Chem. Pharm. Bull. **37**(12) 3286—3293 (1989) Vol. 37, No. 12

Studies on Topical Antiinflammatory Agents. III.[1,2] Synthesis of 17α-Acyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Thio Derivatives and Related Compounds

Morihiro MITSUKUCHI,* Tomoyuki IKEMOTO, Minoru TAGUCHI, Shohei HIGUCHI, Satoshi ABE, Hajime YASUI, Katsuo HATAYAMA and Kaoru SOTA

Research Center, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Omiya, Saitama 330, Japan. *Received May 6, 1989*

A series of 21-thio derivatives of 9α-fluoro-11β,17α-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 17-esters and related compounds were synthesized and evaluated as topical antiinflammatory agents. These compounds were prepared by the reaction of 9α-fluoro-11β,17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (betamethasone, I) 17-ester derivatives and various mercapto compounds. A structure–activity relationship study revealed that the structural combination of a thio group at the 21-position and an ester group at the 17-position contributed to vasoconstrictive activity. Among these compounds, the 21-methylthio 17-propanoate compound (6) was found to have the most potent activity, being more potent than betamethasone 17-valerate (BV).

Keywords corticosteroid; antiinflammatory agent; 9α-fluoro-11β,17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione; 9α-fluoro-11β-hydroxy-16β-methyl-21-methylthio-17α-propanoyloxy-1,4-pregnadiene-3,20-dione; vasoconstrictive activity; structure–activity relationship

We have previously reported that corticosteroid 16α,17α-acetonide derivatives having a mercapto moiety at the 21-position have potent antiinflammatory activities.[2a] The results showed that the lower alkylthio function is a good replacement for the hydroxy group in the corticosteroid 16α,17α-acetonide series. As an extension of our studies to elucidate the possible role of the functional groups in corticosteroids, in order to examine the influence of the 17-esters, we focussed on 17-esters of 9α-fluoro-11β,17α,21-trihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (betamethasone, I).

We describe in this paper the synthesis of new 21-thio derivatives of 21-deoxy betamethasone 17-esters and related compounds, and their vasoconstrictive activities. The structure–activity relationships for these compounds are also described. Among the compounds, the 21-methylthio 17-propanoate compound (**6**) was selected for further evaluation as a promising antiinflammatory agent.

Chemistry

The 21-sulfide derivatives of betamethasone 17-esters listed in Tables I—IV were prepared by the methods shown in Chart 1. The 17-esters of I were prepared from the 17,21-methyl ortho esters by acid-catalyzed hydrolysis in the same manner as that described in the previous paper.[2b] The 21-mesylates (II) were synthesized from the corresponding 17-esters by mesylation with mesyl chloride (MsCl) in pyridine. Reaction of II with various appropriate mercapto compounds in the presence of sodium methoxide (NaOMe) provided the corresponding 21-sulfide (IV). Reaction of II with the mercapto compounds in the presence of excess NaOMe at room temperature resulted in the formation of the dehydrated compounds (III) in 70—86% yields. The structures of III were determined as follows. The proton nuclear magnetic resonance (^{1}H-NMR) spectra showed no signals due to the presence of a methylene group at the 21-position. Compounds III also showed no carbonyl absorption due to the 17-esters in the infrared (IR) spectra. Based on these spectra, the mass spectra (MS) and elemental analyses, the structures of III were determined to be the dehydrated forms (III) shown in Chart 1. It is reasonable to suppose that III was produced from the initially formed IV by intramolecular condensation. Namely further nucleophilic attack of the active 21-CH_2 group on the 17-ester moiety gave rise to the formation of III.

The mesylates (II) were treated with thioacetic *S*-acid in the presence of NaOMe to give the 21-acetylthio derivatives,[3] which were hydrolyzed with hydrazine hydrate to give the 21-mercapto compounds (V). Alkylation of V with the appropriate alkyl halides afforded the corresponding 21-alkylthio compounds (IV) listed in Table I. The 21-

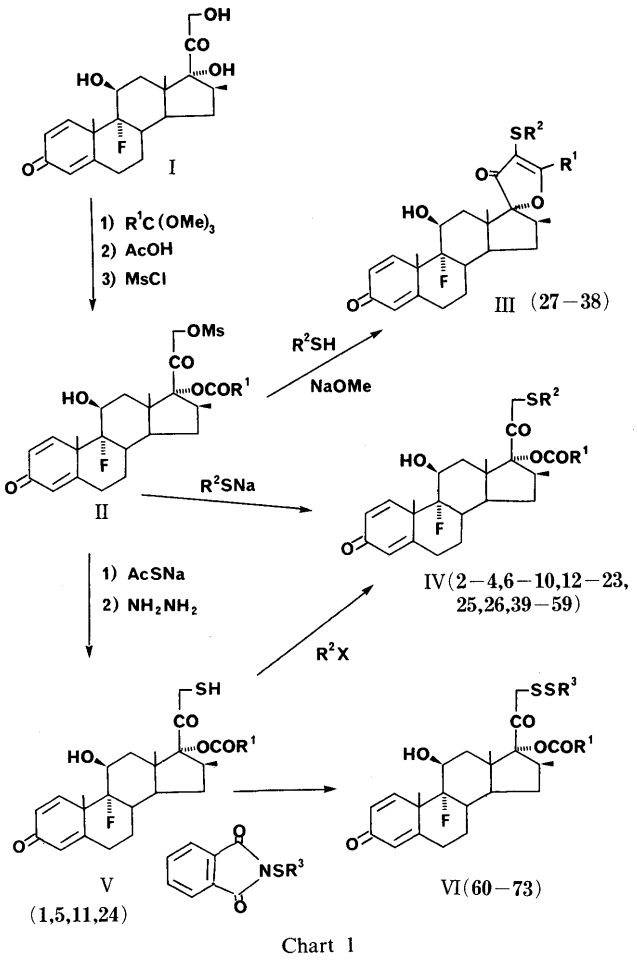

Chart 1

TABLE I. 17α-Acyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Thio Derivatives (IV and V) (**1**—**26**)

No.	R^1	R^2	Yield[a] (%)	mp (°C) (Solvent[b])	Formula (SIMS *m/z*: MH^+)
1	Me	H	71	220—223 (A–H)	$C_{24}H_{31}FO_5S$ (451)
2	Me	Me	81	212—214 (A–H)	$C_{25}H_{33}FO_5S$ (465)
3	Me	Et	53	189—192 (A–H)	$C_{26}H_{35}FO_5S$ (479)
4	Me	Pr	38	195—198 (A–H)	$C_{27}H_{37}FO_5S$ (493)
5	Et	H	52	187—188 (A–H)	$C_{25}H_{33}FO_5S$ (465)
6	Et	Me	88	164—167 (E)	$C_{26}H_{35}FO_5S$ (479)
7	Et	Et	65	185—187 (A–H)	$C_{27}H_{37}FO_5S$ (493)
8	Et	Pr	51	189—192 (E)	$C_{28}H_{39}FO_5S$ (507)
9	Et	iso-Pr	68	105—107 (E–W)	$C_{28}H_{39}FO_5S$ (507)
10	Et	Bu	59	148—150 (E–W)	$C_{29}H_{41}FO_5S$ (521)
11	Pr	H	62	143—146 (A–H)	$C_{26}H_{35}FO_5S$ (479)
12	Pr	Me	58	149—152 (E–W)	$C_{27}H_{37}FO_5S$ (493)
13	Pr	Et	39	145—147 (E–H)	$C_{28}H_{39}FO_5S$ (507)
14	Pr	Pr	64	77—80 (E–W)	$C_{29}H_{41}FO_5S$ (521)
15	Pr	iso-Pr	66	93—96 (E–W)	$C_{29}H_{41}FO_5S$ (521)
16	Pr	Bu	62	72—74 (E–W)	$C_{30}H_{43}FO_5S$ (535)
17	Pr	Ph	41	93—96 (E–W)	$C_{32}H_{39}FO_5S$ (555)
18	Bu	Me	91	91—93 (E)	$C_{28}H_{39}FO_5S$ (507)
19	Bu	Et	53	82—85 (E–W)	$C_{29}H_{41}FO_5S$ (521)
20	Bu	Pr	80	79—82 (E–W)	$C_{30}H_{43}FO_5S$ (535)
21	Bu	Bu	66	68—71 (E–W)	$C_{31}H_{45}FO_5S$ (549)
22	Bu	Ph	45	80—83 (E–W)	$C_{33}H_{41}FO_5S$ (569)
23	iso-Bu	Me	69	102—105 (E–W)	$C_{28}H_{39}FO_5S$[c] (507)
24	CH_2SMe	H	31	196—197 (A–H)	$C_{25}H_{33}FO_5S_2$ (497)
25	CH_2SMe	Me	85	112—115 (A–H)	$C_{26}H_{35}FO_5S_2$ (511)
26	CH_2SMe	Et	99	134—136 (A–H)	$C_{27}H_{37}FO_5S_2$ (525)

a) Yields are based on the preceding isolated intermediates. *b*) Recrystallization solvents: A, AcOEt; H, hexane; E, EtOH; W, H_2O. *c*) 1/2 H_2O.

