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

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The preparation and topical antiinflammatory potencies of a series of halomethyl 17α-(acyloxy)-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carbothioates, carrying combinations of 6α-fluoro, 9α-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 17β-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 17α-substituent. Carboxyl activation with FMPT and reaction with sodium hydrogen selenide led to the halomethyl 16-methyleneandrostane-17β-carboselenoate analogues. Antiinflammatory potencies were measured in humans using the vasoconstriction assay and in rats and mice by a modification the Tonelli croton oil ear assay. Best activities were shown by fluoromethyl and chloromethyl carbothioates with a 17α-propionyloxy group. *S*-Fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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 avilable 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-17β-carbothioic acids with promising separations of activity.[5]

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

We first explored the synthesis of 17α-unsubstituted 17β-carbothioates in making compounds with anaesthetic activity.[9,10] Kertesz and Marx[11] overcame many difficulties while employing carboxyl-activation procedures followed by reactions with alkanethiols in the synthesis of some alkyl 17α-acyloxy 17β-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-ones[1-3]) as halomethanethiols are not known and would be expected to be very unstable. We therefore devised new methods of preparing 17α-hydroxy and 17α-acyloxy 17β-carbothioic acids, which could then be esterified by reacting their salts with dihalomethanes. Furthermore, 17α-acylation of haloalkyl 17α-hydroxy 17β-carbothioates was likely to be unselective in the presence of an 11β-ol, so it would be preferable to 17α-acylate at the carbothioic acid stage, as with the carboxylic acids.[7,8] The antiinflammatory potencies of the halomethyl 17α-acyloxy 17β-carbothioates were in general high, as delineated in Table 3.

Chemistry

The 17α-hydroxyandrostane-17β-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 17α-acylated, without concomitant 11β-acylation, by reaction with excess acyl chloride and triethylamine followed by aminolysis of the resulting 17α-acyloxy 17β-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 17α-propionyloxy 17β-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 17β-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 dimethylcarbamoyl 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

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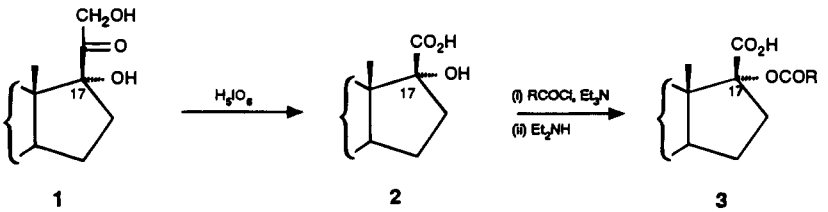
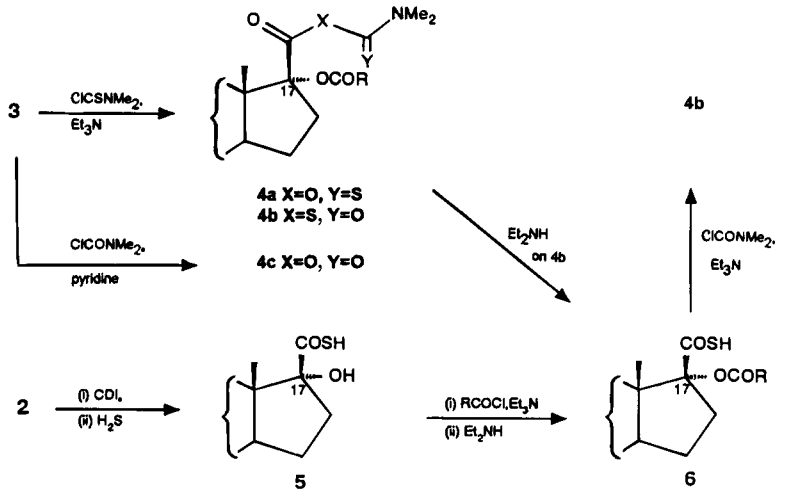
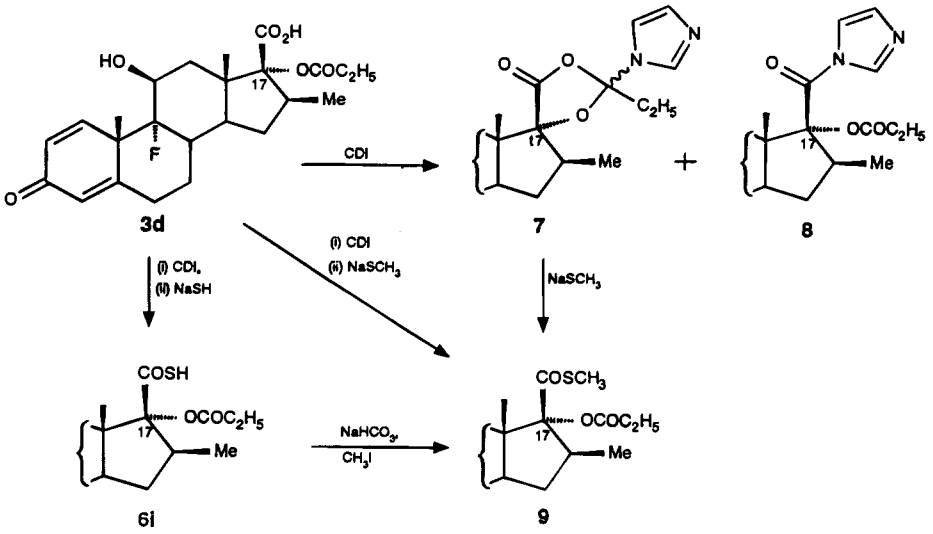
Scheme 1



Scheme 2



Scheme 3

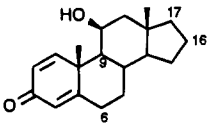


analogue **4ca** (see Scheme 2, also Table 1 for the definition of these compound letters).

Gais[12] 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 alphatic and aromatic thiols to give thioesters in high yields. Kertesz and Marx[11] applied this method to the synthesis of alkyl androstane-17β-carbothioates. We found that the imidazolides from 17α-hydroxy 17β-carboxylic acids also react with hydrogen sulfide to give 17α-hydroxy 17β-carbothioic acids **5**. Like the corresponding carboxylic acids, these were readily and selectively 17α-acylated without concomitant 11β-acylation (Scheme 2).

