

Studies on Topical Antiinflammatory Agents. II.¹⁾ Synthesis and Vasoconstrictive Activity of 21-Substituted Corticosteroids with Sulfur-Containing Moieties

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As part of the search for new topical antiinflammatory agents, various 21-substituted corticosteroids having sulfur-containing moieties were prepared and tested for vasoconstrictive activity in humans. A structure-activity relationship study revealed that substitution of the 21-hydroxy group with a lower alkyl-thio group enhanced the activity. The activities of the 21-methylthio (3Ad) and the 21-ethylthio (3Ae) compounds were more potent than that of 9 α -fluoro-11 β , 21-dihydroxy-16 β -methyl-17 α -valeroyloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV).

Keywords corticosteroid; antiinflammatory agent; 11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione; 21-alkylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione; 21-substituted thiocorticosteroid; vasoconstrictive activity; structure-activity relationship

In the previous paper,¹⁾ we reported the synthesis and the vasoconstrictive activity of corticosteroid 17-succinyl esters. We found that some of them exhibited good antiinflammatory activity on human skin. In our search for new topical antiinflammatory agents, we thought that the substitution of the hydroxy group at the 21-position with a hetero atom might be a suitable structural modification to enhance the activity of corticosteroids. Only a limited number of corticosteroids containing sulfur at the 21-position have so far been described.²⁾ Therefore we have been interested in synthesizing new 21-substituted corticosteroid 16 α ,17 α -acetonide derivatives with sulfur-containing moieties. In the present work, in order to examine the influence of the sulfur atom introduced into the 21-position, we synthesized various 21-sulfide and 21-disulfide derivatives and tested their vasoconstrictive activities.

Chemistry The 21-sulfide derivatives (3) listed in Table I were prepared by the method shown in Chart 1. The 21-mesylates (2A—C) were prepared from the corresponding corticosteroid 16 α ,17 α -acetonides (1A—C) by mesylation with MsCl in pyridine. Reaction of 2A—C with various mercapto compounds in the presence of sodium methoxide

or triethylamine afforded the corresponding 21-sulfides (3Aa—Ca), except for 3Ad, in 35—92% yields. The 21-methylthio compound (3Ad) was obtained from 2A and 15% sodium methanethiolate in acetone in 87% yield: acylthio compounds (3Aa—c, 3Ba and 3Ca), alkylthio compounds (3Ad—h), a phenylthio compound (3Ai), aralkylthio compounds (3Aj—l), cycloalkylthio compounds (3Am and 3An) and alkoxycarbonylmethylthio compounds (3Ao and 3Ap) were also obtained (Table I).

Treatment of 2A with sodium hydrosulfide under reflux in acetone—MeOH provided 3Aq in 87% yield. The chemical structure of 3Aq was determined as follows. The protonated molecular ion peak of 3Aq was observed at m/z 903 in the secondary ionization mass spectrum (SIMS). The proton nuclear magnetic resonance (¹H-NMR) spectrum (Table V) showed two AB pairs of doublets ($J=17$ Hz) at 3.72 and 4.04 ppm assignable to two methylene protons geminal to sulfur. Based on these spectral data and elemental analysis, the structure of 3Aq was determined as bis(6 α , 9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3,20-dioxopregna-1,4-diene-21-yl)sulfide.