alkoxycarbonylthio derivatives (IV) listed in Table III were prepared by reaction of V with alkyl chloroformate and triethylamine. The 21-mercapto derivatives (V) were also treated with various halogenated compounds to give the other 21-thio derivatives (IV) listed in Table III. The 21-disulfide derivatives (VI) listed in Table IV were prepared by treatment of V with the appropriate *N*-alkylthiophthalimides.[4]

Safety of the Compounds Tested Before application to volunteers, the safety of all compounds was checked by the method reported previously.[2]

TABLE II. Steroidal-17-spiro-dihydrofuranones (III)

No.	R^1	R^2	Yield[a] (%)	mp (°C) (Solvent[b])	Formula (SIMS *m/z*: MH^+)
27	Me	Me	73	277—281 (E)	$C_{25}H_{31}FO_4S$ (447)
28	Me	Et	78	277—281 (E)	$C_{26}H_{33}FO_4S$ (461)
29	Et	Et	79	193—194 (A–H)	$C_{27}H_{35}FO_4S$ (475)
30	Et	iso-Pr	86	222—223 (A–H)	$C_{28}H_{37}FO_4S$ (489)
31	Pr	Et	82	183—185 (E–W)	$C_{28}H_{37}FO_4S$ (489)
32	Pr	Pr	71	170—174 (E–W)	$C_{29}H_{39}FO_4S$ (503)
33	Pr	iso-Pr	72	202—204 (A–H)	$C_{29}H_{39}FO_4S$ (503)
34	Pr	Bu	70	177—179 (A–H)	$C_{30}H_{41}FO_4S$ (517)
35	Pr	*p*-Me–$C_6H_4CH_2$	72	121—124 (A–H)	$C_{34}H_{41}FO_4S$[c] (565)
36	Bu	Et	78	160—162 (M)	$C_{29}H_{39}FO_4S$ (503)
37	Bu	Pr	74	187—188 (M)	$C_{30}H_{41}FO_4S$ (517)
38	Bu	Bu	78	88—90 (M)	$C_{31}H_{43}FO_4S$[d] (531)

a) See footnote *a*) in Table I. *b*) Recrystallization solvents: M, MeOH. See also footnote *b*) in Table I. *c*) 1/4 H_2O. *d*) 1/2 H_2O.

Biological Results and Discussion

Primary Skin-Irritating Activity All compounds were evaluated at 1, 2, 3 and 7 d by the Draize method.[5] As shown in Table V, it was considered that none of the compounds causes primary skin irritation.

Mutagenicity As shown in Table V, all tested compounds were negative in Ames' spot test.[6]

Thus, no significant toxic signs were observed in the primary skin irritation and bacterial reverse mutation tests of all the compounds.

Vasoconstrictive Activities A number of methods for evaluating topical antiinflammatory activity of corticosteroids have been described. However, it is well known that corticosteroids that are predicted to be potent on the basis of animal studies may be much less potent in human studies. Only the vasoconstriction activity test is considered to be reliable for predicting the antiinflamatory potency of topical corticosteroids,[7] because a remarkably good correlation had been found to exist between the result of this test and the topical efficacy in the clinic.[8] Using this method, for instance, clobetasol propionate[9] and betamethasone 17-valerate[10] (BV) were selected and are now widely used in the clinic. Evaluation by this method is recommended as a preclinical study for topically applied corticosteroids.[7]

The compounds prepared in this study were tested for vasoconstrictive activities in twenty healthy male volunteers by the method reported previously.[2] The vasoconstrictive activities of the compounds tested were compared with that of BV, which was used as an active control for the activity. Statistical analysis was performed by Wilcoxon's signed-ranks test.[11] The results are summarized in Table VI. The

TABLE III. 17α-Acyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Thio Derivatives (IV)

No.	R^1	R^2	Yield[a] (%)	mp (°C) (Solvent[b])	Formula (SIMS m/z: MH^+)
39	Me	CO_2Me	94	138—141 (A–H)	$C_{26}H_{33}FO_7S$ (509)
40	Me	CO_2Et	94	204—206 (A–H)	$C_{27}H_{35}FO_7S$ (523)
41	Me	CO_2Bu	93	148—150 (A–H)	$C_{29}H_{39}FO_7S$ (551)
42	Me	CH_2CO_2Et	86	151—153 (E–H)	$C_{28}H_{37}FO_7S$ (537)
43	Me	CH_2COMe	62	199—201 (A–H)	$C_{27}H_{35}FO_6S$ (507)
44	Me	$CH_2C\equiv CH$	56	210—212 (A–H)	$C_{27}H_{33}FO_5S$ (489)
45	Et	CO_2Me	99	108—110 (A–H)	$C_{27}H_{35}FO_7S$ (523)
46	Et	CO_2Et	60	177—178 (A–H)	$C_{28}H_{37}FO_7S$ (537)
47	Et	$CO_2CH_2CCl_3$	86	212—216 (A–H)	$C_{28}H_{34}Cl_3FO_7S$ (640)
48	Et	CH_2CH_2OH	44	142—144 (A–H)	$C_{27}H_{37}FO_6S$ (509)
49	Pr	CO_2Et	93	90—95 (E–W)	$C_{29}H_{39}FO_7S$ (550)[e]
50	Pr	CO_2Bu	95	68—71 (E–W)	$C_{31}H_{43}FO_7S$ (579)
51	Pr	CH_2CO_2Et	68	65—68 (E–W)	$C_{30}H_{41}FO_7S$[d] (565)
52	Pr	CH_2COMe	74	132—134 (A–H)	$C_{29}H_{39}FO_6S$ (535)
53	Pr	$CH_2C\equiv CH$	75	180—182 (A–H)	$C_{29}H_{37}FO_5S$[c] (517)
54	Pr	CH_2CH_2OH	40	132—134 (C–H)	$C_{28}H_{39}FO_6S$ (523)
55	Pr	$CH=CH\sim CO_2Et$	85	95—98 (E–W)	$C_{31}H_{41}FO_7S$ (577)
56	CH_2SMe	CO_2Me	99	105—109 (A–H)	$C_{27}H_{35}FO_7S_2$ (555)
57	CH_2SMe	CO_2Et	91	100—104 (A–H)	$C_{28}H_{37}FO_7S_2$ (569)
58	CH_2SMe	$CO_2CH_2CCl_3$	85	189—191 (A–H)	$C_{28}H_{34}Cl_3FO_7S_2$ (672)
59	$(CH_2)_2CO_2Me$	CO_2Et	91	86—89 (E–W)	$C_{30}H_{39}FO_9S$[c] (595)

a) See footnote *a*) in Table I. *b*) Recrystallization solvents: C, CH_2Cl_2. See also footnote *b*) in Table I. *c*) 1/4 H_2O. *d*) 1/2 EtOH. *e*) Electron impact mass spectrum (M^+).

