-furoate)

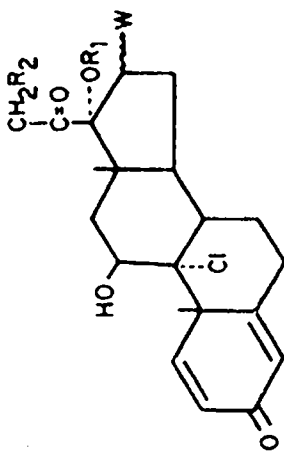
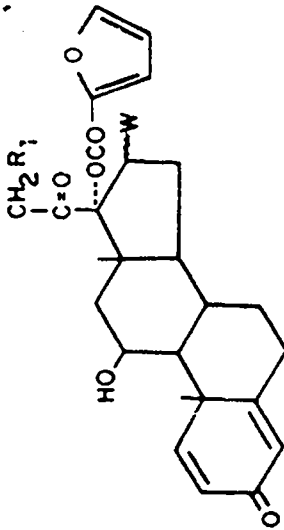
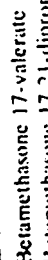
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Table 1. Topical anti-inflammatory potencies of corticosteroid 17-heteroaryl esters in the croton oil assay

Compound no.	R ₁	R ₂	C ₁₆ -CH ₃ /W	Additional feature	Topical potency*
1	2'-Furoyl	OCOCH ₃	α	—	1.2 (0.74-2.10)
2	3'-Furoyl	OCOCH ₃	α	—	1.4 (1.25-1.61)
3	2'-Thienyl	OCOCH ₃	α	—	0.8 (0.23-1.34)
4	3'-Thienyl	OCOCH ₃	α	—	3.2 (2.10-4.27)
5	2'-Furoyl	OCOCH ₃	β	—	1.7 (0.81-2.85)
6	2'-Furoyl	OH	α	—	0.9†
7	2'-Furoyl	OCOCH ₂ OCCH ₃	α	—	3.0 (0.34-4.81)
8	2'-Furoyl	Cl	α	—	8.2 (4.41-13.1)
9	3'-Furoyl	Cl	α	—	1.7 (1.8-2.68)
10	3'-Thienyl	Cl	α	—	3.3 (2.55-4.35)
11	2'-Furoyl	F	α	—	4.0 (2.55-5.35)
12	2'-Furoyl	Cl	β	—	0.8†
13	2'-Furoyl	OCOCH ₃	α	6α-F	1.8 (1.46-2.04)
14	2'-Furoyl	Cl	α	6α-F	3.0 (1.23-4.87)
15	2'-Furoyl	OCOCH ₃	α	—	2.2 (1.53-2.90)
16	3'-Furoyl	OCOCH ₃	α	—	3.2 (1.45-4.64)
17	2'-Thienyl	OCOCH ₃	α	—	2.9 (2.23-3.84)
18	2'-Furoyl	OCOCH ₃	β	—	0.2 (0.19-0.28)
19	2'-Furoyl	OCOCH ₂ H ₅	α	—	6.8 (4.24-9.19)
20	2'-Furoyl	OCOCH ₂ OCCH ₃	α	—	3.2 (2.53-3.55)
21	2'-Furoyl	Cl	α	—	2.3 (1.26-3.77)
22	3'-Furoyl	Cl	α	—	1.2 (0.83-1.54)
23	2'-Thienyl	Cl	α	—	2.6 (1.46-3.82)
24	2'-Furoyl	Cl	β	—	0.9†
25	3'-Furoyl	Cl	α	11-one	1.7†
26	2'-Furoyl	OCOCH ₃	=CH ₂	—	1.1 (0.41-1.92)



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	27	2'-Furoyl	OC(=O)CH ₃	α	—	4.4 (1.28-7.82)
	28	2'-Furoyl	OC(=O)CH ₂ OCH ₃	α	—	4.3 (0.88-7.90)
	29	2'-Furoyl	Cl	α	—	6.1 (2.50-11.55)
	30	2'-Thienyl	Cl	α	—	4.5 (3.40-5.52)
	31	2'-Furoyl	F	α	—	4.4 (2.36-7.67)
	32	2'-Furoyl	Cl	α	6α-F	5.1 (4.50-5.70)
	33	2'-Furoyl	OC(=O)CH ₃	=CH ₂	—	2.2 (2.01-2.48)
	34	OC(=O)CH ₃	—	α	6α-F	2.1 (1.0-3.07)
	35	OC(=O)CH ₃	—	=CH ₂	—	1.2 (0.58-2.20)
	36	OC(=O)CH ₂ CH ₃	—	α	—	1.5 (0.94-2.06)
	37	OC(=O)CH ₃	—	H	—	0.9 (0.64-1.11)
	38	Betamethasone 17-valerate				1.0 (standard)
	39	Betamethasone 17,21-dipropionate				1.4 (0.68-2.20)
	40	Hydrocortisone				0.01 (0.01-0.011)

*Statistically derived estimated cumulative potencies relative to betamethasone 17-valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of pooled estimates.