The 21-sulfide derivatives (4A—5Cb) listed in Table II

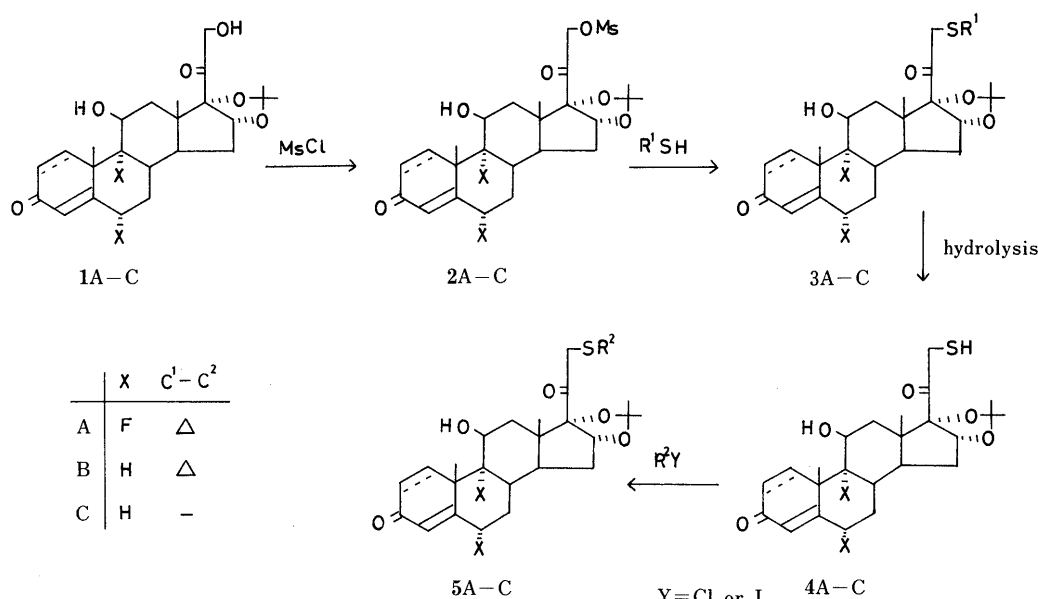


Chart 1

TABLE I. Physical and Biological Properties of 21-Thiocorticosteroids 3

Compd. No.	R ¹	Yield ^{a)} (%)	mp (°C)	Recrystn. solvent ^{b)}	Formula	Analysis (%)		Vasoconstrictive potency ^{c)}	
						Calcd	(Found)	After 2 h	After 4 h
3Aa	COMe	59	279—282	E	C ₂₆ H ₃₂ F ₂ O ₆ S	61.12 (60.86)	6.32 (6.29)	119	110
3Ab	COEt	87	280—283	E	C ₂₇ H ₃₄ F ₂ O ₆ S	61.81 (61.92)	6.53 (6.57)	94	107
3Ac	CO- <i>tert</i> -Bu	88	266—268.5	E	C ₂₉ H ₃₈ F ₂ O ₆ S	63.02 (63.06)	6.93 (6.93)	63 ^{g)}	54 ^{g)}
3Ad	Me	87	287—290	E	C ₂₅ H ₃₂ F ₂ O ₅ S	62.22 (61.93)	6.69 (6.74)	131 ^{e)}	110
3Ae	Et	65	276.5—278	E	C ₂₆ H ₃₄ F ₂ O ₅ S	62.88 (62.87)	6.90 (6.93)	159 ^{g)}	133 ^{g)}
3Af	Pr	73	262—265	E	C ₂₇ H ₃₆ F ₂ O ₅ S	63.51 (63.52)	7.11 (7.14)	72	68 ^{g)}
3Ag	iso-Pr	77	238—240	E	C ₂₇ H ₃₆ F ₂ O ₅ S	63.51 (63.17)	7.11 (7.43)	82 ^{d)}	67 ^{g)}
3Ah	Bu	85	238—240	E	C ₂₈ H ₃₈ F ₂ O ₅ S	64.10 (64.22)	7.30 (7.42)	80	77
3Ai	C ₆ H ₅ —	87	289—292	E	C ₃₀ H ₃₄ F ₂ O ₅ S	66.16 (66.11)	6.29 (6.28)	33 ^{g)}	36 ^{g)}
3Aj	C ₆ H ₅ CH ₂ —	35	235—237	E	C ₃₁ H ₃₆ F ₂ O ₅ S	66.64 (66.47)	6.50 (6.43)	83	83
3Ak	<i>p</i> -Me—C ₆ H ₄ CH ₂ —	50	228—230	E	C ₃₂ H ₃₈ F ₂ O ₅ S	67.11 (66.88)	6.69 (6.69)	55 ^{f)}	45 ^{g)}
3Al	<i>p</i> -Cl—C ₆ H ₄ CH ₂ —	84	260—262	E	C ₃₁ H ₃₅ ClF ₂ O ₅ S	62.77 (62.64)	5.95 (5.89)	55 ^{d)}	38 ^{g)}
3Am	Cyclopentyl	77	254—257	E	C ₂₉ H ₃₈ F ₂ O ₅ S	64.90 (64.59)	7.14 (7.22)	55 ^{f)}	50 ^{g)}
3An	Cyclohexyl	85	265 (dec.)	E	C ₃₀ H ₄₀ F ₂ O ₅ S	65.43 (65.33)	7.32 (7.36)	62 ^{d)}	58 ^{g)}
3Ao	CH ₂ CO ₂ Et	87	223—225	E	C ₂₈ H ₃₆ F ₂ O ₇ S	60.63 (60.67)	6.54 (6.57)	108	89
3Ap	CH ₂ CO ₂ Bu	74	172—174	E	C ₃₀ H ₄₀ F ₂ O ₇ S	61.84 (61.90)	6.92 (6.85)	35 ^{f)}	36 ^{g)}
3Aq	Dimer	87	> 300	F—M	C ₄₈ H ₅₈ F ₄ O ₁₀ S ^{h)}	63.21 (63.22)	6.52 (6.51)	59 ^{d)}	33 ^{g)}
3Ba	COMe	92	240—242	M	C ₂₆ H ₃₄ O ₆ S	65.80 (65.45)	7.22 (6.90)	89	64 ^{g)}
3Ca	COMe	39	242—245	A—H	C ₂₆ H ₃₆ O ₆ S ⁱ⁾	64.90 (64.82)	7.65 (7.44)	N.T. ^{j)}	N.T.

a) Yields are based on the preceding isolated intermediates. b) A=AcOEt, E=EtOH, F=DMF, M=MeOH. c) 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. d) $p < 0.1$. e) $p < 0.05$. f) $p < 0.02$. g) $p < 0.01$ for BV, using Wilcoxon's signed-ranks test.³⁾ h) 1/2 H₂O. i) 1/4 H₂O. j) Not tested.