TABLE IV. 17α-Acyloxy-21-alkyldithio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-diones (VI)

No.	R^1	R^3	Yield[a] (%)	mp (°C) (Solvent[b])	Formula (SIMS m/z: MH^+)
60	Me	Me	83	213—216 (A–H)	$C_{25}H_{33}FO_5S_2$ (497)
61	Me	Et	76	199—201 (A–H)	$C_{26}H_{35}FO_5S_2$ (511)
62	Me	Pr	85	198—201 (A–H)	$C_{27}H_{37}FO_5S_2$ (525)
63	Et	Me	74	209—210 (A–H)	$C_{26}H_{35}FO_5S_2$ (511)
64	Et	Et	76	188—189 (A–H)	$C_{27}H_{37}FO_5S_2$ (525)
65	Et	Pr	46	139—140 (A–H)	$C_{28}H_{39}FO_5S_2$ (539)
66	Et	iso-Pr	30	140—142 (A–H)	$C_{28}H_{39}FO_5S_2$ (539)
67	Pr	Me	73	175—177 (C–H)	$C_{27}H_{37}FO_5S_2$[c] (524)[d]
68	Pr	Et	63	148—150 (C–H)	$C_{28}H_{39}FO_5S_2$ (538)[d]
69	Pr	Pr	79	80—85 (E–W)	$C_{29}H_{41}FO_5S_2$[c] (552)[d]
70	Pr	iso-Pr	61	133—135 (E–H)	$C_{29}H_{41}FO_5S_2$[c] (553)
71	CH_2SMe	Me	66	176—178 (A–H)	$C_{26}H_{35}FO_5S_3$ (526)[e]
72	CH_2SMe	Et	53	163—165 (A–H)	$C_{27}H_{37}FO_5S_3$ (557)
73	$(CH_2)_2CO_2Me$	Me	94	86—90 (E–W)	$C_{28}H_{37}FO_7S_2$[c] (569)

a) See footnote *a*) in Table I. *b*) See footnotes *b*) in Tables I and III. *c*) 1/4 H_2O. *d*) See footnote *e*) in Table III. *e*) Electron impact mass spectrum (M^+-16).

activities of thirteen compounds (**1**, **2**, **6**, **7**, **12**, **25**, **40**, **45**, **46**, **60**, **61**, **63** and **67**) were equal to or greater ($p<0.05$) than that of BV at 2 h. In particular, the activities of three compounds (**2**, **6** and **12**) were equal to or greater ($p<0.05$) than that of BV at both 2 and 4 h. Generally, the activities after 4 h of the compounds tested were considerably reduced as compared with those after 2 h. As regards the size of the 21-*S*-alkyl groups, the compounds with a small alkyl group such as Me (**2**, **6**, **12** and **25**) or Et (**7**) showed potent activities. Bulkier substituents tended to decrease the activity. On the other hand, the lack of a 21-*S*-substituent resulted in relatively reduced activity, although the 17-acetate 21-mercapto compound (**1**) was still as potent as BV at 2 h. Our results in this series of compounds are in accordance with our previous findings.[2a] As for the length of the 17-ester chain, the acetyl or propanoyl group seems to be optimal for potent activity. Lengthening of the ester chain caused a decrease in activity. Among the 17-(methylthio)acetate derivatives (**24**—**26**, **56**—**58**, **71** and **72**), only the 21-methylthio compound (**25**) was as potent as BV at 2 h, but the activities of the other compounds in this series were lower than that of BV. Two of the 17-methylsuccinate derivatives (**59** and **73**) were almost inactive. We found that the size of the 21-*S*-substituents and the length of the 17-ester chain influence the activity.

All the dehydrated compounds (**27**—**38**) were practically inactive. It seems likely that the open pregnane side chain of corticosteroids could be essential for the activity.

In the case of the 21-alkoxycarbonylthio compounds, the activities of the compounds (**40**, **45** and **46**) having small-sized groups at both the 17- and 21-positions were comparable to that of BV. On the other hand, the introduction of various other substituents (**47**—**55**) (Table III) resulted in a decrease in activity.

Among the 21-dithio compounds, the most potent compound was the 17-acetate 21-methyldithio derivative (**60**), whose activity was equal to or greater than that of BV. Other compounds in this series with high potency were the 17-acetate 21-ethyldisulfide (**61**) and the 17-propanoate 21-methyldisulfide (**63**) which were as potent as BV.

These results suggested that the structural combination of a thio group at the 21-position and an ester group at the 17-position plays an important role in enhancing the activity. In addition, the 20-keto function between the 17- and 21-positions might be essential for the activity, because the dehydrated compounds (**27**—**38**) had no activity.

In this study, the 21-methylthio 17-propanoate derivative (**6**) had the highest potency, which was significantly ($p<0.05$) greater than that of BV. Accordingly, compound **6** was selected for further investigation as a possible topical

TABLE V. Primary Skin-Irritating Activity and Mutagenicity of the Compounds (**1**—**73**)

No.	Primary skin irritation	Mutagenicity *S. typhimurium* TA98	TA100	No.	Primary skin irritation	Mutagenicity *S. typhimurium* TA98	TA100
1	–	–	–	**38**	–	–	–
2	–	–	–	**39**	–	–	–
3	–	–	–	**40**	–	–	–
4	–	–	–	**41**	–	–	–
5	–	–	–	**42**	–	–	–
6	–	–	–	**43**	–	–	–
7	–	–	–	**44**	–	–	–
8	–	–	–	**45**	–	–	–
9	–	–	–	**46**	–	–	–
10	–	–	–	**47**	–	–	–
11	–	–	–	**48**	–	–	–
12	–	–	–	**49**	–	–	–
13	–	–	–	**50**	–	–	–
14	–	–	–	**51**	–	–	–
15	–	–	–	**52**	–	–	–
16	–	–	–	**53**	–	–	–
17	–	–	–	**54**	–	–	–
18	–	–	–	**55**	–	–	–
19	–	–	–	**56**	–	–	–
20	–	–	–	**57**	–	–	–
21	–	–	–	**58**	–	–	–
22	–	–	–	**59**	–	–	–
23	–	–	–	**60**	–	–	–
24	–	–	–	**61**	–	–	–
25	–	–	–	**62**	–	–	–
26	–	–	–	**63**	–	–	–
27	–	–	–	**64**	–	–	–
28	–	–	–	**65**	–	–	–
29	–	–	–	**66**	–	–	–
30	–	–	–	**67**	–	–	–
31	–	–	–	**68**	–	–	–
32	–	–	–	**69**	–	–	–
33	–	–	–	**70**	–	–	–
34	–	–	–	**71**	–	–	–
35	–	–	–	**72**	–	–	–
36	–	–	–	**73**	–	–	–
37	–	–	–				
				2NF		+	/
2AN		+	+	ENNG		/	+

2AN, 2-aminoanthracene; 2NF, 2-nitrofluorene; ENNG, *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine.

TABLE VI. Vasoconstrictive Activity of 17α-Acyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Thio Derivatives

No.	After 2 h	After 4 h	No.	After 2 h	After 4 h
1	100	82[b]	**42**	84	63[d]
2	124	102	**44**	75	63[d]
5	71[b]	72[d]	**45**	119	96
6	138[c]	124[b]	**46**	113	97
7	100	82	**53**	58[d]	66[d]
8	71[a]	67[c]	**60**	128[b]	98
12	106	105	**61**	116	94
15	65	61[d]	**62**	94	92
23	79	68[d]	**63**	108	91
25	109	80[a]	**64**	96	79
39	87	73[c]	**66**	69[b]	68[c]
40	103	94	**67**	108	79
41	88	84[a]	**71**	78	59[d]

Vaseline ointment (0.01%) was used. Each compound was tested on 20 volunteers. The potency is expressed as the ratio of vasoconstrictive activity to that of BV taken as 100. The compounds of Tables I—IV not listed here displayed potency <55. *a*) $p<0.1$. *b*) $p<0.05$. *c*) $p<0.02$. *d*) $p<0.01$ for BV, using Wilcoxon's signed-ranks test.[11]

antiinflammatory agent.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded in KBr disks on a JASCO DS-301 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian XL-200 (200 and 50 MHz, respectively) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts are given in δ (ppm). The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. The unit (Hz) of coupling constants (J) is omitted. MS and secondary ion mass spectrometry (SIMS) were taken with a Shimadzu LKB-9000 or Hitachi M-80A spectrometer, respectively. All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was carried out on Wakogel C-200.

All compounds were analyzed for C, H, F and S. The analytical results were within ±0.4% of the calculated values.

Typical examples are given to illustrate the general procedure.

Betamethasone 17-Acetate[12] Triethyl orthoacetate (4.0 ml) and *p*-toluenesulfonic acid (25 mg) were added to a suspension of I (5.0 g) in dimethylformamide (DMF) (7 ml) and benzene (70 ml), and the reaction mixture was stirred at room temperature for 75 min and extracted with AcOEt. The extract was washed successively with H_2O, 5% Na_2CO_3, H_2O and brine, then dried and concentrated. The residue was dissolved in MeOH (200 ml). A 5% aqueous AcOH solution (40 ml) was added, and the mixture was refluxed for 3.5 h and concentrated *in vacuo*. The residue was extracted with AcOEt. The extract was washed with H_2O, dried and concentrated to give a colorless powder (5.3 g, 96%). This product was used directly in the next reaction.