Kertesz and Marx[11] reported that CDI failed to activate 17α-acyloxy 17β-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 H_2S. The reaction of H_2S with other carboxyl-activated species is known to be base-catalyzed.[13] The known thioester **9**[11] 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 ^{13}C 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]



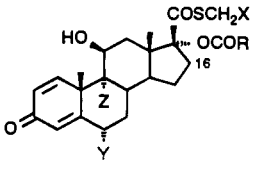
no.	6α	9α	16	17α	17β	mp, °C	$[\alpha]_D$ deg (dioxane)	formula	anal.[b]	UV, λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$)
2a	F	H	H	OH	CO_2H	241–248	+54	$C_{20}H_{25}FO_5$	C,H	242 (15.3)
2b	H	F	H	OH	CO_2H	289–293	+66[q]	$C_{20}H_{25}FO_5$	C,H	239.5 (14.5)
2c	F	F	$=CH_2$	OH	CO_2H	248–252[c]	−24	$C_{21}H_{24}F_2O_5$	C,H	238 (16.0)
3a	F	H	H	$OCOC_2H_5$	CO_2H	224–227	+3	$C_{23}H_{29}FO_6$	C,H	242 (14.3)
4ba	H	F	α-CH_3	$OCOC_2H_5$	$COSCONMe_2$	191–193	+82	$C_{27}H_{36}FNO_6S$	C,H,N,S	239 (18.7)
4bb	H	F	β-CH_3	$OCOCH_3$	$COSCONMe_2$	foam	+172	$C_{26}H_{34}FNO_6S$	C,H,N,S[e]	238 (19.6)
4bc	H	F	β-CH_3	$OCOC_2H_5$	$COSCONMe_2$	167–170	+185	$C_{27}H_{36}FNO_6S$	C,H,N	237.5 (19.8)
4bd	H	F	$=CH_2$	$OCOC_2H_5$	$COSCONMe_2$	189–192	+6	$C_{27}H_{34}FNO_6S$	C,H,N,S[f]	236.5 (19.2)
4ca	H	F	β-CH_3	$OCOC_2H5$	CO_2CONMe_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	$C_{20}H_{25}FO_4S$	C,H	244 (19.3)
5b	H	F	α-CH_3	OH	COSH	209–214	+104	$C_{21}H_{27}FO_4S$	C,H,S[g]	245 (17.6)
5c	F	F	α-CH_3	OH	COSH	230–232	+94	$C_{21}H_{26}F_2O_4S$	C,H,S	243 (21.0)
5d	H	F	β-CH_3	OH	COSH	198–201[c]	+189	$C_{21}H_{27}FO_4S$	C,H,S[h]	243 (19.5)
5e	F	F	$=CH_2$	OH	COSH	251–256[c]	+58	$C_{21}H_{24}F_2O_4S$	C,H,S	242 (20.5)
6a	F	H	H	$OCOC_2H_5$	COSH	189–193	+72	$C_{23}H_{29}FO_5S$	C,H,S	247 (18.1)
6b	H	F	H	$OCOC_2H_5$	COSH	136–138	+75	$C_{23}H_{29}FO_5S$	C,H,S	245 (18.4)
6c	H	F	α-CH_3	$OCOC_2H_5$	COSH	141–143	+30	$C_{24}H_{31}FO_5S$	C,H	243 (16.3)
6d	F	F	α-CH_3	$OCOCH_3$	COSH	175–177	−10	$C_{23}H_{28}F_2O_5S$	C,H,S	242.5 (18.0)
6e	F	F	α-CH_3	$OCOC_2H_5$	COSH	161–164	−27	$C_{24}H_{30}F_2O_5S$	C,H,S	243 (18.9)
6f	F	F	α-CH_3	$OCOC_3H_7$	COSH	155–157	+21	$C_{25}H_{32}F_2O_5S$	C,H,S	242.5 (18.4)
6g	H	H	β-CH_3	$OCOC_2H_5$	COSH	159–163	+113	$C_{24}H_{32}O_5S$	C,H,S	247 (17.8)
6h	H	F	β-CH_3	$OCOCH_3$	COSH	178.5–179	+98	$C_{24}H_{29}FO_5S$	C,H,S[h]	242 (17.8)
6i	H	F	β-CH_3	$OCOC_2H_5$	COSH	177–179	+110	$C_{24}H_{31}FO_5S$	C,H,S	242 (18.3)
6j	H	F	β-CH_3	$OCOC_3H_7$	COSH	175–176	+107	$C_{25}H_{33}FO_5S$	C,H,S[k]	244 (18.1)
6k	H	F	$=CH_2$	$OCOC_2H_5$	COSH	236–239	−71	$C_{24}H_{29}FO_5S$	C,H,S[f]	242 (17.7)
7a	H	F	β-CH_3	spiro($C_9H_8N_2O_3$)[i]		193–195	+96	$C_{27}H_{33}FN_2O_5$	C,H,N[e]	240 (14.3)
7b	H	F	β-CH_3	spiro($C_9H_8N_2O_3$)[j]		168–176	−8	$C_{27}H_{33}FN_2O_5$	C,H,N[l]	240 (14.5)
8	H	F	β-CH_3	$OCOC_2H_5$	$CO(C_3H_3N_2)$	190–203	+52	$C_{27}H_{33}FN_2O_5$	C,H,N[m]	240 (17.3)
10i	F	H	H	$OCOC_2H_5$	$COSCH_2Cl$	188–191	+48	$C_{24}H_{30}ClFO_5S$	C,H,Cl,S[n]	240 (18.7)
10j	H	F	α-CH_3	$OCOC_2H_5$	$COSCH_2Cl$	247–250	+50.5	$C_{25}H_{32}ClFO_5S$	C,H,Cl,S	238 (19.0)
10k	F	F	α-CH_3	$OCOCH_3$	$COSCH_2Cl$	280–283	+45	$C_{24}H_{29}ClF_2O_5S$	C,H,Cl,S	238.5 (19.8)
10l	F	F	α-CH_3	$OCOC_3H_7$	$COSCH_2Cl$	235–238	+49	$C_{26}H_{33}ClF_2O_5S$	C,H,Cl,S	238.5 (19.9)
11b	F	H	H	$OCOC_2H_5$	$COSCH_2I$	195–197	+18	$C_{24}H_{30}FIO_5S$	C,H,I,S	243.5 (20.7)
11c	H	F	H	$OCOC_2H_5$	$COSCH_2I$	175–178	+4	$C_{24}H_{30}FIO_5S$	C,H,I[o]	242 (17.9)
11d	F	F	α-CH_3	$OCOCH_3$	$COSCH_2I$	241–243	+78	$C_{24}H_{29}F_2IO_5S$	C,H,I,S	240 (20.2)
11e	F	F	α-CH_3	$OCOC_2H_5$	$COSCH_2I$	233–236[c]	+87	$C_{25}H_{31}F_2IO_5S$	C,H,I,S	241 (20.6)
11f	F	F	α-CH_3	$OCOC_3H_7$	$COSCH_2I$	210–212	+89	$C_{26}H_{33}F_2IO_5S$	C,H,I,S[m]	241 (20.7)
11g	H	F	β-CH_3	$OCOCH_3$	$COSCH_2I$	204–205	−29	$C_{24}H_{30}FIO_5S$	C,H,I,S	241 (20.6)
11h	H	F	$=CH_2$	$OCOC_2H_5$	$COSCH_2I$	191–199	−31	$C_{25}H_{30}FIO_5S$	C,H,I,S	241 (19.8)
16	H	F	β-CH_3	epoxide	$COSCH_2Cl$	246–251	+131	$C_{22}H_{26}ClFO_4S$	C,H,Cl	239 (20.5)
17	H	F	$=CH_2$	OH	$COSCH_2Cl$	242–243	+36	$C_{22}H_{26}ClFO_4S$	C,H	239.5 (19.4)
18a	H	F	β-CH_3	epoxide	$COSeCH_3$	297–299	+156	$C_{22}H_{27}FO_4Se$	C,H,Se	239 (16.3)
18b	H	F	β-CH_3	epoxide	$COSeCH_2Cl$	229–232[c]	+111	$C_{22}H_{26}ClFO_4Se$	C,H,Cl[h]	237.5 (16.5)
19a	H	F	$=CH_2$	OH	$COSeCH_3$	248–254[c]	+82.5	$C_{22}H_{27}FO_4Se$	C,H,Se	240.5 (15.9)
19b	H	F	$=CH_2$	OH	$COSeCH_2Cl$	237–239	+45.5	$C_{22}H_{26}ClFO_4Se$	C,H,Cl,Se	240.5 (16.3)
20a[d]	H	F	$=CH_2$	OH	$COSeCH_3$	225–235[c]	+124	$C_{22}H_{25}FO_4S$	C,H	238 (15.7)
20b[d]	H	F	$=CH_2$	OH	$COSeCH_2Cl$	209–210	+142	$C_{22}H_{24}ClFO_4Se$	C,H	237 (16.1)
21a[d]	H	F	$=CH_2$	$OCOC_2H_5$	$COSeCH_3$	209–211	−9	$C_{25}H_{29}FO_5Se$	C,H,Se	237 (16.0)
21b[d]	H	F	$=CH_2$	$OCOC_2H_5$	$COSeCH_2Cl$	156–158	−8	$C_{25}H_{28}ClFO_5Se$	C,H	237 (16.1)
22c	H	F	$=CH_2$	$OCOC_2H_5$	$COSeCH_2I$	174–175	−70	$C_{25}H_{30}FIO_5Se$	C,H,Se	238 (16.7)
22d	H	F	$=CH_2$	$OCOC_2H_5$	$COSeCH_2F$	216–218	−43.5	$C_{25}H_{30}F_2O_5Se$	C,H	239.5 (16.8)
24	H	F	β-CH_3	$OCOC_2H_5$	$COS]_2$[p]	234–235	+107	$C_{48}H_{60}F_2O_{10}S_2$	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 (0.25Me_2CO). [g] Solvate (1.0H_2O). [h] Solvate (0.25H_2O). [i] Isomer A. [j] Isomer B. [k] Solvate (0.16EtOAc). [l] Solvate (0.2EtOAc). [m] Solvate (0.5H_2O). [n] Solvate (0.33H_2O). [o] Solvate (0.6MeOH). [p] Disulfide.