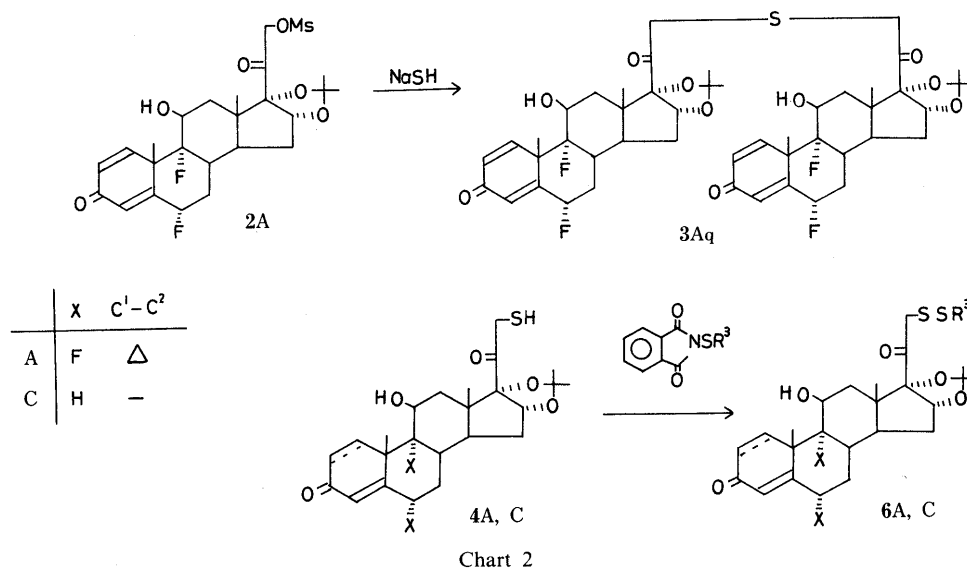


TABLE II. Physical and Biological Properties of 21-Thiocorticosteroids **4** and **5**

Compd. No.	R ²	Yield ^{a)} (%)	mp (°C)	Recrystn. solvent ^{b)}	Formula	Analysis (%) Calcd (Found)		Vasoconstrictive potency ^{c)}	
						C	H	After 2 h	After 4 h
4A	H	67	265—269	D-H	C ₂₄ H ₃₀ F ₂ O ₅ S	61.52 (61.25)	6.45 (6.49)	89	89
4B	H	85	267—270	F	C ₂₄ H ₃₂ O ₅ S	66.43 (66.65)	7.46 (7.22)	86	70 ^{a)}
4C	H	74	250—253	A-H	C ₂₄ H ₃₄ O ₅ S	66.33 (66.14)	7.89 (7.65)	78	52 ^{a)}
5Aa	CO ₂ Et	96	242—245	D-H	C ₂₇ H ₃₄ F ₂ O ₇ S	59.99 (59.77)	6.34 (6.26)	115	111
5Ab	CO ₂ Bu	96	223—225	D-H	C ₂₉ H ₃₈ F ₂ O ₇ S	61.25 (61.22)	6.74 (6.71)	65	50 ^{a)}
5Ba	Me	78	258—261	C-M	C ₂₅ H ₃₄ O ₅ S	67.23 (67.04)	7.67 (7.46)	125 ^{c)}	76 ^{f)}
5Bb	Et	39	236—239	C-M	C ₂₆ H ₃₆ O ₅ S	67.79 (67.41)	7.88 (7.62)	75 ^{d)}	54 ^{a)}
5Bc	CO ₂ Me	77	241—243	C-M	C ₂₆ H ₃₄ O ₇ S	63.65 (63.63)	6.99 (6.79)	60 ^{a)}	56 ^{a)}
5Bd	CO ₂ Et	62	241—244	M	C ₂₇ H ₃₆ O ₇ S	64.26 (64.48)	7.19 (7.18)	65 ^{e)}	61 ^{a)}
5Ca	Me	87	213—215	A-H	C ₂₅ H ₃₆ O ₅ S	66.93 (66.72)	8.09 (7.84)	54 ^{f)}	40 ^{a)}
5Cb	CO ₂ Me	88	207—210	A-H	C ₂₆ H ₃₆ O ₇ S	63.39 (63.65)	7.37 (7.14)	54 ^{f)}	54 ^{a)}

a) See footnote a in Table I. b) A = AcOEt, C = CHCl₃, D = CH₂Cl₂, F = DMF, H = hexane, M = MeOH. c) to g) See footnotes c to g in Table I.