†Single assay.

Table 2. Topical potencies of corticosteroid 17-heteroaryl esters in the *P. ovale* guinea-pig ear assay

Compound No.	Topical potency*
1	5.24 (3.20-9.57)
8	6.06 (5.59-6.53)
10	0.68 (0.36-1.23)
15	2.28 (1.67-2.89)
21	3.00 (0.47-8.40)
27	3.92 (2.38-7.08)
29	3.82 (1.99-10.36)
37	—†
38 (betamethasone 17-valerate)	1.00 (standard)
39 (bethamethasone 17,21-dipropionate)	1.87 (1.09-3.85)
40 (hydrocortisone)	0.036 (0.01-0.08)

*Statistically derived potency relative to betamethasone 17-valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of pooled estimate.

†Inhibition (62%) at 0.05% (100 μ l/day).

21-methoxyacetate (compound 20), 17(3'-furoate) 21-acetate (compound 16) and 17(2'-thenoate) 21-acetate (compound 17), all 3 times as potent as betamethasone valerate. Two compounds in this series (compounds 15 and 21) were tested in the guinea pig *P. ovale* model (Table 2) showing comparable potency to that measured in the croton oil ear assay. The 21-chloro 17-esters (compounds 21 and 23) were twice as potent as standard. Thus in the 9 α -fluoro 11 β -hydroxy series introduction of a 21-halogen has not shown the strong potency-enhancing effect observed in the 9 α ,11 β -dichloro series and in the 9 α -chloro 11 β -hydroxy series.

In the 9 α -chloro 11 β -hydroxy series both the 21-halogeno 17-esters and a few representative 17,21-diester showed high topical anti-inflammatory potencies. Thus, the 21-chloro 17(2'-furoate) (compound 29) was 6 times as potent as betamethasone valerate. In the guinea-pig *P. ovale* assay (Table 2), (compound 29) was approximately 4 times as potent as standard. The 21-chloro 17(2'-thenoate) (compound 30), the 21-fluoro 17(2'-furoate) (compound 31) and the 6 α -fluoro analog (compound 32) were all at least 4 times as potent as standard. Two diesters in this series (compounds 27 and 28) also showed the same high topical potency noted for the 21-halogeno 17-esters. The high potency of compound 27 was also confirmed in the guinea-pig *P. ovale* model (Table 2). Overall, the 9 α -chloro 11 β -hydroxy series provided the most consistently potent topical anti-inflammatory agents.

Among the 17-acyl functions the 2'-furoates were examined most extensively. Representative 3'-furoates, 2'-thenoates, and 3'-thenoates were prepared in most active series, and did not show significant differences from the 2'-furoates. In the course of this work a few nitrogen-containing heteroaromatic esters as well as substituted furoates

and thenoates were also prepared, but showed lower potencies. It is worthwhile to note that the 17(2'-furoate) 21-methoxyacetates (compounds 7, 20 and 28) consistently showed high topical anti-inflammatory potencies compared with other 17,21-di-esters.

The influence of the 16-substituent is quite consistent throughout the 3 series, with 16 α -methyl substitution being the most favorable. Although only a few 16 β -methyl 17-heteroaryl carboxylates were prepared, their topical anti-inflammatory potency was usually lower than the corresponding 16 α -methyl epimers, i.e. compound 12 vs 8, compound 24 vs 21, compound 18 vs 15, the only exception being compound 5, somewhat more potent than the 16 α -methyl (compound 1). However, compound 1 has shown unusually high potency in the guinea-pig *P. ovale* model (Table 2), an assay where compound 5 was not tested. A few representative 16-methylene 17-heteroaryl carboxylates were synthesized, and, at least in two cases, compound 26 vs 15 and compound 33 vs 27, their topical potencies were significantly lower than those of the corresponding 16 α -methyl analogs.