Betamethasone 17-Acetate 21-Mesylate[13] **[II (R^1 = Me)]** Mesyl chloride (3.0 ml) was added to a solution of betamethasone 17-acetate (9.88 g) in pyridine (70 ml) under ice-cooling with stirring. The reaction mixture was stirred at 0—5 °C for 1.5 h and then poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% HCl, 5% Na_2CO_3 and brine, then dried and concentrated to give II (R^1 = Me) (11.5 g, 99%). This product was used for the next reaction without further purification. ^{1}H-NMR: 1.02 (3H, s), 1.37 (3H, d, J = 7), 1.56 (3H, s), 2.12 (3H, s), 3.23 (3H, s), 4.43 (1H, m), 4.64, 4.84 (2H, each d, J = 16), 6.15 (1H, s), 6.35 (1H, dd, J = 10, 2), 7.22 (1H, d, J = 10).

9α-Fluoro-11β-hydroxy-16β-methyl-21-methylthio-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (6) A solution of betamethasone 17-propanoate 21-mesylate[13] [II (R^1 = Et)] (3.58 g) and 15% sodium methanethiolate (NaSMe) (4.76 ml) in acetone (36 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% Na_2CO_3, H_2O, 10% HCl, H_2O and brine and dried. After removal of the solvent, the residue was purified by column chromatography with AcOEt–hexane (1 : 3) to give **6** (2.87 g, 88%), which was recrystallized from EtOH to give colorless needles. IR: 3460, 1715, 1660 cm^{-1}. ^{1}H-NMR: 1.05 (3H, s), 1.15 (3H, t, J = 8), 1.39 (3H, d, J = 8), 1.57 (3H, s), 2.24 (3H, s), 3.08, 3.24 (2H, each d, J = 16), 4.43 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J = 10, 2), 7.19 (1H, d, J = 10).

The following compounds were similarly prepared.

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-methylthio-1,4-pregnadiene-3,20-dione (12) IR: 3320, 1725, 1655 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, J = 8), 1.04 (3H, s), 1.39 (3H, d, J = 8), 1.56 (3H, s), 2.23 (3H, s), 3.10, 3.24 (2H, each d, J = 16), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J = 10, 2), 7.23 (1H, d, J = 10).

9α-Fluoro-11β-hydroxy-16β-methyl-21-methylthio-17α-valeryloxy-1,4-pregnadiene-3,20-dione (18) IR: 3380, 1720, 1655 cm^{-1}. ^{1}H-NMR: 0.91 (3H, t, J = 8), 1.04 (3H, s), 1.38 (3H, d, J = 8), 1.56 (3H, s), 2.23 (3H, s), 3.09, 3.24 (2H, each d, J = 16), 4.42 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J = 10, 2), 7.20 (1H, d, J = 10).

9α-Fluoro-11β-hydroxy-17α-isovaleryloxy-16β-methyl-21-methylthio-1,4-pregnadiene-3,20-dione (23) IR: 3400, 1720, 1660 cm^{-1}. ^{1}H-NMR: 0.96 (6H, d, J = 8), 1.05 (3H, s), 1.40 (3H, d, J = 8), 1.58 (3H, s), 2.22 (3H, s), 3.14, 3.26 (2H, each d, J = 16), 4.45 (1H, m), 6.16 (1H, s), 6.36 (1H, dd, J = 10, 2), 7.26 (1H, d, J = 10).

9α-Fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-21-propylthio-1,4-pregnadiene-3,20-dione (8) Propanethiol (0.34 ml) and NaOMe (227 mg) were added to a solution of II (R^1 = Et) (1.034 g) in dry acetone (30 ml). The mixture was stirred at room temperature for 50 min. Removal of the solvent gave an oil, which was extracted with AcOEt. The extract was washed successively with H_2O, 10% Na_2CO_3, H_2O and brine and dried. Evaporation of the solution left a residue, which was recrystallized

from EtOH, giving **8** (504 mg, 51%) as colorless needles. IR: 3550, 1715, 1660 cm^{-1}. ^{1}H-NMR: 0.99 (3H, t, J=8), 1.05 (3H, s), 1.15 (3H, t, J=9), 1.39 (3H, d, J=7), 1.58 (3H, s), 3.12, 3.22 (2H, each d, J=15), 4.43 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.20 (1H, d, J=10).

The following compounds were similarly prepared.

9α-Fluoro-11β-hydroxy-21-isopropylthio-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (9) IR: 3400, 1720, 1655 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.16 (3H, t, J=7), 1.23—1.31 (6H, m), 1.39 (3H, d, J=7), 1.56 (3H, s), 2.39 (2H, q, J=7), 3.19, 3.26 (2H, each d, J=12), 3.23 (1H, m), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.23 (1H, d, J=10).

21-Butylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (10) IR: 3450, 1720, 1710, 1660 cm^{-1}. ^{1}H-NMR: 0.92 (3H, t, J=8), 1.04 (3H, s), 1.14 (3H, t, J=8), 1.39 (3H, d, J=7), 1.56 (3H, s), 3.12, 3.24 (2H, each d, J=16), 4.43 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.21 (1H, d, J=10).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-propylthio-1,4-pregnadiene-3,20-dione (14) IR: 3400, 1725, 1655 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, J=7), 0.98 (3H, t, J=7), 1.04 (3H, s), 1.39 (3H, d, J=7), 1.56 (3H, s), 2.67 (2H, q, J=7), 3.14, 3.24 (2H, each d, J=16), 4.43 (1H, m), 6.16 (1H, s), 6.36 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-21-isopropylthio-16β-methyl-1,4-pregnadiene-3,20-dione (15) IR: 3400, 1725, 1660 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, J=7), 1.04 (3H, s), 1.25 (3H, d, J=7), 1.28 (3H, d, J=7), 3.19, 3.28 (2H, each d, J=16), 3.22 (1H, m), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.24 (1H, d, J=10).

17α-Butanoyloxy-21-butylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (16) IR: 3400, 1720, 1655 cm^{-1}. ^{1}H-NMR: 0.91 (3H, t, J=7), 0.94 (3H, t, J=8), 1.04 (3H, s), 1.38 (3H, d, J=7), 1.56 (3H, s), 3.14, 3.24 (2H, each d, J=16), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.24 (1H, d, J=10).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-phenylthio-1,4-pregnadiene-3,20-dione (17) IR: 3400, 1720, 1665 cm^{-1}. ^{1}H-NMR: 0.88 (3H, s), 0.94 (3H, t, J=7), 1.38 (3H, d, J=8), 1.52 (3H, s), 2.34 (2H, t, J=8), 3.65, 3.78 (2H, each d, J=16), 4.34 (1H, m), 6.14 (1H, s), 6.36 (1H, dd, J=11, 2), 7.19 (1H, d, J=11), 7.26—7.48 (5H, m).

21-Ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (19) IR: 3380, 1720, 1655 cm^{-1}. ^{1}H-NMR: 0.91 (3H, t, J=7), 1.05 (3H, s), 1.26 (3H, t, J=8), 1.38 (3H, d, J=7), 1.56 (3H, s), 2.36 (2H, t, J=7), 2.60—2.80 (2H, m), 3.19, 3.22 (2H, each d, J=16), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

9α-Fluoro-11β-hydroxy-16β-methyl-21-propylthio-17α-valeryloxy-1,4-pregnadiene-3,20-dione (20) IR: 3400, 1730, 1660 cm^{-1}. ^{1}H-NMR: 0.92 (3H, t, J=7), 1.00 (3H, t, J=7), 1.05 (3H, s), 1.39 (3H, d, J=7), 1.57 (3H, s), 2.35 (2H, t, J=7), 2.50—2.80 (2H, m), 3.15, 3.22 (2H, each d, J=16), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

21-Butylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (21) IR: 3400, 1725, 1660 cm^{-1}. ^{1}H-NMR: 0.91 (3H, t, J=7), 0.92 (3H, t, J=7), 1.05 (3H, s), 1.38 (3H, d, J=7), 1.56 (3H, s), 2.35 (2H, t, J=7), 2.50—2.80 (2H, m), 3.15, 3.22 (2H, each d, J=16), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

9α-Fluoro-11β-hydroxy-16β-methyl-21-phenylthio-17α-valeryloxy-1,4-pregnadiene-3,20-dione (22) IR: 3380, 1720, 1655 cm^{-1}. ^{1}H-NMR: 0.88 (3H, s), 0.91 (3H, t, J=7), 1.38 (3H, d, J=7), 1.54 (3H, s), 3.65, 3.78 (2H, each d, J=16), 4.34 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.17 (1H, d, J=10), 7.25—7.50 (5H, m).