TABLE III. Physical and Biological Properties of 21-Dithiocorticosteroids **6**

Compd. No.	R ³	Yield ^{a)} (%)	mp (°C)	Recrystn. solvent ^{b)}	Formula	Analysis (%) Calcd (Found)		Vasoconstrictive potency ^{c)}	
						C	H	After 2 h	After 4 h
6Aa	Me	88	250—254	D-H	C ₂₅ H ₃₂ F ₂ O ₅ S ₂	58.35 (58.26)	6.27 (6.37)	104	92
6Ab	Et	84	227—230	D-H	C ₂₆ H ₃₄ F ₂ O ₅ S ₂ ^{k)}	56.78 (56.62)	6.32 (6.28)	104	92
6Ac	Pr	78	204—205	D-H	C ₂₇ H ₃₆ F ₂ O ₅ S ₂ ^{h)}	58.78 (58.95)	6.76 (6.73)	57 ^{a)}	56 ^{a)}
6Ad	iso-Pr	98	230—233	D-H	C ₂₇ H ₃₆ F ₂ O ₅ S ₂ ⁱ⁾	59.26 (59.12)	6.72 (6.66)	96	77 ^{c)}
6Ca	Et	86	210—212	A-H	C ₂₆ H ₃₈ O ₅ S ₂	63.12 (63.14)	7.74 (7.56)	38 ^{a)}	40 ^{a)}

a) to i) See footnotes a to i in Tables I and II. k) 1/4 CH₂Cl₂.

were also prepared as shown in Chart 1. Hydrolysis of 21-thiopropionate (**3Ab**) with potassium *tert*-butoxide in MeOH at room temperature for 15 min gave the mercapto derivative (**4A**) in 67% yield. The other two 21-mercapto compounds (**4B** and **4C**) were prepared by reaction of **3Ba** and **3Ca** with hydrazine hydrate in tetrahydrofuran (THF) at -15—-10 °C for 15 min in 85% and 74% yields, respectively. Alkylation of **4B** and **4C** with the appropriate alkyl iodide in *N,N*-dimethylformamide (DMF) in the presence of triethylamine afforded the corresponding 21-alkylthio compounds (**5Ba**, **5Bb** and **5Ca**), respectively. Compounds **4A**—**C** were also converted to the corresponding alkoxy carbonylthio derivatives (**5Aa**, **5Ab**, **5Bc**, **5Bd** and **5Cb**) by reaction with alkyl chloroformate and triethylamine in either CH₂Cl₂ or DMF. The 21-disulfide derivatives (**6Aa**—**Ca**) listed in Table III were prepared by treatment of **4A** and **4C** with the appropriate *N*-

alkylthiophthalimides⁴⁾ at room temperature as shown in Chart 2.

Safety of the Compounds Tested Before application to volunteers, the safety of all the compounds was checked by the method reported previously.^{1,5c)}

Results and Discussion

Primary Skin Irritability All the compounds were evaluated at 1, 2, 3 and 7 d by the Draize method.⁶⁾ As shown in Table IV, it was considered that none of the compounds exhibits primary skin irritability.

Mutagenicity As shown in Table IV, all the compounds tested were negative in the Ames spot test.⁷⁾

Thus, none of the compounds exhibited significant toxic signs in the primary skin irritability or bacterial reverse mutation test.

Vasoconstrictive Activities A number of methods for

TABLE IV. Primary Skin Irritability and Mutagenicity of Compounds 3, 4, 5 and 6

Compd. No.	Primary skin irritability	Mutagenicity <i>S. typhimurium</i>		Compd. No.	Primary skin irritability	Mutagenicity <i>S. typhimurium</i>	
		TA98	TA100			TA98	TA100
3Aa	—	—	—	4A	—	—	—
3Ab	—	—	—	4B	—	—	—
3Ac	—	—	—	4C	—	—	—
3Ad	—	—	—	5Aa	—	—	—
3Ae	—	—	—	5Ab	—	—	—
3Af	—	—	—	5Ba	—	—	—
3Ag	—	—	—	5Bb	—	—	—
3Ah	—	—	—	5Bc	—	—	—
3Ai	—	—	—	5Bd	—	—	—
3Aj	—	—	—	5Ca	—	—	—
3Ak	—	—	—	5Cb	—	—	—
3Al	—	—	—	6Aa	—	—	—
3Am	—	—	—	6Ab	—	—	—
3An	—	—	—	6Ac	—	—	—
3Ao	—	—	—	6Ad	—	—	—
3Ap	—	—	—	6Ca	—	—	—
3Aq	—	—	—				
3Ba	—	—	—				
2AN		+	+	2NF		+	/
				ENNG		/	+

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

evaluating corticosteroids for topical antiinflammatory activity have been described. However, it is well known that certain corticosteroids that are predicted to be potent on the basis of animal studies are frequently found to be much less potent in human studies. Only the vasoconstriction activity test has been considered to be reliable for predicting the antiinflammatory potency of topical corticosteroids,⁸⁾ because a remarkably good correlation has been found between the results of this test and topical efficacy in the clinic.⁹⁾ For instance, clobetasol propionate¹⁰⁾ and betamethasone 17-valerate¹¹⁾ (BV) were selected using this method, and are widely used in the clinic. Evaluation by this method is recommended as a preclinical study for topically applied corticosteroids.⁸⁾