The effect of the 6 α -fluoro group, normally a potency-enhancing substituent, was somewhat inconsistent. In the 9,11-dichloro series, compound 14, the 6 α -fluoro derivative of compound 8, reduced the very high potency by a factor of two, while compound 13 was more potent than the 6-unfluorinated compound, 1. In the 9,21-dichloro series both compound 29 and its 6-fluorinated derivative, compound 32 showed very high topical anti-inflammatory potencies.

In summary, introduction of heteroaryl esters, particularly the 2'-furoate function into the 17-position of 9 α ,11 β -dichloro-, 9 α -chloro 11 β -hydroxy, and 9 α -fluoro 11 β -hydroxy corticosteroids, resulted in significant enhancement of topical anti-inflammatory potency. The 9,21-dichloro 17(2'-furoate) (compound 29) has been evaluated in the clinic and was found to be a highly efficacious, long-acting topical anti-inflammatory agent.

Acknowledgements—We thank Dr Edwin Peets for helpful discussions and Mrs Trudi Pier for the expert typing of the manuscript.

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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).

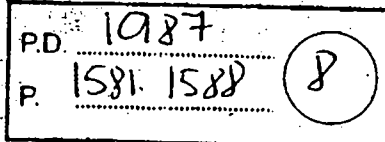
The other compounds were prepared similarly. In cases where the monohydrochloride salt was not crystalline, recrystallization from MeOH/EtOAc/HCl gave the crystalline dihydrochloride salts (see Table II). Many of the compounds were hygroscopic and crystallized as hydrates.

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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-

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XP-002153839



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

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The preparation and topical antiinflammatory potencies of a series of 17-furoyl and -thenoyl esters of 9 α -fluoro-11 β -hydroxy-16-methyl and 9 α -chloro-11 β -hydroxy-16-methyl corticosteroids are described. The 17 α -esters were introduced to the 9 α -fluoro 11-ketones or to the appropriate $\Delta^{(11)}$ compounds by direct acylation with the appropriate heteroaroyl 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 9 α -chloro series, both being 6 times as potent as betamethasone 17-valerate. Several other 9 α -chloro-11 β -hydroxy-17-heteroaroyl 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-heteroaroyl ester groups.¹ The preceding publication focused on 9 α ,11 β -dichloro corticosteroids,² herein described are their 11 β -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 an-

tiinflammatory potencies in the 9,11-dichloro series,² we expected high topical antiinflammatory potencies in the 11 β -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 9 α -fluorinated compounds are delineated in Table I, while the 9 α -chloro and 9-unsubstituted compounds are in Table II, with appropriate substitution at positions 6, 16, and 21.

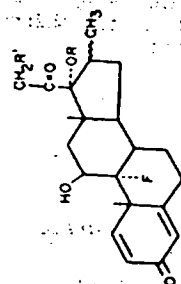
Chemistry

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

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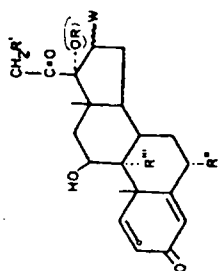
Table I. 9 α -Fluoro-11 β -hydroxy-Corticosteroid 17 α -Heterocyclic Esters^a



no.	R	R'	C ₁₇ CH ₃	mp, °C	[α] _D ²⁰ , deg (dioxane)	formula	M, mol wt	FAB (M + 1)	UV: λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)		topical potency ^b	
											5 h	5 day
1a	2'-furoyl	OCOCH ₃	α	238-239	+0.9	C ₂₇ H ₃₃ O ₈ F	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 ₂₇ H ₃₃ O ₈ F	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 ₂₇ H ₃₃ O ₈ F	528.55	529	234 (18.78)	2.9 (0.69-7.40)	3.2 (1.45-4.64)	
1d	2'-thenoyl	OCOCH ₃	α	245-247 ^c	-1.0	C ₂₇ H ₃₃ O ₈ SF	544.63	545	242 (22.31)	1.6 (0.65-3.99)	2.9 (2.23-3.84)	
1e	2'-furoyl	OCOC ₂ H ₅	α	226-228 ^c	+3.3	C ₂₈ H ₃₅ O ₈ F	542.58	543	248 (26.30)	2.1 (0.93-3.67)	6.8 (4.24-9.19)	
1f	2'-furoyl	OCOC ₂ H ₅	α	235	+2.2	C ₂₈ H ₃₅ O ₈ F	556.61	557	247 (26.39)	1.1 (1.11-1.14)	-	
1g	2'-furoyl	OCOCH ₂ OCH ₃	α	180-209/	-	C ₂₉ H ₃₇ O ₉ F	558.59	559	248 (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 ₃₃ O ₈ FCI	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 ₃₃ O ₈ FCI	504.97	505	248 (24.8)	0.6 (0.42-0.77)	0.9 ^d	
1j	2'-furoyl	Cl	α	226-228	+36.9	C ₂₇ H ₃₃ O ₈ FCI	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 ₃₃ O ₈ SFCI	521.04	521	243 (24.46)	1.3 (0.89-1.71)	2.6 (1.46-3.82)	
1l	3'-furoyl	Cl	α	208-210	+86.2	C ₂₇ H ₃₃ O ₈ FCI	502.95	503	237 (18.57)	0.6 (0.54-0.75)	1.7 ^d	
1m	2'-furoyl	OCOCH ₃	-CH ₃	217-218	-44.8	C ₂₈ H ₃₅ O ₈ F	526.54	527	245 (25.27)	0.5 ^d	1.1 (0.41-1.92)	
1n	5 β -methyl-2'-thenoyl	OCOCH ₃	α	215-220 ^c	-6.1	C ₂₉ H ₃₉ O ₈ SF	558.65	559	244 (21.77)	2.4 (1.62-3.09)	1.7 (1.18-2.12)	
20	betamethasone 17-valerate								277 (13.45)	1.0 (standard)	1.0 (standard)	