(17*R*)-9α-Fluoro-11β-hydroxy-5′,16β-dimethyl-4′-methylthio-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (27) MeSNa (15%, 1.2 ml) was added to a solution of II (R^1=Me) (1.30 g) in acetone (50 ml). The resulting mixture was stirred at room temperature for 7 h. Removal of the solvent gave a residue, which was extracted with AcOEt. The extract was washed successively with H_2O, 5% Na_2CO_3, H_2O, 5% HCl, H_2O and brine and dried. After removal of the solvent, the residue was chromatographed with $CHCl_3$ to afford **27** (820 mg, 73%) as crystals. Recrystallization from EtOH gave colorless needles. IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 1.18 (3H, d, J=7), 1.33 (3H, s), 1.60 (3H, s), 2.16 (3H, s), 2.30 (3H, s), 3.35 (1H, s), 4.41 (1H, m), 6.14 (1H, s), 6.33 (1H, dd, J=10, 2), 7.25 (1H, d, J=10).

The following compounds were similarly prepared.

(17*R*)-4′-Ethylthio-9α-fluoro-11β-hydroxy-5′,16β-dimethyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (28) IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 1.15 (3H, t, J=7), 1.18 (3H, d, J=7), 1.33 (3H, s), 1.60 (3H, s), 2.31 (3H, s), 3.22 (1H, s), 4.43 (1H, m), 6.15 (1H, s), 6.34 (1H, dd, J=10, 2), 7.25 (1H, d, J=10).

(17*R*)-5′-Ethyl-4′-ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (29) IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 1.10—1.20 (6H, m), 1.26 (3H, t, J=7), 1.33 (3H, s), 1.60 (3H, s), 3.21 (1H, s), 4.44 (1H, m), 6.15 (1H, s), 6.34 (1H, dd, J=10, 2), 7.26 (1H, d, J=10). ^{13}C-NMR: 11.1 (s), 14.9 (s), 15.2 (s), 18.8 (s), 22.8 (s), 23.1 (d), 27.7 (s), 31.0 (s), 33.8 (d), 34.9 (s), 36.2 (s), 42.7 (s), 45.4 (s), 48.3 (d), 49.1 (s), 71.8 (d), 99.2 (s), 100.6 (d), 107.1 (s), 125.1 (s), 129.7 (s), 152.3 (s), 166.2 (s), 186.6 (s), 194.3 (s), 201.0 (s).

(17*R*)-5′-Ethyl-9α-fluoro-11β-hydroxy-4′-isopropylthio-16β-methyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (30) IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 1.10—1.28 (12H, m), 1.33 (3H, s), 1.61 (3H, s), 3.14 (1H, m), 3.37 (1H, s), 4.47 (1H, m), 6.15 (1H, s), 6.33 (1H, dd, J=10, 2), 7.27 (1H, d, J=10). ^{13}C-NMR: 11.0 (s), 15.2 (s), 18.8 (s), 22.8 (s), 23.1 (d), 27.7 (s), 31.0 (s), 33.8 (d), 35.0 (s), 36.2 (s), 37.2 (s), 42.8 (s), 45.4 (s), 48.4 (d), 49.2 (s), 71.7 (d), 99.3 (s), 100.6 (d), 107.1 (s), 125.1 (s), 129.7 (s), 152.3 (s), 166.1 (s), 186.5 (s), 195.0 (s), 201.3 (s).

(17*R*)-4′-Ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-5′-propyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (31) IR: 3360, 1655 cm^{-1}. ^{1}H-NMR: 0.95 (3H, t, J=7), 1.15 (3H, t, J=7), 1.32 (3H, s), 1.58 (3H, s), 4.42 (1H, m), 6.15 (1H, s), 6.34 (1H, dd, J=10, 2), 7.22 (1H, d, J=10).

(17*R*)-9α-Fluoro-11β-hydroxy-16β-methyl-5′-propyl-4′-propylthio-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (32) IR: 3370, 1660 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, J=7), 0.96 (3H, t, J=7), 1.16 (3H, d, J=7), 1.32 (3H, s), 1.60 (3H, s), 3.16 (1H, s), 4.45 (1H, m), 6.14 (1H, s), 6.33 (1H, dd, J=10, 2), 7.25 (1H, d, J=10).

(17*R*)-9α-Fluoro-11β-hydroxy-4′-isopropylthio-16β-methyl-5′-propyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (33) IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, J=7), 1.10—1.24 (9H, m), 1.33 (3H, s), 1.61 (3H, s), 3.16 (1H, m), 4.48 (1H, m), 6.16 (1H, s), 6.33 (1H, dd, J=10, 2), 7.27 (1H, d, J=10).

(17*R*)-4′-Butylthio-9α-fluoro-11β-hydroxy-16β-methyl-5′-propyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (34) IR: 3380, 1660 cm^{-1}. ^{1}H-NMR: 0.89 (3H, t, J=7), 0.94 (3H, t, J=7), 1.17 (3H, d, J=7), 1.33 (3H, s), 1.60 (3H, s), 3.17 (1H, s), 4.46 (1H, m), 6.16 (1H, s), 6.34 (1H, dd, J=10, 2), 7.26 (1H, d, J=10).

(17*R*)-9α-Fluoro-11β-hydroxy-16β-methyl-4′-(*p*-methylbenzyl)thio-5′-propyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (35) IR: 3300, 1660 cm^{-1}. ^{1}H-NMR: 0.78 (3H, t, J=7), 1.20 (3H, d, J=7), 1.28 (3H, s), 1.59 (3H, s), 2.31 (3H, s), 3.73, 3.81 (2H, each d, J=13), 4.34 (1H, m), 6.16 (1H, s), 6.31 (1H, dd, J=10, 2), 7.07 (4H, s), 7.19 (1H, d, J=10). ^{13}C-NMR: 13.6 (s), 15.1 (s), 18.8 (s), 19.8 (s), 21.1 (s), 23.1 (d), 27.6 (s), 30.75 (s), 30.84 (s), 33.8 (d), 35.0 (s), 35.9 (s), 37.3 (s), 42.6 (s), 45.3 (s), 48.3 (d), 49.1 (s), 71.8 (d), 99.2 (s), 100.5 (d), 106.9 (s), 125.1 (s), 129.0 (s), 129.04 (s), 129.8 (s), 134.8 (s), 136.8 (s), 152.3 (s), 166.1 (s), 186.5 (s), 193.9 (s), 200.8 (s).

(17*R*)-5′-Butyl-4′-ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (36) IR: 3360, 1660 cm^{-1}. ^{1}H-NMR: 0.91 (3H, t, J=7), 1.15 (3H, t, J=7), 1.17 (3H, d, J=8), 1.33 (3H, s), 1.61 (3H, s), 2.63 (2H, q, J=7), 2.65 (2H, t, J=7), 3.51 (1H, br s), 4.46 (1H, m), 6.15 (1H, br s), 6.33 (1H, dd, J=10, 2), 7.27 (1H, d, J=10). ^{13}C-NMR: 13.7 (s), 14.8 (s), 15.2 (s), 18.8 (s), 22.4 (s), 23.2 (d), 27.7 (s), 28.7 (s), 29.0 (s), 31.0 (s), 33.8 (d), 35.0 (s), 36.2 (s), 42.9 (s), 45.4 (s), 48.4 (d), 49.2 (s), 71.8 (d), 99.2 (s), 100.6 (d), 107.7 (s), 125.1 (s), 129.7 (s), 152.3 (s), 166.2 (s), 186.6 (s), 193.5 (s), 201.0 (s).

(17*R*)-5′-Butyl-9α-fluoro-11β-hydroxy-16β-methyl-4′-propylthio-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (37) IR: 3360, 1665 cm^{-1}. ^{1}H-NMR: 0.90 (3H, t, J=7), 0.95 (3H, t, J=7), 1.15 (3H, d, J=7), 1.31 (3H, s), 1.58 (3H, s), 2.58 (2H, t, J=7), 2.63 (2H, t, J=7), 3.17 (1H, s), 4.45 (1H, m), 6.13 (1H, s), 6.32 (1H, dd, J=10, 2), 7.27 (1H, d, J=10). ^{13}C-NMR: 13.1 (s), 13.7 (s), 15.2 (s), 18.8 (s), 22.4 (s), 22.8 (s), 23.1 (d), 27.7 (s), 28.8 (s), 29.0 (s), 31.0 (s), 33.8 (d), 35.0 (s), 35.7 (s), 36.3 (s), 42.9 (s), 45.4 (s), 48.4 (d), 49.1 (s), 71.8 (d), 99.1 (s), 100.6 (d), 108.0 (s), 125.1 (s), 129.7 (s), 152.3 (s), 166.2 (s), 186.6 (s), 193.2 (s), 201.0 (s).