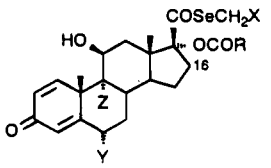
C-17 resonances (92.1 and 91.1 ppm) were structurally characteristic, and the ^1H NMR confirmed that the ethyl groups in each isomer were no longer part of an ester function; the configurations of the two isomers were not established. From a further experiment, in which the reaction mixture was treated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



10,11,12,13

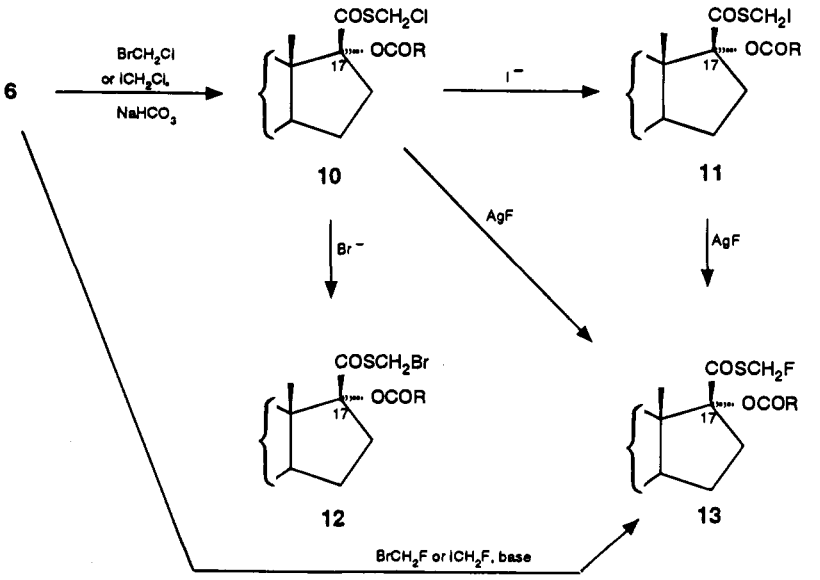


22

no.	Z	Y	X	R	16	mp, °C	$[\alpha]_D$, detg (dioxane)	formula	anal.	UV, λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$)
13a	H	F	F	C_2H_5	H	224–225	+70	$C_{24}H_{30}F_2O_5S$	C,H,F,S	238.5 (17.4)
10a	F	H	Cl	C_2H_5	H	196–199	+38	$C_{24}H_{30}ClFO_5S$	C,H,S	238 (16.9)
13b	F	H	F	C_2H_5	H	207–211	+70	$C_{24}H_{30}F_2O_5S$	C,H,F,S	237 (17.1)
13c	F	H	F	C_2H_5	α-CH_3	242–243	+37	$C_{25}H_{32}F_2O_5S$	C,H,S	237 (18.0)
10b	F	F	Cl	C_2H_5	α-CH_3	272–275	+49	$C_{25}H_{31}ClF_2O_5S$	C,H	238 (20.0)
13d	F	F	F	CH_3	α-CH_3	308–310	+29	$C_{24}H_{29}F_3O_5S$	C,H,S	236 (19.0)
13e	F	F	F	C_2H_5	α-CH_3	274–275	+32	$C_{25}H_{31}F_3O_5S$	C,H,F,S	236.5 (18.6)
13f	F	F	F	C_3H_7	α-CH_3	249–252	+32	$C_{26}H_{33}F_3O_5S$	C,H,F,S	237 (19.1)
10c	H	H	Cl	C_2H_5	β-CH_3	192–193	+65	$C_{25}H_{33}ClO_5S$	C,H,Cl,S	241 (17.8)
13g	H	H	F	C_2H_5	β-CH_3	223–225	+103	$C_{25}H_{33}FO_5S$	C,H,S	240 (16.3)
10d	F	H	Cl	CH_3	β-CH_3	220–223	+39.5	$C_{24}H_{30}ClFO_5S$	C,H,Cl,S	238 (18.4)
13h[b]	F	H	F	CH_3	β-CH_3	248–249	+101	$C_{24}H_{30}F_2O_5S$	C,H,F,S	237 (17.7)
10e	F	H	Cl	C_2H_5	β-CH_3	212–214	+44	$C_{25}H_{32}ClFO_5S$	C,H,Cl,S	238.5 (18.8)
12[c]	F	H	Br	C_2H_5	β-CH_3	186.5–187	+2	$C_{25}H_{32}BrFO_5S$	C,H,Br,S	241 (19.9)
11a[c]	F	H	I	C_2H_5	β-CH_3	196–197	−32	$C_{25}H_{32}FIO_5S$	C,H,I,S	242 (20.2)