^aNMR 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. ^bStatistically derived estimated cumulative potencies relative to betamethasone valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of the pooled estimates. ^cDecomposition. ^dSingle assay. ^e11-Ketone. ^fIndeterminant.

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

no.	R	R'	R''	R'''	W	mp, °C	[α] _D ²⁰ , deg (dioxane)	formula	mol wt	FAB (M + 1)	UV: λ_{max} (MeOH), nm	topical potency ^d	
												5 h	5 day
2a	2'-furoyl	OCOCH ₃	H	Cl	α -CH ₃	254-255	+25.9	C ₂₇ H ₃₃ O ₆ Cl	545.01	545	247 (23.32)	1.7 (1.49-1.82)	4.4 (1.28-7.82)
2b	2'-furoyl	OCOCH ₂ OCH ₃	H	Cl	α -CH ₃	247-249 ^c	+33.6	C ₂₈ H ₃₅ O ₇ Cl	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 ₃₃ O ₆ Cl 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 ₃₃ O ₆ Cl ₂ S	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 ₃₃ O ₆ ClF	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 ₂₇ H ₃₃ O ₆ F	528.55	-	247 (27.80)	2.7 (1.62-3.43)	2.1 (1.10-3.07)
2g	2'-furoyl	Cl	F	H	α -CH ₃	-	-	C ₂₇ H ₃₃ O ₆ ClF	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 ₂₈ H ₃₅ O ₆	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 ₂₈ H ₃₃ O ₆	543.00	543	246 (24.37)	2.3 ^d	2.2 (2.01-2.48)
2j	2'-furoyl	OCOC ₂ H ₅	H	H	α -CH ₃	205-207	+1.0	C ₂₉ H ₃₇ O ₆	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 ₃₅ O ₆	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)

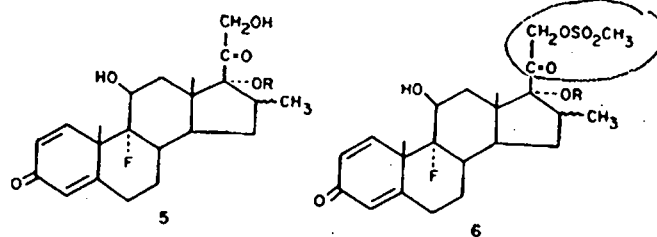
^a NMR and infrared spectra were obtained for all targeted compounds, and NMR spectral data are in the Experimental Section for selected compounds. Mass spectra (EI) were also taken of all compounds reported, although not listed in this report. Microanalyses were determined for most targeted compounds. 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 chlorides⁴ 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, 9 β ,11 β -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.