(17*R*)-5′-Butyl-4′-butylthio-9α-fluoro-11β-hydroxy-16β-methyl-spiro[androst-1,4-diene-17,2′(3′*H*)-furan]-3,3′-dione (38) IR: 3380, 1660 cm^{-1}. ^{1}H-NMR: 0.88 (3H, t, J=7), 0.91 (3H, t, J=7), 1.13 (3H, d, J=8), 1.32 (3H, s), 1.59 (3H, s), 2.60 (2H, t, J=7), 2.67 (2H, t, J=7), 3.08 (1H, br s), 4.43 (1H, m), 6.14 (1H, br s), 6.32 (1H, dd, J=10, 2), 7.24 (1H, d, J=10).

Betamethasone 17-Acetate 21-Thioacetate[3] A solution of NaOMe (3.8 g) in MeOH (6 ml) was added to a solution of thioacetic *S*-acid (6.9 ml) in acetone (70 ml), and the resulting mixture was stirred at room temperature for 1 h. Then, a solution of II (R^1=Me) (11.5 g) in acetone (200 ml) was added to the mixture. After being refluxed for 6 h, the reaction mixture was concentrated and extracted with AcOEt. The extract was washed successively with 10% HCl, 5% Na_2CO_3 and brine, then dried and concentrated. The residue was recrystallized from EtOH–hexane, giving colorless needles (7.1 g, 71%), mp 205—207 °C. ^{1}H-NMR: 0.96 (3H, s), 1.36 (3H, d, J=7), 1.57 (3H, s), 2.13 (3H, s), 2.39 (3H, s), 3.56, 3.86 (2H,

each d, $J=17$), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-21-mercapto-16β-methyl-1,4-pregnadiene-3,20-dione (1) Hydrazine hydrate (0.87 ml) was added dropwise to a solution of betamethasone 17-acetate 21-thioacetate[3] (5.80 g) in tetrahydrofuran (60 ml) with stirring on an ice-salt bath. After being stirred at −15—−10 °C for 30 min, the reaction mixture was extracted with AcOEt. The extract was washed successively with 10% HCl, H_2O, 10% Na_2CO_3, H_2O and brine, and dried. After removal of the solvent, the residue was chromatographed with AcOEt–$CHCl_3$–hexane (1 : 2 : 2) to give **1** (3.74 g, 71%) as colorless crystals. IR: 3300, 2560, 1740, 1655 cm^{-1}. ^{1}H-NMR: 1.00 (3H, s), 1.40 (3H, d, $J=7$), 1.56 (3H, s), 2.10 (3H, s), 3.19 (1H, dd, $J=16$, 9), 3.30 (1H, dd, $J=16$, 6), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

The following compounds were similarly prepared.

9α-Fluoro-11β-hydroxy-21-mercapto-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (5) IR: 3420, 2560, 1720, 1655 cm^{-1}. ^{1}H-NMR: 1.01 (3H, s), 1.17 (3H, t, $J=7$), 1.40 (3H, d, $J=7$), 1.57 (3H, s), 2.04 (1H, dd, $J=6$, 4), 2.39 (2H, q, $J=7$), 3.21, 3.25 (2H, each d, $J=16$), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-21-mercapto-16β-methyl-1,4-pregnadiene-3,20-dione (11) IR: 3370, 2530, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.95 (3H, t, $J=10$), 1.00 (3H, s), 1.40 (3H, d, $J=7$), 1.56 (3H, s), 2.06 (1H, dd, $J=10$, 6), 2.34 (2H, t, $J=8$), 3.17 (1H, dd, $J=16$, 10), 3.28 (1H, dd, $J=16$, 6), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-21-mercapto-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (24) IR: 3280, 2530, 1720, 1715, 1650 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.41 (3H, d, $J=7$), 1.56 (3H, s), 2.05 (1H, dd, $J=6$, 3), 2.22 (3H, s), 3.15, 3.23 (2H, each d, $J=14$), 3.22—3.44 (2H, m), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-methylthio-1,4-pregnadiene-3,20-dione (2) A solution of **1** (370 mg), MeI (0.154 ml) and triethylamine (0.342 ml) in CH_2Cl_2 (15 ml) was stirred at 0—5 °C for 45 min. The reaction mixture was extracted with AcOEt. The extract was washed successively with 10% HCl, H_2O and brine and dried. After removal of the solvent, the residue was purified by column chromatography with AcOEt–hexane (1 : 2) to give **2**, which was recrystallized from AcOEt–hexane to give colorless needles (0.31 g, 81%). IR: 3460, 1720, 1695, 1660 cm^{-1}. ^{1}H-NMR: 1.05 (3H, s), 1.40 (3H, d, $J=7$), 1.58 (3H, s), 2.10 (3H, s), 2.23 (3H, s), 3.13, 3.27 (2H, each d, $J=16$), 4.45 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$).

The following compounds were similarly prepared.

17α-Acetoxy-21-ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (3) IR: 3440, 1725, 1660 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.26 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 2.10 (3H, s), 3.17, 3.26 (2H, each d, $J=16$), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-propylthio-1,4-pregnadiene-3,20-dione (4) IR: 3390, 1730, 1650 cm^{-1}. ^{1}H-NMR: 0.99 (3H, t, $J=7$), 1.04 (3H, s), 1.38 (3H, d, $J=7$), 1.76 (3H, s), 2.10 (3H, s), 3.14, 3.25 (2H, each d, $J=16$), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-Ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (7) IR: 3280, 1715, 1650 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.14 (3H, t, $J=7$), 1.25 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.38 (2H, q, $J=7$), 2.60—2.82 (2H, m), 3.15, 3.24 (2H, each d, $J=16$), 4.44 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-21-ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (13) IR: 3250, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, $J=7$), 1.02 (3H, s), 1.24 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.33 (2H, t, $J=7$), 3.17, 3.25 (2H, each d, $J=14$), 4.44 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.26 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-21-methylthio-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (25) IR: 3400, 1720, 1715, 1655 cm^{-1}. ^{1}H-NMR: 1.06 (3H, s), 1.40 (3H, d, $J=7$), 1.56 (3H, s), 2.23, 2.24 (6H, each s), 3.16, 3.27 (2H, each d, $J=14$), 3.22 (2H, dd, $J=16$, 14), 4.45 (1H, m), 6.16 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-Ethylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (26) IR: 3260, 1720, 1715, 1650 cm^{-1}. ^{1}H-NMR: 1.05 (3H, s), 1.27 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.23 (3H, s), 2.64—2.81 (2H, m), 3.14, 3.22 (2H, each d, $J=14$), 3.30 (2H, dd, $J=16$, 6), 4.44 (1H, m), 6.15 (1H, s), 6.35 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-methoxycarbonylthio-1,4-pregnadiene-3,20-dione (39) Triethylamine (0.323 ml) and methyl chloroformate (0.222 ml) were added to a stirred solution of **1** (350 mg) in dry CH_2Cl_2 (20 ml) at 0—5 °C. After being stirred at 0—5 °C for 30 min, the reaction mixture was extracted with AcOEt. The extract was washed with H_2O and brine and dried. Removal of the solvent under reduced pressure afforded a colorless solid, which was purified by column chromatography (AcOEt–hexane) to give **39** (370 mg, 94%). Recrystallization from AcOEt–hexane gave colorless prisms. IR: 3420, 1730, 1700, 1655 cm^{-1}. ^{1}H-NMR: 0.98 (3H, s), 1.36 (3H, d, $J=8$), 1.57 (3H, s), 2.13 (3H, s), 3.61, 3.82 (2H, each d, $J=16$), 3.82 (3H, s), 4.46 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$).

The following compounds were similarly prepared.