13i	F	H	F	C_2H_5	β-CH_3	237–241	+98	$C_{25}H_{32}F_2O_5S$	C,H,F,S	237 (17.4)
10f	F	H	Cl	C_3H_7	β-CH_3	172–175	+46	$C_{26}H_{34}ClFO_5S$	C,H,Cl,S	239 (18.7)
10g	F	H	Cl	C_2H_5	=CH_2	212–221	−56	$C_{25}H_{30}ClFO_5S$	C,H,Cl,S	239 (19.5)
13j	F	H	F	C_2H_5	=CH_2	205–215	−58	$C_{25}H_{30}F_2O_5S$	C,H,F,S	237 (18.1)
10h	F	F	Cl	C_2H_5	=CH_2	242–245	−56	$C_{25}H_{29}ClF_2O_5S$	C,H,Cl,S	238.5 (19.9)
13k	F	F	F	C_2H_5	=CH_2	251–255[d]	−56	$C_{25}H_{29}F_3O_5S$	C,H,S	236.5 (19.1)
22a	F	H	H	C_2H_5	=CH_2	225–227	−37	$C_{25}H_{31}FO_5Se$	C,H,Se	239.5 (16.3)
22b	F	H	Cl	C_2H_5	=CH_2	212–214	−48	$C_{25}H_{30}ClFO_5Se$	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 H_2O. [c] Solvated with 0.33 mol of H_2O. [d] Decomposition.

Scheme 4

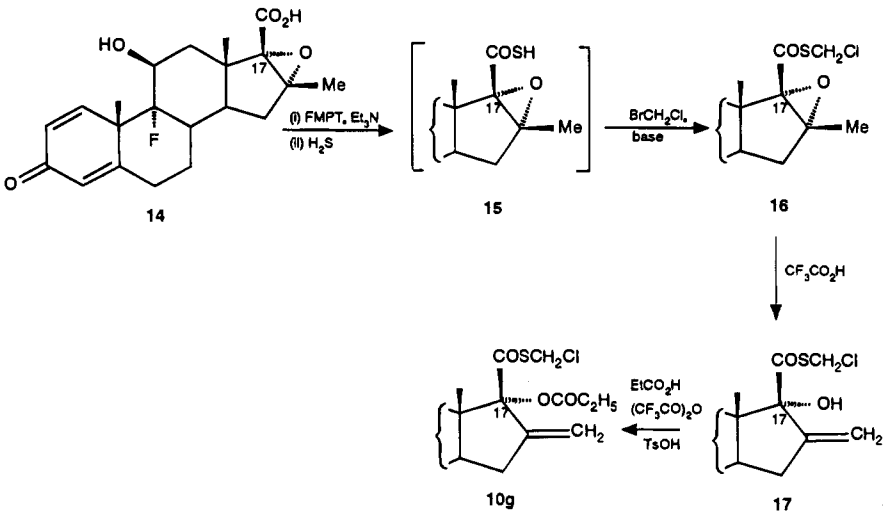


to give the bromomethyl and fluoromethyl thioesters **12** and **13**, respectively. The fluoromethyl thioester **13e** was also prepared directly from the potassium salt of the carbothioic acid **6e**, using fluoroiodomethane[14] or bromofluoromethane[15] (Scheme 4).

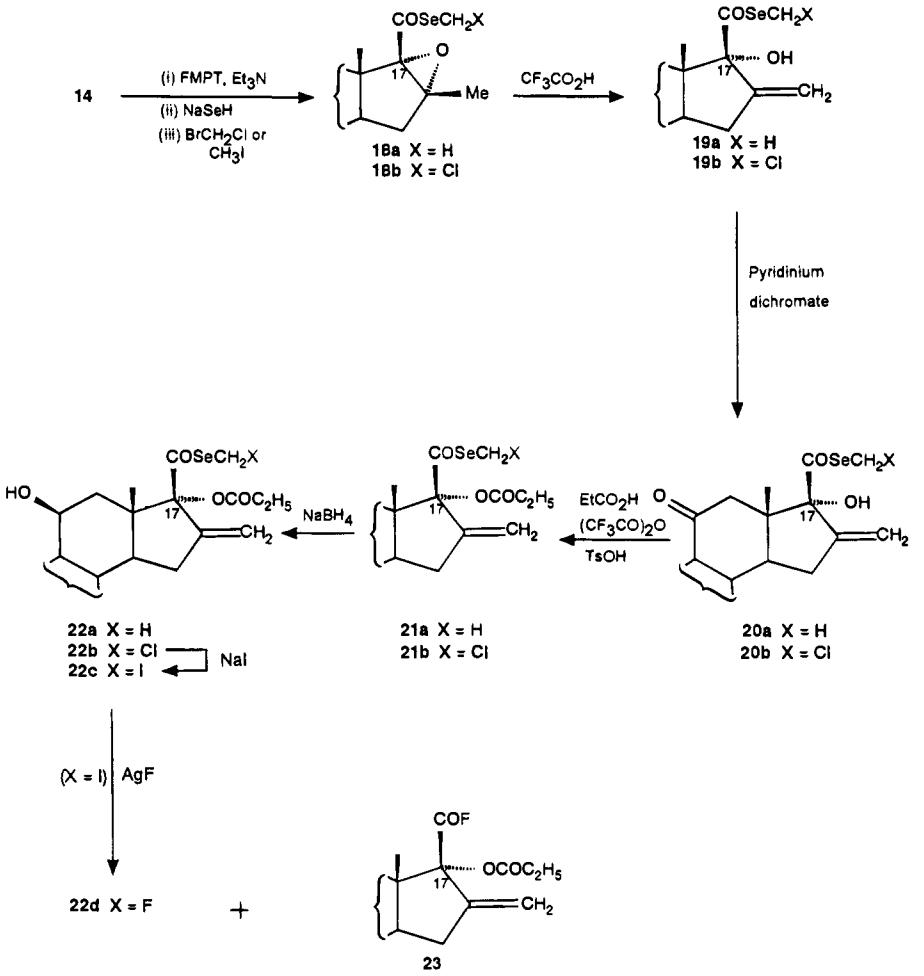
Kertesz and Marx[11] reported that 2-fluoro-*N*-methylpyridinium tosylate (FMPT) could be used for the activation of 17β-carboxylic acids in the presence of a 16α,17α-acetonide but that neighboring group participation dominated the chemistry of 17α-hydroxy or 17α-acyloxy compounds. FMPT also activated the 16α,17α-epoxy-16β-methyl 17β-carboxylic acids **14** to reaction with H_2S. 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 17α-ol **17** which on propionylation in the presence of acid gave a mixture of the 17α-ester **10g** and the isomeric 11β-monoester (Scheme 5).