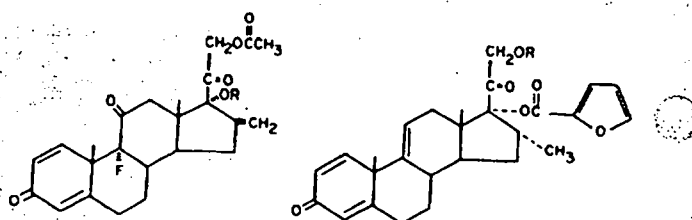
Esterification of the 17-hydroxy group was generally effected with the appropriate heteroaromatic acid chloride, although occasionally for the preparation of the 2'-furoates, 2-furoic anhydride (2-FA)⁶ was used instead of 2-furoyl chloride (2-FC). Our generalized process consisted of reaction of the 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 16 α -methyl-9 α -fluoro 11-ketones for first-time preparation. In the 16 β -methyl series the yields of the 17-acylation step were lower.

Thus, 3a⁷ gave the 17-(2'-furoate) 4a, the 17-(3'-furoate) and the 17-(2'-thenoate) 4d. The isomeric 3b⁸ gave the 2'-furoate 4b.



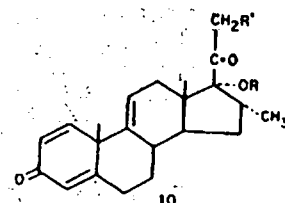
- a. R = 2'-furoyl; 16 α
b. R = 2'-furoyl; 16 β
c. R = 3'-furoyl; 16 α
d. R = 2'-thenoyl; 16 α

16-methylene series, acylation of 7¹⁰ 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.

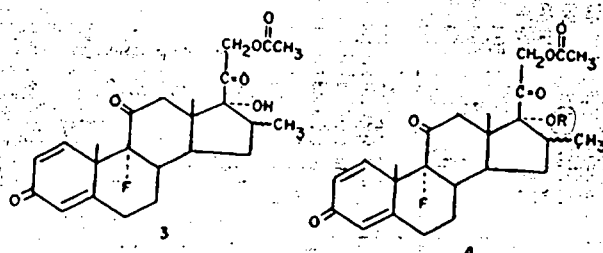


7. R = H
8. R = 2'-furoyl

- a. R = COCH₃
b. R = COCH₂CH₃
c. R = H



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



- a. 16 α
b. 16 β

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

Selective reduction of the 11-ketone in 4a-d with sodium borohydride proceeded in high yield to give the desired 11 β -hydroxy 1a-d (Table I). Hydrolysis of the 21-acetate with perchloric acid in methanol⁹ 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 inversion 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 1l with chromic acid. In the

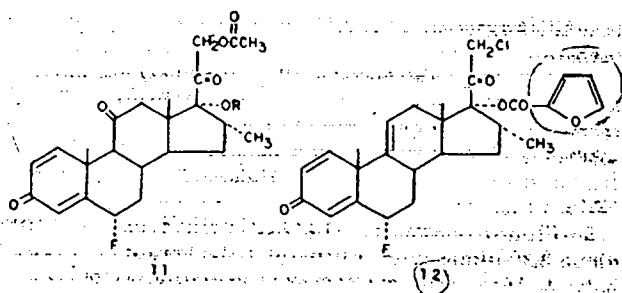
In Table II are listed the 17-heteroaromatic esters bearing 9 α -chloro and 9 α -hydrogen substituents with various 21-functionalities. The chlorohydrins 2a-e (Table II) were obtained from the appropriate $\Delta^9(11)$ compounds² by using 1,3-dichloro-5,5-dimethylhydantoin (DDH) in aqueous tetrahydrofuran 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 9 α -chloro-11 β -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 9 α -chloro-21-fluoro steroid 2e was prepared from the 21-fluoro- $\Delta^9(11)$ steroid 10c with DDH.

Preparation of the two 6 α -fluoro analogues 2f and 2g was initiated by esterification of 11-keto 11a¹¹ to afford the 17-(2'-furoyl) 11b in low yield. Reduction of the 11-ketone in 11b gave the 9-unsubstituted 11 β -hydroxy steroid 2f. Exposure of 12² to DDH afforded the 6 α -fluoro-9 α -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, 16 α -methylprednisolone 17-(2'-furoate) 21-propionate,

- (3) Korb, U.; Stahnke, M.; Wierch, R. German Patent 2748442, May 3, 1979; *Chem. Abstr.* 1980, 93, 168494h.
(4) Where not commercially available, the requisite acid chloride was prepared by standard methods (SOCl₂, 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 10759f.
(8) Scherico Ltd. British Patent 901093, July 11, 1962; *Chem. Abstr.* 1963, 58, 3489g.
(9) Shapiro, E. L.; Finckel, L.; Pluchet, H.; Weber, L.; Robinson, C. H.; Oliveto, E. P.; Herzog, H. L.; Tabachnick, I. A.; Collins, E. J. *Steroids* 1967, 9, 143.