17α-Acetoxy-21-ethoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (40) IR: 3280, 1720, 1660 cm^{-1}. ^{1}H-NMR: 0.98 (3H, s), 1.28—1.38 (6H, m), 1.56 (3H, s), 2.12 (3H, s), 3.60, 3.81 (2H, each d, $J=17$), 4.27 (2H, q, $J=7$), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

17α-Acetoxy-21-butoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (41) IR: 3280, 1725, 1705, 1655 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, $J=8$), 0.96 (3H, s), 1.36 (3H, d, $J=7$), 1.56 (3H, s), 2.12 (3H, s), 3.58, 3.82 (2H, each d, $J=17$), 4.22 (2H, t, $J=7$), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

21-Acetonylthio-17α-acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (43) IR: 3280, 1730, 1700, 1650 cm^{-1}. ^{1}H-NMR: 1.00 (3H, s), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.09 (3H, s), 2.30 (3H, s), 3.23, 3.34 (2H, each d, $J=16$), 3.37, 3.46 (2H, each d, $J=14$), 4.44 (1H, m), 6.15 (1H, s), 6.37 (1H, dd, $J=9$, 2), 7.24 (1H, d, $J=9$).

9α-Fluoro-11β-hydroxy-21-methoxycarbonylthio-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (45) IR: 3410, 1715, 1660 cm^{-1}. ^{1}H-NMR: 0.98 (3H, s), 1.16 (3H, t, $J=7$), 1.36 (3H, d, $J=7$), 1.56 (3H, s), 2.41 (2H, q, $J=7$), 3.57, 3.82 (2H, each d, $J=16$), 3.82 (3H, s), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

21-Ethoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (46) IR: 3300, 1730, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.98 (3H, s), 1.16 (3H, t, $J=8$), 1.31 (3H, t, $J=7$), 1.36 (3H, d, $J=7$), 1.57 (3H, s), 2.42 (2H, q, $J=8$), 3.58, 3.82 (2H, each d, $J=16$), 4.27 (2H, q, $J=7$), 4.45 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

21-(2,2,2-Trichloroethoxy)carbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (47) IR: 3280, 1730, 1710, 1655 cm^{-1}. ^{1}H-NMR: 0.97 (3H, s), 1.16 (3H, t, $J=7$), 1.36 (3H, d, $J=7$), 1.56 (3H, s), 2.42 (2H, q, $J=7$), 3.66, 3.87 (2H, each d, $J=18$), 4.46 (1H, m), 4.84 (2H, dd, $J=10$, 8), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

17α-Butanoyloxy-21-ethoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (49) IR: 3340, 1715, 1650 cm^{-1}. ^{1}H-NMR: 0.94—1.01 (6H, m), 1.28—1.40 (6H, m), 1.56 (3H, s), 2.37 (2H, t, $J=7$), 3.58, 3.82 (2H, each d, $J=17$), 4.28 (2H, d, $J=7$), 4.46 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-21-butoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (50) IR: 3380, 1720, 1660 cm^{-1}. ^{1}H-NMR: 0.91—1.01 (9H, m), 1.37 (3H, d, $J=7$), 1.57 (3H, s), 2.36 (2H, t, $J=8$), 3.58, 3.82 (2H, each d, $J=17$), 4.22 (2H, t, $J=6$), 4.46 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

21-Acetonylthio-17α-butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (52) IR: 3340, 1720, 1655 cm^{-1}. ^{1}H-NMR: 0.94 (3H, t, $J=7$), 1.00 (3H, s), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.30 (3H, s), 3.23, 3.32 (2H, each d, $J=16$), 3.42 (2H, s), 4.46 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.25 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-21-methoxycarbonylthio-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (56) IR: 3360, 1715, 1655 cm^{-1}. ^{1}H-NMR: 1.01 (3H, s), 1.39 (3H, d, $J=7$), 1.57 (3H, s), 2.24 (3H, s), 3.18, 3.25 (2H, each d, $J=14$), 3.79 (2H, dd, $J=18$, 13), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-Ethoxycarbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (57) IR: 3400, 1715, 1655 cm^{-1}. ^{1}H-NMR: 1.00 (3H, s), 1.31 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.24 (3H, s), 3.17, 3.24 (2H, each d, $J=13$), 3.77 (2H, dd, $J=18$, 14), 4.28 (2H, q, $J=7$), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

21-(2,2,2-Trichloroethoxy)carbonylthio-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (58) IR: 3400, 1715, 1655 cm^{-1}. ^{1}H-NMR: 0.99 (3H, s), 1.38 (3H, d, $J=8$), 1.56 (3H, s), 2.24 (3H, s), 3.18, 3.26 (2H, each d, $J=14$), 3.84 (2H, dd, $J=18$, 4), 4.46 (1H, m), 4.83 (2H, dd, $J=12$, 10), 6.16 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.23

(1H, d, $J=10$).

21-Ethoxycarbonylthio-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)-propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (59) IR: 3400, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.98 (3H, s), 1.30 (3H, t, $J=7$), 1.36 (3H, d, $J=7$), 1.56 (3H, s), 3.66, 3.81 (2H, each d, $J=17$), 3.67 (3H, s), 4.26 (2H, q, $J=7$), 4.44 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

17α-Acetoxy-21-(ethoxycarbonyl)methylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (42) A solution of **1** (400 mg), ethyl bromoacetate (0.15 ml) and *N,N*-diisopropylethylamine (0.21 ml) in CH_2Cl_2 (40 ml) was stirred at 0—5 °C for 30 min. The reaction mixture was worked up as described for **39**. The product was recrystallized from EtOH–hexane to afford **42** (410 mg, 86%). IR: 3280, 1720, 1660 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.29 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.10 (3H, s), 3.28—3.56 (4H, m), 4.20 (2H, q, $J=7$), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=9$, 2), 7.24 (1H, d, $J=9$).

The following compounds were similarly prepared.

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-(2-propynyl)thio-1,4-pregnadiene-3,20-dione (44) IR: 3360, 3260, 1730, 1710, 1650 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.11 (3H, s), 2.30 (1H, t, $J=3$), 3.30—3.58 (4H, m), 4.40 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-21-(2-hydroxyethyl)thio-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (48) IR: 3500, 3320, 1725, 1655 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.14 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.38 (2H, q, $J=7$), 3.21, 3.32 (2H, each d, $J=16$), 3.78 (2H, q, $J=7$), 4.44 (1H, m), 6.16 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.20 (1H, d, $J=10$).

17α-Butanoyloxy-21-(ethoxycarbonyl)methylthio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (51) IR: 3420, 1725, 1660 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, $J=8$), 1.02 (3H, s), 1.30 (3H, t, $J=7$), 1.40 (3H, d, $J=7$), 1.56 (3H, s), 2.34 (2H, t, $J=8$), 3.34, 3.44 (2H, each d, $J=15$), 3.43 (2H, s), 4.20 (2H, q, $J=7$), 4.45 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-(2-propynyl)-thio-1,4-pregnadiene-3,20-dione (53) IR: 3340, 3240, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, $J=8$), 1.02 (3H, s), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.28 (1H, t, $J=3$), 2.35 (2H, t, $J=7$), 3.35, 3.52 (2H, each dd, $J=16$, 3), 3.42 (2H, s), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-21-(2-hydroxyethyl)thio-16β-methyl-1,4-pregnadiene-3,20-dione (54) IR: 3500, 3320, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, $J=7$), 1.02 (3H, s), 1.39 (3H, d, $J=7$), 1.58 (3H, s), 2.18 (1H, br s), 2.34 (2H, t, $J=8$), 3.08 (1H, br s), 3.23, 3.34 (2H, each d, $J=16$), 3.78 (2H, m), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$).

17α-Butanoyloxy-21-(2-ethoxycarbonylvinylene)thio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (55) One drop of *N,N*-diisopropylethylamine was added to a solution of **1** (500 mg) and ethyl propiolate (0.13 ml) in CH_3CN (50 ml) at 0—5 °C. After being stirred at 0—5 °C for 1 h, the reaction mixture was worked up as described for **39**. The product was purified by column chromatography with AcOEt–hexane (1 : 2) to give **55**, which was recrystallized from EtOH–H_2O to afford colorless crystals (509 mg, 85%). IR: 3400, 1720, 1700, 1660 cm^{-1}. ^{1}H-NMR: 0.94—1.02 (6H, m), 1.26—1.40 (6H, m), 1.56 (3H, s), 3.37 (2/7 H, d, $J=16$), 3.51 (2/7 H, d, $J=16$), 3.56 (5/7 H, d, $J=16$), 3.66 (5/7 H, d, $J=16$), 4.20 (2H, q, $J=7$), 4.45 (1H, m), 5.78 (5/7 H, d, $J=15$), 5.95 (2/7 H, d, $J=11$), 6.37 (1H, dd, $J=11$, 2), 6.16 (1H, s), 7.25 (1H, d, $J=11$), 7.29 (2/7 H, d, $J=11$), 7.68 (5/7 H, d, $J=15$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-methyldithio-1,4-pregnadiene-3,20-dione (60) *N*-Methylthiophthalimide (500 mg) was added to a solution of **1** (400 mg) in CH_2Cl_2 (50 ml) with stirring. The mixture was stirred at room temperature for 1 h and then evaporated to give a residue, which was purified by column chromatography with AcOEt–hexane. Recrystallization from AcOEt–hexane gave **60** (364 mg, 83%) as colorless crystals. IR: 3260, 1725, 1660 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.12 (3H, s), 2.50 (3H, s), 3.58, 3.66 (2H, each d, $J=16$), 4.45 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

The following compounds were similarly prepared.