Activation of **14** with FMPT and reaction with NaSeH[16] gave the corresponding carboselenoic acid, which could be alkylated *in situ* to the methyl or

Scheme 5



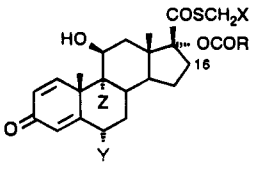
Scheme 6



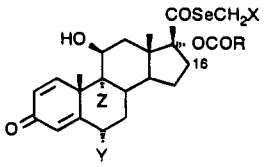
chloromethyl carboselenoates **18a,b**. Epoxide rearrangement (CF_3CO_2H) then gave the corresponding 11β-17α-diols **19a,b**. In this series, oxidation of **19a,b** to the 11-ketones **20a,b** prior to 17α-propionylation followed by selective reduction of 11-oxo esters **21a,b** to the 11β-alcohols **22a,b** avoided unwanted 11β-esterification (Scheme 6).

Reaction of the iodomethyl selenoester **22c** with silver fluoride in acetonitrile gave the corresponding fluoromethyl 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-17β-carbothioates and -17β-carboselenoates



10,11,12,13



22

							mouse		rat	
no.	Z	Y	X	R	16	human V[a]	AIT[b]	HPA[c]	AIT[b]	HPA[c]
13a	H	F	F	C_2H_5	H	697 (230–2438)	56 (36–86)	>200 (G)	97 (62–156)	–
10a	F	H	Cl	C_2H_5	H	916 (471–1874)	20 (14–29)	100 (G)	–	–
13b	F	H	F	C_2H_5	H	1984 (1023–4013)	63 (39–105)	149 (103–219)	39 (27–56)	1.5 (G)
13c	F	H	F	C_2H_5	α-CH_3	653 (311–1395)	–	–	–	–
10b	F	F	Cl	C_2H_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_2H_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_3H_7	α-CH_3	299 (98–953)	55 (34–87)	0.7 (G)	55 (35–86)	–
10c	H	H	Cl	C_2H_5	β-CH_3	295 (72–1148)	27 (17–44)	–	29 (19–44)	1.4 (0.5–3.2)
13g	H	H	F	C_2H_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_2H_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_2H_5	β-CH_3	254 (G)	–	–	–	–
11a	F	H	I	C_2H_5	β-CH_3	41 (G)	–	–	–	–
13i	F	H	F	C_2H_5	β-CH_3	1262 (597–2669)	89 (45–169)	450[h]	39 (30–52)	13 (8–24)
10f	F	H	Cl	C_3H_7	β-CH_3	143 (41–435)	–	–	–	–
10g	F	H	Cl	C_2H_5	$=CH_2$	365 (198–665)	42 (28–64)	2 (1–3)	12 (9–17)	0.8 (G)
13j	F	H	F	C_2H_5	$=CH_2$	1497 (575–4085)	41 (28–64)	44 (27–76)	20 (14–26)	2.5 (G)
10h	F	F	Cl	C_2H_5	$=CH_2$	170 (G)	108 (70–171)	>100 (G)	–	–
13k	F	F	F	C_2H_5	$=CH_2$	1048 (G)	197 (G)	>100 (G)	–	–
22a	F	H	H	C_2H_5	$=CH_2$	187 (85–415)	27 (16–44)	–	19 (12–29)	<0.2
22b	F	H	Cl	C_2H_5	$=CH_2$	200 (103–388)	40 (27–61)	2 (G)	16 (9–26)	–
(fluocinolone acetonide)[i]						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 ^{1}H NMR spectra of carbothioic acids were best measured in deuteriochloroform if solubility was sufficient, as in Me_2SO-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 17α-acyloxy 17β-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 16α-methyl substituent was present but decreasing when a 16β-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 16α-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 analogues[1] in the vasoconstriction test, while the methyl carbothioate analogue of FP (**13e**) has been reported[11] 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 reported[5] to be rapidly converted by liver homogenates (from mouse, rat, or dog) into the known carboxylic acid **3f**.[11] This acid has since been confirmed to be the principal metabolite in a study[20] 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 (Flixonase[21]), asthma (in UK, Flixotide[21]), and steroid-responsive dermatoses (in USA, Cutivate[21]).

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined in dioxane at 20–22 °C; ^{1}H NMR spectra were determined in Me_2SO-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 ^{19}F NMR. A JEOL FX100 Fourier-transform spectrometer was used at 25.05 MHz for ^{13}C NMR or at 100 MHz for ^{1}H NMR. Chemical shifts are relative to $Me_3Si(CH_2)_3SO_3Na$ in Me_2SO-d_6 and $SiMe_4$ in $CHCl_3$-d for ^{1}H and ^{13}C NMR and to $CFCl_3$ for ^{19}F NMR, as internal standards. IR spectra were recorded for Nujol mulls, or in $CHBr_3$ 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 F_{254} 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 $PF_{254+366}$. 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. ^{1}H NMR (in Me_2SO-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.

6α-Fluoro-11β,17α-dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (2a). A solution of 6α-fluoro-11β,17α,-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%).

9α-Fluoro-11β,17α-dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (2b). A stirred suspension of 9α-fluoro-11β-17α,21-trihydroxypregna-1,4-diene-3,20-dione (**1b**)[23] (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%).

6α,9α-Difluoro-11β,17α-dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (2c). 6α,9α-Difluoro-11β,17α,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%).