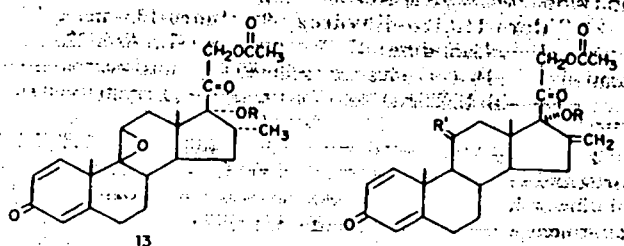
- (10) Irmischer, K.; Orth, D. British Patent 1213118, Nov 18, 1970; *Chem. Abstr.* 1971, 74, 63183k.
(11) Upjohn Co. British Patent 902294, Aug 1, 1962; *Chem. Abstr.* 1963, 59, 14078c.



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

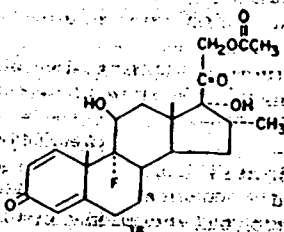
and 2k, prednisolone 17-(2'-furoate) 21-acetate. The latter compound lacks both the potency-enhancing 9 α -halo and 16 α -methyl groups. The syntheses of 2h-k followed known sequences of transformations and are presented in the Experimental Section.

An alternative route to the 9 α , 11 β -halohydrins is exemplified in the preparation of the 9,11-chlorohydrin 2a. Acylation of the 9,11-epoxide 13a¹² 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.



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

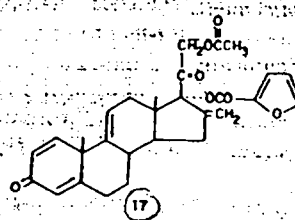
14a. R = H, R' = β -OH, α -H
14b. R = H, R' = β -OH, α -H
14c. R = 2'-furoyl, R' = β -OH, α -H



An alternative process for the preparation of 2a involves direct and selective esterification of the 17-hydroxyl function in 11 β , 17 α -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)thienoyl chloride in the presence of 4-DMAP resulted in formation of the 17-monoester 1n in 11% yield. Studies on selective esterification of 11 β , 17 α -dihydroxy substrates are being

published in a separate paper.¹⁴



17a. R = CH₃, R' = H, R'' = C₂H₅
17b. R = CH₃, R' = 2'-furoyl, R'' = C₂H₅
17c. R = H, R' = H, R'' = CH₃
17d. R = H, R' = 2'-furoyl, R'' = CH₃

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 9 α -fluoro-11 β -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 9 α -fluoro compounds (Table I), the 17,21-diester showed consistently higher activity than the standard in the 16 α -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'-thienoate) 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 9 α -fluoro series the 21-halo has not shown the strong potency-enhancing effect observed in the 9 α , 11 β -dichloro series² or in the 9 α -chloro-11 β -hydroxy series below.

In the 9 α -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'-thienoate), 2e, the 21-fluoro 17-(2'-furoate), and 2g, the 6 α -fluoro analogue of 2c, were at least 4 times as potent as betamethasone valerate. In this series the 17,21-diester 2a and 2b have shown equally high topical antiinflammatory potency.

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

(12) Oliveto, E. P.; Rausser, R.; Weber, L.; Nussbaum, A. L.; Gebert, W.; Coniglio, C. T.; Hershberg, E. B.; Tolsdorf, 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 3068 226, Dec 11, 1962; *Chem. Abstr.* 1963, 58, 11451g.

(14) A more extensive study on selective esterification of 11 β , 17 α -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.

16 α -methyl corticosteroids results in significant topical antiinflammatory 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 antiinflammatory agent. Similarly, the 9 α -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 Me₂SO-*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(CH₃)₄ standard in Me₂SO-*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 μ m, PLC) and analytical thin-layer chromatography (250 μ m, TLC) plates were obtained from Ansh, Inc. Silica gel used for column chromatography was 60–200 μ m, grade 62, supplied by the Davison Chemical Division of Grace, Inc.