17α-Acetoxy-21-ethyldithio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (61) IR: 3380, 1730, 1655 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.34 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.12 (3H, s), 2.80 (2H, q, $J=7$), 3.57, 3.66 (2H, each d, $J=15$), 4.46 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, $J=11$, 2), 7.23 (1H, d, $J=11$).

17α-Acetoxy-9α-fluoro-11β-hydroxy-16β-methyl-21-propyldithio-1,4-pregnadiene-3,20-dione (62) IR: 3300, 1725, 1650 cm^{-1}. ^{1}H-NMR: 0.96—1.04 (6H, m), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.10 (3H, s), 2.76 (2H, t, $J=7$), 3.56, 3.64 (2H, each d, $J=15$), 4.44 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-21-methyldithio-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (63) IR: 3240, 1715, 1650 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.16 (3H, t, $J=7$), 1.38 (3H, d, $J=7$), 1.57 (3H, s), 2.40 (2H, q, $J=7$), 2.49 (3H, s), 3.56, 3.65 (2H, each d, $J=16$), 4.45 (1H, m), 6.16 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

21-Ethyldithio-9α-fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (64) IR: 3280, 1715, 1650 cm^{-1}. ^{1}H-NMR: 1.02 (3H, s), 1.14 (3H, t, $J=7$), 1.32 (3H, t, $J=7$), 1.37 (3H, d, $J=7$), 1.55 (3H, s), 2.39 (2H, q, $J=7$), 2.79 (2H, q, $J=7$), 3.54, 3.63 (2H, each d, $J=16$), 4.45 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-17α-propanoyloxy-21-propyldithio-1,4-pregnadiene-3,20-dione (65) IR: 3280, 1715, 1650 cm^{-1}. ^{1}H-NMR: 0.99 (3H, t, $J=7$), 1.02 (3H, s), 1.15 (3H, t, $J=8$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 1.60—1.84 (2H, m), 2.39 (2H, q, $J=8$), 2.76 (2H, q, $J=7$), 3.55, 3.63 (2H, each d, $J=16$), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-21-isopropyldithio-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (66) IR: 3280, 1730, 1715, 1655 cm^{-1}. ^{1}H-NMR: 1.03 (3H, s), 1.15 (3H, t, $J=7$), 1.30, 1.31 (6H, each d, $J=8$), 1.38 (3H, d, $J=8$), 1.56 (3H, s), 2.39 (2H, q, $J=7$), 3.12 (1H, m), 3.59 (2H, s), 4.46 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-methyldithio-1,4-pregnadiene-3,20-dione (67) IR: 3240, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, $J=7$), 1.03 (3H, s), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.35 (2H, t, $J=7$), 2.50 (3H, s), 3.56, 3.65 (2H, each d, $J=16$), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

17α-Butanoyloxy-21-ethyldithio-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (68) IR: 3240, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.97 (3H, t, $J=7$), 1.04 (3H, s), 1.34 (3H, t, $J=7$), 1.57 (3H, s), 2.36 (2H, t, $J=7$), 2.80 (2H, q, $J=7$), 3.57, 3.66 (2H, each d, $J=16$), 4.47 (1H, m), 6.18 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-21-propyldithio-1,4-pregnadiene-3,20-dione (69) IR: 3360, 1720, 1650 cm^{-1}. ^{1}H-NMR: 0.93—1.03 (9H, m), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.76 (2H, t, $J=7$), 3.60 (2H, s), 4.46 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

17α-Butanoyloxy-9α-fluoro-11β-hydroxy-21-isopropyldithio-16β-methyl-1,4-pregnadiene-3,20-dione (70) IR: 3300, 1730, 1655 cm^{-1}. ^{1}H-NMR: 0.96 (3H, t, $J=7$), 1.03 (3H, s), 1.30 (3H, d, $J=7$), 1.31 (3H, d, $J=7$), 1.38 (3H, d, $J=7$), 1.56 (3H, s), 2.34 (2H, t, $J=8$), 3.12 (1H, m), 3.60 (2H, s), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.22 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-16β-methyl-21-methyldithio-17α-(methylthio)-acetoxy-1,4-pregnadiene-3,20-dione (71) IR: 3270, 1730, 1720, 1655 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.40 (3H, d, $J=7$), 1.57 (3H, s), 2.24 (3H, s), 2.50 (3H, s), 3.17, 3.25 (2H, each d, $J=14$), 3.70 (2H, s), 4.46 (1H, m), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$).

21-Ethyldithio-9α-fluoro-11β-hydroxy-16β-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (72) IR: 3320, 1730, 1710, 1655 cm^{-1}. ^{1}H-NMR: 1.04 (3H, s), 1.34 (3H, t, $J=7$), 1.39 (3H, d, $J=7$), 1.56 (3H, s), 2.24 (3H, s), 2.81 (2H, q, $J=7$), 3.15, 3.23 (2H, each d, $J=14$), 3.61 (2H, s), 4.46 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

9α-Fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-21-methyldithio-1,4-pregnadiene-3,20-dione (73) IR: 3380, 1725, 1655 cm^{-1}. ^{1}H-NMR: 1.03 (3H, s), 1.37 (3H, d, $J=7$), 1.56 (3H, s), 2.50 (3H, s), 2.60—2.70 (4H, m), 3.62, 3.72 (2H, each d, $J=17$), 3.68 (3H, s), 4.44 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, $J=10$, 2), 7.21 (1H, d, $J=10$).

References and Notes

1) A part of this work was presented at the 108th Annual Meeting of the Pharmaceutical Society of Japn, Hiroshima, April 1988.
2) *a*) Part II: M. Mitsukuchi, T. Ikemoto, M. Taguchi, S. Higuchi, S. Abe, H. Yasui, K. Hatayama and K. Sota, *Chem. Pharm. Bull.*, **37**, 1795 (1989); *b*) Part I: M. Mitsukuchi, J. Nakagami, T. Ikemoto, S. Higuchi, Y. Tarumoto, H. Yasui and K. Sota, *ibid.*, **37**, 1534 (1989).
3) D. R. Torossian, G. G. Aubard, C. P. J. Roux and A. G. Grouhel, Belg. Patent 893957 (1983) [*Chem. Abstr.*, **98**, 198601*m* (1983)].
4) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, **1970**, 3547.
5) J. H. Draize, "The Appraisal of Chemicals in Foods, Drugs and Cosmetics," Association of Food and Drug Officials of the United

States, Austin, 1959, pp. 36—45.
6) B. N. Ames, J. McCann and E. Yamasaki, *Mutat. Res.*, **31**, 347 (1975).
7) *a*) M. Ishihara, *Nishinihon J. Dermatol.*, **37**, 86 (1975); *b*) *Idem*, *ibid.*, **38**, 286 (1976); *c*) *Idem*, *Clinical Evaluation*, **4**, 323 (1976).
8) A. W. McKenzie and R. B. Stoughton, *Arch. Dermatol.*, **86**, 608 (1962).
9) C. G. Sparkes and L. Wilson, *Br. J. Dermatol.*, **90**, 197 (1974).
10) A. W. McKenzie and R. M. Atkinson, *Arch. Dermatol.*, **89**, 741 (1964).
11) F. Wilcoxon, *Biometrics*, **1**, 80 (1945).
12) Glaxo Group Ltd., Belg. Patent 649171 (1964) [*Chem. Abstr.*, **64**, 15958*g* (1966)].
13) J. Elks and G. H. Phillipps, Ger. Offen. 1902340 (1969) [*Chem. Abstr.*, **72**, 44021*y* (1970)].