Thirty-four compounds (3, except for 3Ca, and 4–6) were tested for vasoconstrictive activities in twenty healthy male volunteers by the method reported previously.¹⁾ The vasoconstrictive activities of the compounds prepared in this work were compared with that of BV, which is more potent than the mother compound (1A).¹¹⁾ Statistical analysis was performed by Wilcoxon's signed-ranks test.¹³⁾ The results are summarized in Tables I–III. The activities of eight compounds, 3Aa, 3Ad, 3Ae, 3Ao, 5Aa, 5Ba, 6Aa and 6Ab, at 2 h were equal to or greater ($p < 0.05$) than that of BV. On the other hand, the activities of five compounds, 3Aa, 3Ab, 3Ad, 3Ae and 5Aa, at 4 h were equal to or greater ($p < 0.01$) than that of BV. In particular, the activities of four compounds, 3Aa, 3Ad, 3Ae and 5Aa, were equal to or greater ($p < 0.05$) than that of BV at both 2 and 4 h. The highest activity ratio was observed with compounds 3A and 5A having fluoro atoms at both the 6- and 9-positions. As regards the size of the 21-S-alkyl groups, the compounds with small alkyl group such as methyl (3Ad) and ethyl (3Ae) showed potent activities. Lengthening of the alkyl group generally caused a decrease in activity. The compounds having a phenyl (3Ai), aralkyl (3Aj, 3Ak and 3Al) or cycloalkyl (3Am and 3An) groups as 21-S-

substituents showed lower activities. The activity of the dimer-type compound (3Aq) was also considerably reduced. In the case of 5Ba, which is the defluoro derivative of 3Ad and the 21-ethoxycarbonylmethylsulfide (3Ao), these activities were equal to or greater than that of BV at 2 h, but were remarkably decreased after 4 h. In the series of the alkoxycarbonylthio derivatives (5Aa, 5Ab, 5Bc, 5Bd and 5Cb) and the disulfides (6), the effect of the S-substituents on the activity was similar to that in the sulfides 3, but their activities were weaker than those of 3. We found that the size of the 21-S-substituent influences the vasoconstrictive activity. These results suggest that the 21-hydroxyl group of corticosteroids may not be essential for their biological activities. The higher activities of the sulfur-containing compounds (3Ad and 3Ae) might be due to the higher lipophilicity⁵⁾ of the sulfur atom. Among the compounds synthesized, 3Ae was found to have the most potent vasoconstrictive activity, which was significantly ($p < 0.01$) greater than that of BV. In conclusion, we can say that substitution of the 21-hydroxy group of corticosteroids with a lower alkyl thio group is a potentially useful approach to obtain effective topical antiinflammatory agents.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr disks on a JASCO DS-301 spectrophotometer. ¹H-NMR spectra were obtained with a Varian XL-200 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet; d=doublet; t=triplet, q=quartet; m=multiplet; br=broad. MS and SIMS were taken with a Shimadzu LKB-9000 or Hitachi M-80A spectrometer, respectively. All organic extracts were dried over anhydrous MgSO₄. Column chromatography was carried out on Wakogel C-200.

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-mesyloxy-1,4-pregnadiene-3,20-dione (2A) Mesyl chloride (5 ml) was added dropwise to a stirred suspension of 1A (10.0 g) in pyridine (80 ml) under ice-cooling. After being stirred for 30 min, the resulting solution was poured into ice-cold 10% HCl (300 ml) with stirring and the solid was collected by filtration, washed with H₂O and dried to yield 2A (11.6 g, 99%) as an amorphous powder. ¹H-NMR δ : 0.94 (3H, s), 1.22 (3H, s), 1.44 (3H, s),

1.53 (3H, s), 3.26 (3H, s), 4.44 (1H, m), 4.96, 5.22 (2H, each d, $J=18$ Hz), 5.03 (1H, d, $J=4$ Hz), 5.41 (1H, dm, $J=44$ Hz), 6.39 (1H, dd, $J=10, 2$ Hz), 6.46 (1H, s), 7.11 (1H, dd, $J=10, 2$ Hz).

The following compounds (2B and 2C) were similarly prepared.

11 β -Hydroxy-16 α ,17 α -isopropylidenedioxy-21-mesyloxy-1,4-pregnadiene-3,20-dione (2B) Yield 99%, colorless prisms, mp 124–128 °C (from MeOH). $^1\text{H-NMR}$ δ : 0.95 (3H, s), 1.21 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 3.26 (3H, s), 4.51 (1H, m), 4.91, 5.27 (2H, each d, $J=18$ Hz), 5.00–5.06 (1H, m), 6.05 (1H, br s), 6.30 (1H, dd, $J=10, 2$ Hz), 7.28 (1H, d, $J=10$ Hz).

11 β -Hydroxy-16 α ,17 α -isopropylidenedioxy-21-mesyloxy-4-pregnene-3,20-dione (2C) Yield 99%, amorphous powder. $^1\text{H-NMR}$ δ : 0.92 (3H, s), 1.21 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 3.24 (3H, s), 4.50 (1H, m), 4.91, 5.28 (2H, each d, $J=18$ Hz), 5.03 (1H, d, $J=4$ Hz), 5.70 (1H, s).