9 α -Fluoro-16 α -methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (1a). 4-(Diethylamino)pyridine (4-DMAP) (2.8 g, 23 mmol) and 2-furoyl chloride (2-FC) (0.46 mL, 4.6 mmol) were mixed in CH₂Cl₂ (14 mL) while the temperature was maintained at 0–5 °C. After removal of the cooling bath, 9 α -fluoro-17 α ,21-dihydroxy-16 α -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) (CHCl₃-EtOAc, 39:1), affording 4a, 0.6 g (50%), crystallized from CH₂Cl₂-hexane: mp 228–231 °C; $[\alpha]_D^{25} +48.9^\circ$; λ_{max} 248 nm (25.3 $\times 10^3$); FAB MS, *m/e* 527 (*M* + 1); NMR δ 0.96 (16 α -CH₃, d, 6 H₂), 4.82 and 5.07 (21-CH₂, d's, 17 H₂), 6.07 (4-H, 1 H, d of d, 10 Hz, 1 H₂), 6.63–6.67 (4'-H, q, 1.5 H₂), 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 N₂ was added NaBH₄ (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 (CHCl₃-EtOAc, 9:1) affording 1a, 0.78 g (79%), crystallized from CH₂Cl₂-Et₂O: NMR δ 4.19 (11 α -H, 9 H₂), 5.45 (11 β -OH, br), 6.68 (4'-H, q, 1.9 H₂), 7.13–7.22 (5'-H, 7.99 (3'-H).

9 α -Fluoro-16 β -methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (1b). As in the previous experiment, 3b⁸ was converted to 4b (18%), which on reduction with NaBH₄ afforded 1b (80% from 4b), crystallized from CH₂Cl₂-EtOAc.

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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 NaBH₄ afforded 1c (76%), crystallized from CH₂Cl₂-Et₂O.

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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 NaBH₄ afforded 1d (62%), crystallized from CH₂Cl₂-Et₂O.

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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% HClO₄ (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 (CHCl₃-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 (CHCl₃-EtOAc, 15:1) to give 0.15 g (68%) of 1e, crystallized from CH₂Cl₂-hexane: NMR δ 1.20 (21-OCOCH₂CH₃, t).

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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 CH₂Cl₂-hexane.

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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-11 β ,17 α -dihydroxy-9 α -fluoro-16 α -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 (CHCl₃-EtOAc, 8:1) to give 21-chloro steroid 1h (0.184 g, 74%), crystallized from CH₂Cl₂-hexane: NMR δ 4.47 and 4.57 (21-CH₂, d's, 15 H₂).

21-Chloro-11 β ,17 α -dihydroxy-9 α -fluoro-16 β -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 CH₂Cl₂-hexane.

21-Chloro-11 β ,17 α -dihydroxy-9 α -fluoro-16 α -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 CH₂Cl₂-hexane.

21-Chloro-11 β ,17 α -dihydroxy-9 α -fluoro-16 α -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 CH₂Cl₂-hexane.

21-Chloro-9 α -fluoro-17 α -hydroxy-16 α -methyl-1,4-pregnadiene-3,11,20-trione 17-(3'-Furoate) 21-Acetate (1l). A chromic acid solution (0.075 g of CrO₃, 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 NaHSO₃ (0.3 g). The collected insolubles were purified by PLC (CHCl₃-EtOAc, 19:1) to afford 1l (0.2 g, 81%), crystallized from acetone-Et₂O-hexane: NMR δ 4.55 (21-CH₂), 6.12 (4-H), 6.18 (2-H, d of d, 10 Hz, 2 H₂), 7.32 (1-H, d, 10 H₂).

9 α -Fluoro-16 α -methylene-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (1m). 9 α -Fluoro-16 α -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 CH₂Cl₂ (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 (CHCl₃-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), NaBH₄ (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 (CHCl₃-EtOAc, 6:1) purification, 1m (0.046 g, 33%), crystallized from CH₂Cl₂-hexane: NMR δ 4.78 and 4.99 (21-CH₂, d's, 15 H₂), 5.30 (11-OH, and 16-CH₂, 11-OH exchangeable).

9 α -Chloro-16 α -methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (2a). 16 α -Methyl-17 α ,21-dihydroxy-1,4,9(11)-pregnatriene-3,20-dione 17-(2'-furoate) 21-acetate (9a) (0.618 g, 1.25 mmol) was dissolved in THF (12.5 mL) and maintained at 0–2 °C under N₂. A solution of 70% HClO₄ (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 -Et₂O: NMR δ 4.27-4.43 (11 α -H, br), 5.55 (11 β -OH, d, 4 Hz).

9 α -Chloro-16 α -methyl-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Methoxyacetate (2b). 16 α -Methyl-17 α ,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 -Et₂O: NMR δ 4.33-4.43 (11 α -H), 5.99 (11 β -OH, d, 4 Hz). The related 9 α ,11 β -dichloro steroid was also obtained, in 7% yield.