6α-Fluoro-11β-hydroxy-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic Acid (3a). A solution of **2a** (4.49 g, 12.3 mmol) and Et_3N (4.46 mL, 31.6 mmol) in CH_2Cl_2 (160 mL) at −5 °C was treated dropwise with stirring with propionyl chloride (2.80 mL, 32 mmol) in CH_2Cl_2 (5 mL) during 5 min. After 20 min the reaction mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and then H_2O, dried, and evaporated to give the intermediate mixed anhydride as a solid (5.70 g). This was stirred in acetone (30 mL) with Et_2NH (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 17β-[(*N,N*-dimethylcarbamoyl)thio]carbonyl Compounds 4b. General Method A. The steroid 17β-carboxylic acid **3** (1 equiv) stirred in CH_2Cl_2 (*ca.* 15 mL/g of **3**) was treated successively with Et_3N (1 equiv) and *N,N*-dimethylthiocarbamoyl chloride (2 equiv) under N_2 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% $NaHCO_3$, and water, dried, and evaporated to give the crude anhydride **4b**, purified by crystallization or by PLC then crystallization.

17β-[[(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9α-fluoro-11β-hydroxy-16α-methyl-17α-(propionyloxy)androsta-1,4-dien-3-one (4ba). 9α-Fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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 ($CHBr_3$) 3610 (OH), 1740, 1710 (w) (COSCON, propionate), 1670, 1632, 1618 ($\Delta^{1,4}$-3-one) cm^{-1}.

17α-Acetoxy-17β-[[(*N,N*-dimethylcarbamoyl)thio]carbonyl]-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-dien-3-one (4bb). 17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methylandrosta-1,4-diene-17β-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 ($CHBr_3$) 3590 (OH), 1735 (COSCON, propionate), 1665, 1630, 1612 ($\Delta^{1,4}$-3-one) cm^{-1}.

17β-[[(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9α-fluoro-11β-hydroxy-16β-methyl-17α-(propionyloxy)androsta-1,4-dien-3-one (4bc). 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid (**3d**),[11] solvated with 0.75 mol of EtOAc (4.99 g, 9.96 mmmol) 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 ($CHBr_3$) 3670 (OH), 1740 (COSCON, propionate), 1670, 1636, 1618 ($\Delta^{1,4}$-3-one) cm^{-1}; ^{1}H NMR (90 MHz) 0.99 (13-CH_3 s) 1.07 (propionate CH_3, t, J = 7 Hz), 1.29 (16β-CH_3, *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, 9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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%): $[\alpha]_D$ +168° (*c* 1.05); MS *m/e* 522 (MH^+), 417 ($MH^+ - Me_2NCOSH$), with mass, IR, and ^1H NMR spectra closely similar to those of the above. Anal. ($C_{27}H_{36}FNO_6S$·0.5EtOAc) C, H, N, S.

17β-[[(*N,N*-Dimethylcarbamoyl)thio]carbonyl]-9α-fluoro-11β-hydroxy-16-methylene-17α-(propionyloxy)androsta-1,4-dien-3-one (4bd). 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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 of **4bd** (43%): IR ($CHBr_3$) 3620 (OH), 1740, 1710 (COSCON, propionate), 1665, 1630, 1612 ($\Delta^{1,4}$-3-one) cm^{-1}.

17β-[[(*N,N*-Dimethylcarbamoyl)oxy]carbonyl]-9α-fluoro-11β-hydroxy-16β-methyl-17α-(propionyloxy)androsta-1,4-dien-3-one (4ca). 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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 ($\Delta^{1,4}$-3-one) cm^{-1}.

Formation of 17α-Hydroxy 17β-Carbothioic Acids 5. General Method B. A solution of the 17α-hydroxy 17β-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.

9α-Fluoro-11β,17α-dihydroxy-3-oxoandrosta-1,4-diene-17β-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%).

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

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

9α-Fluoro-11β,17α-dihydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic Acid (5d). 9α-Fluoro-11β,17α-dihydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-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 (16β-CH_3, d, J = 6 Hz), 1.56 (10-CH_3, s), 4.22 (11α-H, m), 4.09 (4-H, m), 6.28 (2-H, dd, J = 10, 2 Hz), 7.37 (1-H, d, J = 10 Hz).

6α,9α-Difluoro-11β,17α-dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17β-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 17α-Acyloxy 17β-Carbothioic Acids 6. General Method C. The crude 17β-[(*N,N*-dimethylcarbamoyl)thio]carbonyl compound **4b** prepared by general method A was refluxed under nitrogen in Et_2NH (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 17α-hydroxy 17β-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_2NH (*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**.

6α-Fluoro-11β-hydroxy-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioic Acid (6a). The 17β-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 **5a** (46%).

9α-Fluoro-11β-hydroxy-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioic Acid (6b). The 17β-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%).

9α-Fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioic Acid (6c). 9α-Fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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 17α-hydroxy compound **5b** also gave **6c** (90%), mp 134–137 °C, by general method D, using propionyl chloride.

17α-Acetoxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic Acid (6d). The 17α-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%).

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioic Acid (6e). The 17α-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 (16α-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 (11α-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). 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid (**3f**)[11] also gave **6e** (25%) using general methods A then C.

17α-(Butyryloxy)-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic Acid (6f). The 17α-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%).

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

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17β-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%).

9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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**: ^{1}H NMR (90 MHz) 1.00 (13-CH_3, s), 1.07 (propionate CH_3, t, J = 7 Hz), 1.29 (16β-CH_3, d, J = 6 Hz), 1.54 (10-CH_3, s), 2.37 (propionate CH_2, q, J = 7 Hz), 4.30 (11α-H, broad m), 5.45 (11β-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; ^{1}H NMR (90 MHz in $CHCl_3$-*d*) 1.07 (13-CH_3, s), 1.17 (propionate CH_3, t, J = 7 Hz), 1.37 (16β-CH_3, d, J = 6 Hz), 1.57 (10-CH_3, s), 2.38 (propionate CH_2, q, J = 7 Hz), 4.46 (11α-H, broad m), 6.17 (4-H, m), 6.37 (2-H, d, J = 10 Hz), 7.27 (1-H, d, J = 10 Hz).

The 17α-hydroxy compound **5d** was also converted into **6i** (53%), mp 174–179 °C from EtOAc, using general method D with propionyl chloride. In a third method, the carboxylic acid **3d**[11] (0.70 g, 1.40 mmol) and CDI (0.473 g, 2.9 mmol) in DMF (26 mL) were stirred at 22 °C under N_2 for 19.5 h. A dark-blue solution, prepared by passing H_2S 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%).

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

9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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%).