21-Acetylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Aa) Sodium methoxide (310 mg) was added to a solution of *S*-thioacetic acid (0.43 ml) in dry acetone (20 ml). After 30 min, a solution of 2A (2.01 g) in dry acetone (45 ml) was added to the solution, and the mixture was refluxed for 6 h. After removal of the solvent, the residue was suspended with H_2O , and extracted with AcOEt. The extract was washed successively with 5% HCl, 5% Na_2CO_3 and H_2O , dried and concentrated. The residue was purified by column chromatog-

raphy using CHCl_3 as an eluent and the product was recrystallized from EtOH to give 3Aa (1.13 g) as colorless needles.

The following compounds (6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-propanoylthio-1,4-pregnadiene-3,20-dione (3Ab), 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-pivaloylthio-1,4-pregnadiene-3,20-dione (3Ac), 21-acetylthio-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Ba) and 21-acetylthio-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-4-pregnene-3,20-dione (3Ca)) were similarly prepared. The physical properties of 3Aa–c, 3Ba and 3Ca are summarized in Tables I, V and VI.

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-methylthio-1,4-pregnadiene-3,20-dione (3Ad) An aqueous NaSMe (2.0 ml, ca. 15%) solution was added to a solution of 2A (2.0 g) in acetone (30 ml) under ice-cooling with stirring. After 1 h, the reaction mixture was poured into ice- H_2O . The separated precipitate was collected, washed with H_2O and dried. Recrystallization from EtOH gave 3Ad (1.58 g) as colorless needles.

The physical properties of 3Ad are summarized in Tables I and V.

21-Ethylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Ae) Sodium methoxide (453 mg) was added to a solution of ethanethiol (0.58 ml) in dry acetone (20 ml). The mixture was stirred for 0.5 h, then a solution of 2A (2.02 g) in dry acetone (40 ml) was added. After being stirred for 2.5 h, the reaction mixture was concentrated, diluted with ice- H_2O , and extracted with AcOEt. The extract was washed successively with 5% HCl, 5% Na_2CO_3 and H_2O , dried and concentrated. The residue was chromatographed using CHCl_3 as an eluent, followed by recrystallization from EtOH to give 3Ae (1.22 g) as colorless needles.

The following compounds (6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-propylthio-1,4-pregnadiene-3,20-dione (3Af), 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-isopropylthio-1,4-pregnadiene-3,20-dione (3Ag), 21-butylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Ah), 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-phenylthio-1,4-pregnadiene-3,20-dione (3Ai), 21-benzylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Aj), 6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-(*p*-methylbenzylthio)-1,4-pregnadiene-3,20-dione (3Ak), 21-(*p*-chlorobenzylthio)-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Al), 21-cyclopentylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Am) and 21-cyclohexylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3An)) were similarly prepared.

The physical properties of 3Ac–n are summarized in Tables I, V, and VI.

21-Ethoxycarbonylmethylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Ao) Ethyl 2-mercaptoacetate (2.0 ml) and triethylamine (2.5 ml) were added to a solution of 2A (1.20 g) in dry acetone (30 ml) under ice-cooling with stirring. After being stirred for 8 h at 40 °C, the reaction mixture was evaporated *in vacuo* to dryness. The residue was recrystallized from EtOH to give 3Ao (1.09 g) as colorless needles.

The following compound (21-butoxycarbonylmethylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (3Ap)) was similarly prepared. The physical properties of 3Ao and 3Ap are summarized in Tables I and VI.

Bis(6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-3,20-dioxopregna-1,4-diene-21-yl)sulfide (3Aq) Sodium hydrosulfide (970 mg, about 70%) was added to a solution of 2A (3.08 g) in acetone (80 ml) and MeOH (8 ml). The mixture was refluxed for 1 h. After cooling, the reaction mixture was acidified with 10% HCl. The separated precipitate was collected and washed successively with H_2O and acetone. Recrystallization from DMF–MeOH gave 3Aq (2.27 g) as a colorless powder.

The physical properties of 3Aq are summarized in Tables I and VI.

6 α ,9 α -Difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-mercapto-1,4-pregnadiene-3,20-dione (4A) Potassium *tert*-butoxide (550 mg) was added to a solution of 3Aa (1.00 g) in MeOH (180 ml). The mixture was stirred for 15 min at room temperature, then acidified with saturated aqueous NH_4Cl solution. The resulting precipitate was collected and purified by column chromatography using CHCl_3 as an eluent to give 4A (620 mg) as colorless needles.