9 α ,21-Dichloro-11 β ,17 α -dihydroxy-16 α -methyl-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) (2c). As in the preparation of **2a**, 21-chloro-16 α -methyl-17 α -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 (11 α -H, br), 5.62 (11 β -OH, d, 4 Hz). The related 9 α ,11 β -dichloro steroid was also obtained, in 9% yield.

9 α ,21-Dichloro-11 β ,17 α -dihydroxy-16 α -methyl-1,4-pregnadiene-3,20-dione 17-(2'-Thenoate) (2d). As in the preparation of **2a**, 21-chloro-17 α -hydroxy-16 α -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 (11 α -H, br), 5.57 (11 β -OH, d, 5 Hz). The related 9 α ,11 β -dichloro steroid was also obtained, in 8% yield.

9 α -Chloro-11 β ,17 α -dihydroxy-21-fluoro-16 α -methyl-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) (2e). As in the preparation of **2a**, 21-fluoro-17 α -hydroxy-16 α -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 9 α ,11 β -dichloro steroid was also obtained, in 8% yield.

6 α -Fluoro-16 α -methyl-11 β ,17 α ,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 Et₂O-hexane.

21-Dichloro-11 β ,17 α -dihydroxy-6 α -fluoro-16 α -methyl-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) (2g). As in the preparation of **2a**, 21-chloro-6 α -fluoro-17 α -hydroxy-16 α -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 -Et₂O: EI MS, m/e 489 (M - CH_2Cl), NMR δ 4.34-4.57 (21- CH_2 and 11 α -H), 5.30 and 5.90 (6 α -H, br), 5.66 (11 β -OH, d, 5 Hz).

16 α -Methylene-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (2h). As in the preparation of **4a**, **16a**¹² was converted to **16b** (40%), which on reduction with NaBH_4 afforded **2h** (30%), crystallized from EtOAc-hexane.

9 α -Chloro-16-methylene-11 β ,17 α ,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-(2'-Furoate) 21-Acetate (2i). To a solution of the 11 β -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 17 α ,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 $\Delta^{11(11)}$ **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 (11 α -H), 5.45 (16- CH_2), 5.68 (11 β -OH, d, 5 Hz).

16 α -Methyl-11 β ,17 α ,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.

11 β ,17 α ,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 -Et₂O-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 17 α ,21-dihydroxy-16 α -methyl-9,11 β -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-11 β ,17 α ,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-11 β ,17 α ,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).

9 α -Fluoro-16 α -methyl-11 β ,17 α ,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)thienoyl 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 -Et₂O: NMR δ 4.18 (11 α -H), 5.44 (11 β -OH, exchangeable); NMR δ (CDCl₃) 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.¹⁸ 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,

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

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Analogues of 4-[[2-(1H-imidazol-1-yl)-1-[(4-methoxyphenyl)methoxy]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.¹⁻⁶ 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 GG_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

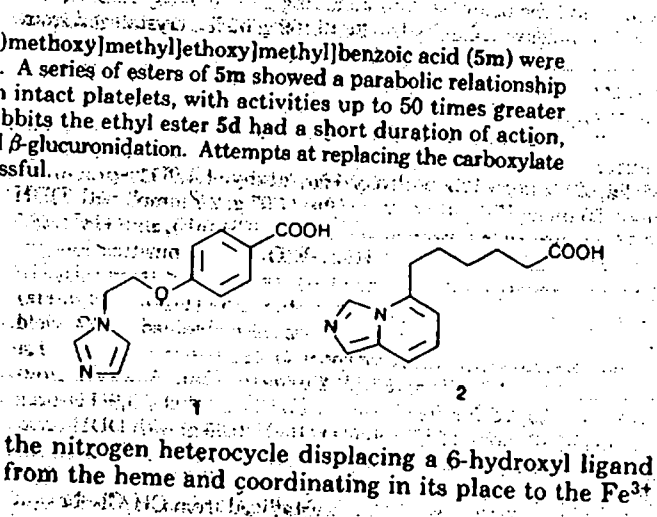
Purified TxA_2 synthase is a P-450 hemoprotein,⁷ and studies suggest that the heme thiolate group of the enzyme is responsible for the coordination of the 9-O atom of the endoperoxide bond of PGH_2 , which results in its cleavage and rearrangement to the oxetane acetal TxA_2 (Scheme 1). The structure 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

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.

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

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