9α-Fluoro-11β-hydroxy-16β-methyl-3-oxoandrosta-1,4-diene-17(*R*)-spiro-5′-[2′ξ-ethyl-2′ξ-(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 N_2 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% Na_2CO_3, 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}; ^{1}H NMR (90 MHz) 0.85 (ethyl CH_3, t, J = 8 Hz), 1.14 (13-CH_3, s), 1.17 (16β-CH_3 d, J = 7 Hz), 1.47 (10-CH_3, s), 2.31 (ethyl CH_2, q, J = 8 Hz), 7.02, 7.27, 7.81 (imidazole protons); ^{13}C 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}; ^{1}H NMR (90 MHz) 0.82 (ethyl CH_3, t, J = 8 Hz), 0.85 (16β-CH_3, d, J = 7 Hz), 1.25 (13-CH_3, s), 1.56 (10-CH_3, s), 2.27 (ethyl CH_2, q, J = 8 Hz), 7.02, 7.37, 7.87 (imidazole protons); ^{13}C 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-[(9α-fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-propionyloxyandrosta-1,4-dien-17β-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}; ^{1}H NMR (90 MHz) 0.94 (propionate CH_3, t, J = 7 Hz), 1.08 (13-CH_3, s), 1.35 (16β-CH_3, d, J = 7 Hz), 1.54 (10-CH_3, s), 2.43 (propionate CH_2, q, J = 7 Hz), 7.08, 7.69, 8.31 (imidazole protons).

***S*-Methyl 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (9).** A mixture of **6i** (0.277 g, 0.61 mmol) and $NaHCO_3$ (0.167 g, 1.99 mmol) in CH_3I (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% $NaHCO_3$, 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 N_2 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– Na_2CO_3, H_2O, 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 17β-Carbothioates 10. General Method E. A solution of the carbothioic acid **6** (1 equiv) in dimethylacetamide (3.5–10 mL/g) was stirred with $NaHCO_3$ (2 equiv) and bromochloromethane (2–5 equiv) for 1–2 h, diluted with EtOAc (*ca* 200 mL/g), washed with 5% $NaHCO_3$ and water, dried, and evaporated *in vacuo* to give crude **10**.

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

***S*-Chloromethyl 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (10b).** General method E on **6e** and crystallization from EtOAc gave **10b** (67%): ^{1}H NMR (90 MHz) 0.94 (16α-CH_3, d, J = 7 Hz), 1.06 (13-CH_3, s), 1.06 (propionate CH_3, t, J = 7 Hz), 1.54 (10-CH_3, s), 2.40 (propionate CH_2, q, J = 7 Hz), 4.29 (11α-H, broad m), 5.22 (CH_2Cl, 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 11β-Hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (10c).** General method E on **6g** and crystallization from EtOAc gave **10c** (76%).

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

***S*-Chloromethyl 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (10e).** General method E on **6i** and two crystallizations from methanol gave **10e** (36%): ^{1}H NMR (90 MHz) 0.98 (13-CH_3, s), 1.06 (propionate CH_3, t, J = 7 Hz), 1.37 (16β-CH_3, d, J = 7 Hz), 1.53 (10-CH_3, s), 2.38 (propionate CH_2, q, J = 7 Hz), 4.28 (11α-H, broad m), 5.11 (CH_2Cl, 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 ICH_2Cl in place of $BrCH_2Cl$.

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

***S*-Chloromethyl 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (10g).** General method E on **6k** and PLC followed by two crystallizations from EtOAc gave **10g** (50%): ^{1}H NMR (90 MHz) 1.01 (propionate CH_3, t, J = 7 Hz), 1.01 (13-CH_3, s), 1.54 (10-CH_3, s), 2.32 (propionate CH_2, q, J = 7 Hz), 4.30 (11α-H, m), 5.21 (CH_2Cl, s), 5.50–5.71 (16=CH_2 and 11β-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 6α,9α-Difluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (10h).** General methods D then E on **5e**, with PLC and crystallization from aqueous methanol, gave **10h** (19.7%).

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

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

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

Formation of *S*-Iodomethyl 17β-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 (10–30 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% $NaHCO_3$, and water, dried, and evaporated *in vacuo* to give crude **11**.

***S*-Iodomethyl 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (11a).** General method F on **10e** and PLC and then two crystallizations from acetone gave **11a** (41%): ^{1}H NMR (90 MHz in $CHCl_3$-*d*) 4.26 and 4.52 (CH_2I, dd, J = 11 Hz).

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

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

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

***S*-Iodomethyl 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (11e).** General method F on **10b** and crystallization from EtOAc gave **11e** (85%): ^{1}H NMR (90 MHz) 4.63 (CH_2I, s).

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

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

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

***S*-Bromomethyl 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-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%): ^{1}H NMR (90 MHz in $CHCl_3$-*d*) 4.51 and 4.89 (CH_2Br, dd, J = 11 Hz).

Formation of *S*-Fluoromethyl 17β-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 CH_3CN (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 6α-Fluoro-11β-hydroxy-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (13a).** General method G on **11b** and two crystallizations from acetone and petroleum ether (bp 60–80 °C) gave **13a** (62%).

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

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

***S*-Fluoromethyl 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioate (13e).** Small pieces of AgF (2.46 g, 19.4 mmol) were stirred in CH_3CN (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 $MgSO_4$, 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 ($\Delta^{1,4}$-3-one) cm^{-1}; ^{1}H NMR (90 MHz) 0.96 (16α-CH_3, d, J = 7 Hz), 1.06 (propionate CH_3, t, J = 7 Hz), 1.07 (13-CH_3, s), 1.56 (10-CH_3, s), 2.33 (propionate CH_2, q, J = 7 Hz), 4.32 (11α-H, broad m), 5.63 (11-OH, broad d, J = 4 Hz), *ca.* 5.75 (6-H, broad dm, J = 50 Hz), 6.00 (SCH_2F, 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 K_2CO_3 (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% Na_2CO_3, and the aqueous layer was extracted with EtOAc (6 mL). The combined organic extracts were washed with H_2O (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 $KHCO_3$ (11.26 g, 112 mmol) at room temperature for 10 min under N_2. Fluoroiodomethane (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 ^{1}H NMR spectra resembling those detailed above. The latter showed solvation with DMF (*ca.* 0.05 mol).

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

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

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

ioate (13i). General method G on 11a with PLC and crystallization from MeOH then MeOH and Et_2O 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 CH_3CN (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-CH_3, s), 1.06 (propionate CH_3, t, J = 7 Hz), 1.35 (16β-CH_3, d, J = 7 Hz), 1.52 (10-CH_3, s), 2.38 (propionate CH_2, q, J = 7 Hz), 4.27 (11α-H, m), 5.84 (CH_2F, 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); ^{19}F NMR (84.68 MHz) −187.5 (CH_2F, 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%).