11 β -Hydroxy-16 α ,17 α -isopropylidenedioxy-21-mercapto-1,4-pregnadiene-3,20-dione (4B) Hydrazine hydrate (0.20 ml) was added to a solution of 3Ba (1.02 g) in THF (13 ml) at below -10 °C. The mixture was

TABLE V. Spectral Data for 3Aa–h

Compd. No.	IR cm^{-1}	MS m/z (M^+)	$^1\text{H-NMR}$ δ (ppm, J =Hz) in CDCl_3
3Aa	3360 1720 1680 1660	510	0.90 (3H, s), 1.18 (3H, s), 1.46 (3H, s), 1.54 (3H, s), 2.42 (3H, s), 3.96, 4.08 (2H, each d, $J=18$), 4.45 (1H, m), 5.03 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.13 (1H, d, $J=10$)
3Ab	3360 1720 1660	524	0.90 (3H, s), 1.18 (3H, s), 1.20 (3H, t, $J=8$), 1.44 (3H, s), 1.54 (3H, s), 2.68 (2H, q, $J=8$), 3.96, 4.10 (2H, each d, $J=18$), 4.43 (1H, m), 5.03 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.15 (1H, dd, $J=10, 2$)
3Ac	3360 1720 1660	552	0.92 (3H, s), 1.20 (3H, s), 1.30 (9H, s), 1.46 (3H, s), 1.56 (3H, s), 3.91, 4.12 (2H, each d, $J=18$), 4.47 (1H, m), 5.05 (1H, d, $J=4$), 5.41 (1H, dm, $J=50$), 6.41 (1H, dd, $J=10, 2$), 6.47 (1H, s), 7.15 (1H, dd, $J=10, 2$)
3Ad	3300 1705 1650	483 ^{a)}	0.96 (3H, s), 1.16 (3H, s), 1.44 (3H, s), 1.53 (3H, s), 2.20 (3H, s), 3.45, 3.58 (2H, each d, $J=16$), 4.43 (1H, m), 5.03 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.45 (1H, s), 7.12 (1H, dd, $J=10, 2$)
3Ae	3320 1710 1660	496	0.96 (3H, s), 1.17 (3H, s), 1.29 (3H, t, $J=8$), 1.43 (3H, s), 1.53 (3H, s), 3.51, 3.60 (2H, each d, $J=13$), 4.43 (1H, m), 5.04 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.45 (1H, s), 7.11 (1H, dd, $J=10, 2$)
3Af	3320 1710 1660	510	0.96 (3H, s), 1.00 (3H, t, $J=8$), 1.16 (3H, s), 1.43 (3H, s), 1.53 (3H, s), 3.50, 3.58 (2H, each d, $J=16$), 4.43 (1H, m), 5.05 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.43 (1H, s), 7.12 (1H, dd, $J=10, 2$)
3Ag	3360 1710 1655	511 ^{a)}	0.96 (3H, s), 1.17 (3H, s), 1.24–1.36 (6H, m), 1.44 (3H, s), 1.54 (3H, s), 3.10 (1H, septet, $J=7$), 3.56, 3.64 (2H, each d, $J=16$), 4.43 (3H, s), 5.05 (1H, d, $J=4$), 5.40 (1H, dm, $J=50$), 6.40 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.16 (1H, dd, $J=10, 2$)
3Ah	3320 1700 1655	525 ^{a)}	0.92 (3H, t, $J=6$), 0.96 (3H, s), 1.16 (3H, s), 1.43 (3H, s), 1.53 (3H, s), 3.50, 3.58 (2H, each d, $J=16$), 4.43 (1H, m), 5.03 (1H, d, $J=4$), 5.40 (1H, dm, $J=50$), 6.39 (1H, dd, $J=10, 2$), 6.45 (1H, s), 7.12 (1H, d, $J=10$)

a) Secondary ionization mass spectrum (MH^+).