S-Fluoromethyl 6α,9α-Difluoro-11β-hydroxy-16-methylene-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carbothhioate (13k). General methods F then G on 10h, without purification of the intermediate S-iodomethyl carbothioate, PLC, and crystallization from aqueous acetone gave 13k (79%): ^1H NMR 0.98 (13-CH_3, s), 1.03 (propionate CH_3, t, J = 7 Hz), 1.55 (10-CH_3, s), 2.34 (propionate CH_2, q, J = 7 Hz), 4.32 (11α-H, m), 5.63 (16=CH_2, broad m), *ca.* 5.7 (6-H, broad dm, J = 50 Hz), 5.95 (SCH_2F, 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 CH_2Cl_2 (7 mL) was treated dropwise at 0 °C with Et_3N (1.39 mL, 10 mmol) and then stirred at 0 °C for 1 h. H_2S was passed through the mixture for 15 min, and the resultant solution was stirred at 0 °C for 1 h. After addition of $BrCH_2Cl$ (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% $NaHCO_3$, 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 CF_3CO_2H (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% $NaHCO_3$ 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 $(CF_3CO)_2O$ (0.7 mL) was treated with a dry solution of *p*-toluenesulfonic acid in $CHCl_3$ (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% $NaHCO_3$, H_2O, 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 N_2 at 0 °C, and Et_3N (0.70 mL, 5.0 mmol) was added dropwise. After 70 min a solution of NaSeH [prepared under N_2 by the addition of EtOH (3 mL) to a mixture of $NaBH_4$ (0.063 g, 1.66 mmol) and powered 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 N_2, 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% $NaHCO_3$, 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 $CHBr_3$) 1680 (carboselenoate) cm^{-1}; ^1H NMR (90 MHz) 1.38 (13-CH_3, s), 1.54 and 1.58 (16β-CH_3 and 10-CH_3, singlets), 2.22 ($SeCH_3$, 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−NEt_3, NaSeH [from Se (2.0 mmol)] and $BrCH_2Cl$ (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-CH_3, s), 1.54 and 1.58 (16β-CH_3 and 10-CH_3, singlets), 5.06 ($SeCH_2Cl$, 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 CF_3CO_2H (25 mL) was stirred at room temperature for 2.5 h and then diluted with 5% $NaHCO_3$ (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-CH_3, s), 1.53 (10-CH_3, s), 2.06 ($SeCH_3$, s), 4.97 and 5.22 (16=CH_2, 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-CH_3, s), 1.53 (10-CH_3, s) 5.01 ($SeCH_2Cl$, s), 5.00 and 5.25 (16=CH_2, 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 dichromate[27] (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-CH_3, s), 1.53 (10-CH_3, s), 2.09 ($SeCH_3$, s), 5.04 and 5.29 (16=CH_2, 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-CH_3, s), 1.54 (10-CH_3, s), 5.06 ($SeCH_2Cl$, s), 5.06 and 5.34 (16=CH_2, 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 $(CF_3CO)_2O$ (5.8 mL) was stirred and treated with a solution of *p*-toluenesulfonic acid (0.016 g) in $CHCl_3$ (0.20 mL) for 38 h at room temperature. The mixture was poured into 5% $NaHCO_3$ (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-CH_3, s), 1.05 (propionate CH_3, t, J = 7 Hz), 1.55 (10-CH_3, s), 2.23 ($SeCH_3$, s), 2.39 (propionate CH_2, q, J = 7 Hz), 5.64 and 5.70 (16=CH_2, 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-CH_3, s), 1.06 (propionate CH_3, t, J = 7 Hz), 1.55 (10-CH_3, s), 2.42 (propionate CH_2, q, J = 7 Hz), 5.21 ($SeCH_2Cl$, s), 4.30 (16=CH_2, 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 $NaBH_4$ (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-CH_3, s), 1.02 (propionate CH_3, t, J = 7 Hz), 1.54 (10-CH_3, s), 2.20 ($SeCH_3$, s), 2.32 (propionate CH_2, q, J = 7 Hz), 5.61 and 5.66 (16=CH_2, broad singlets).

***Se*-Chloromethyl 9α-Fluoro-11β-hydroxy-16-methylene-3-oxo-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 twice from EtOAc to give the analytical sample of **22b** (0.297 g): IR 3310 (broad, OH), 1740 (propionate), 1724 (carboselenoate) cm^{-1}; ^1H NMR (90 MHz) 1.01 (13-CH_3, s), 1.01 (propionate CH_3, t, J = 8 Hz), 1.55 (10-CH_3, s), 2.33 (propionate CH_2, q, J = 8 Hz), 4.29 (11α-H, m) 5.19 ($SeCH_2Cl$, s), 5.60 (11β-OH, m), 5.62 (16=CH_2, 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% $NaHCO_3$ (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-CH_3, s), 1.53 (10-CH_3, s), 1.00 (propionate CH_3, t, J = 8 Hz), 1.02 (13-CH_3 s), 1.53 (10-CH_3, s), 2.31 (propionate CH_2, q, J = 8 Hz), 4.43 ($SeCH_2I$, s), 5.53–5.71 (16=CH_2, 11-OH, broad).

Reaction of 22c with Silver Fluoride. 22c (1.0 g) and AgF (2.0 g, 10 equiv) in CH_3CN (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 $CHCl_3$ 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-CH_3, s), 1.00 (propionate CH_3, t, J = 7 Hz), 1.51 (10-CH_3, s) 2.32 (propionate CH_2, q, J = 7 Hz), 5.5–5.6 (16=CH_2, 11-OH, broad), 6.22 ($SeCH_2F$, 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 − $SeCH_2F$), 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 $C_{25}H_{31}F_2O_5{}^{80}Se$ (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; $[\alpha]_D$ −82° (*c* 0.93); λ_{max} 239 nm ($E_{1cm}{}^{1\%}$ 346); IR ($CHBr_3$) 3605 (OH), 1842 (COF), 1738 and 1262 (propionate), 1668, 1630, and 1612 ($\Delta^{1,4}$-3-one) cm^{-1}; ^1H NMR (90 MHz) 1.01 (propionate, t, J = 8 Hz), 1.10 (13-CH_3, s), 1.54 (10-CH_3, s), 2.38 (propionate, q, J = 8 Hz), 6.55 and 6.65 (16=CH_2, 11-OH, broad); ^{19}F NMR (84.68 MHz) +29 (COF, s), −161.7 (9α-F, m); ^{13}C 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=CH_2; off-resonance t), 87.8 (d, $^2J_{CF}$ = 50 Hz, C17), 10.1 (s, propionate CH_3, 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 $C_{24}H_{29}F_2O_5$ (MH^+) 435.1983, found 435.1982. Anal. ($C_{24}H_{28}F_2O_5$) 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% $NaHCO_3$ 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-CH_3, s), 1.06 (propionate CH_3, t, J = 7 Hz), 1.32 (16β-CH_3, d, J = 6 Hz), 1.52 (10-CH_3, s), 2.42 (propionate CH_2, 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. ($C_{48}H_{60}F_2O_{10}S_2{\cdot}0.5H_2O$) 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 cm^2) 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 soluton was prepared by mixing croton oil (5 vol), EtOH (20 vol), and Et_2O (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 CO_2 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 Et_2O (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 cm^2) 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 Et_2O vapor for 1 min. Twenty minutes later, the rats were re-anaesthetised 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 Et_2O. 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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