TABLE VI. Spectral Data for 3Ai–3Ca

Compd. No.	IR cm^{-1}	SIMS m/z (MH^+)	$^1\text{H-NMR}$ δ (ppm, $J=\text{Hz}$) in CDCl_3
3Ai	3440 1710 1660 1605	545	0.82 (3H, s), 1.11 (3H, s), 1.42 (3H, s), 1.51 (3H, s), 3.92, 4.13 (2H, each d, $J=16$), 4.38 (1H, m), 5.04 (1H, d, $J=5$), 5.38 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.45 (1H, s), 7.10 (1H, dd, $J=10, 2$), 7.24–7.54 (5H, m)
3Aj	3360 1690 1660 1620 1605	559	0.85 (3H, s), 1.08 (3H, s), 1.38 (3H, s), 1.51 (3H, s), 3.34, 3.45 (2H, each d, $J=16$), 3.84 (2H, s), 4.30 (1H, m), 5.01 (1H, d, $J=4$), 5.38 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.44 (1H, s), 7.11 (1H, d, $J=10$), 7.24–7.46 (5H, m)
3Ak	3360 1690 1660 1620 1605	573	0.86 (3H, s), 1.09 (3H, s), 1.40 (3H, s), 1.51 (3H, s), 2.36 (3H, s), 3.40 (2H, s), 3.80 (2H, s), 4.28 (1H, m), 5.01 (1H, d, $J=4$), 5.38 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.44 (1H, s), 7.09 (1H, d, $J=10$), 7.12–7.32 (4H, m)
3Al	3300 1690 1655 1615	595	0.89 (3H, s), 1.10 (3H, s), 1.40 (3H, s), 1.52 (3H, s), 3.34 (2H, s), 3.81 (2H, s), 4.35 (1H, m), 5.05 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.44 (1H, s), 7.10 (1H, dd, $J=10, 2$), 7.34 (4H, s)
3Am	3360 1710 1655 1615	537	0.95 (3H, s), 1.16 (3H, s), 1.43 (3H, s), 1.53 (3H, s), 3.27 (1H, m), 3.59 (2H, s), 4.43 (1H, m), 5.04 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.38 (1H, dd, $J=10, 2$), 6.45 (1H, s), 7.13 (1H, dd, $J=10, 2$)
3An	3240 1705 1660 1615	550 ^{a)}	0.96 (3H, s), 1.16 (3H, s), 1.43 (3H, s), 1.54 (3H, s), 3.58 (2H, s), 4.44 (1H, m), 5.04 (1H, d, $J=5$), 5.40 (1H, dm, $J=48$), 6.40 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.12 (1H, dd, $J=10, 2$)
3Ao	3360 1735 1685 1660	555	0.94 (3H, s), 1.17 (3H, s), 1.30 (3H, t, $J=7$), 1.43 (3H, s), 1.55 (3H, s), 3.35 (2H, s), 3.74, 3.88 (2H, each d, $J=18$), 4.21 (2H, q, $J=7$), 4.45 (1H, m), 5.06 (1H, d, $J=4$), 5.41 (1H, dm, $J=50$), 6.40 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.16 (1H, d, $J=10$)
3Ap	3360 1735 1660	582 ^{a)}	0.96 (6H, s and t, $J=7$), 1.16 (3H, s), 1.43 (3H, s), 1.54 (3H, s), 3.36 (2H, s), 3.73, 3.87 (2H, each d, $J=18$), 4.14 (2H, t, $J=7$), 4.44 (1H, m), 5.05 (1H, d, $J=5$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.15 (1H, dd, $J=10, 2$)
3Aq	3410 1700 1660	903	^{b)} 0.82 (6H, s), 1.10 (6H, s), 1.36 (6H, s), 1.49 (6H, s), 3.72, 4.04 (4H, each d, $J=17$), 4.23 (2H, brs), 4.93 (2H, s), 5.56 (2H, d, $J=5$), 5.64 (2H, dm, $J=48$), 6.14 (2H, s), 6.33 (2H, dd, $J=11, 2$), 7.31 (2H, d, $J=11$)
3Ba	3340 1720 1690 1650	475	0.90 (3H, s), 1.17 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 2.41 (3H, s), 3.90, 4.18 (2H, each d, $J=18$), 4.55 (1H, m), 5.00–5.08 (1H, m), 6.05 (1H, brs), 6.30 (1H, dd, $J=10, 2$), 7.29 (1H, d, $J=10$)
3Ca	3360 1720 1685 1645	477	0.88 (3H, s), 1.18 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 2.40 (3H, s), 3.91, 4.18 (2H, each d, $J=18$), 4.51 (1H, m), 5.03 (1H, d, $J=4$), 5.70 (1H, s)

a) Electron impact mass spectrum (M^+). b) Measured in $\text{DMSO}-d_6$.

stirred for 15 min at below -5°C , then diluted with ice- H_2O (80 ml) under stirring for 30 min. The separated crystals were collected, washed with H_2O , and dried. Recrystallization from DMF gave **4B** (0.79 g) as colorless needles.

The following compound (11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-21-mercapto-4-pregnene-3,20-dione (**4C**)) was similarly prepared.

TABLE VII. Spectral Data for **4** and **5**

Compd. No.	IR cm^{-1}	SIMS m/z (MH^+)	$^1\text{H-NMR}$ δ (ppm, $J=\text{Hz}$) in CDCl_3
4A	3420 1725 1655	469	0.90 (3H, s), 1.14 (3H, s), 1.43 (3H, s), 1.52 (3H, s), 2.05 (1H, dd, $J=8, 6$), 3.42, 3.79 (2H, each dd, $J=17, 7$), 4.44 (1H, m), 5.05 (1H, d, $J=5$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.11 (1H, dd, $J=10, 2$)
4B	3325 2540 1713 1645	433	0.85 (3H, s), 1.08 (3H, s), 1.38 (3H, s), 1.43 (3H, s), 2.04 (1H, t, $J=7$), 3.41, 3.81 (2H, each dd, $J=18, 7$), 4.38 (1H, m), 5.01 (1H, d, $J=4$), 5.96 (1H, brs), 6.20 (1H, dd, $J=10, 2$), 7.33 (1H, d, $J=10$)
4C	3370 2540 1710 1650	435	0.89 (3H, s), 1.15 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 3.42, 3.83 (2H, each dd, $J=18, 7$), 4.51 (1H, m), 5.08 (1H, d, $J=4$), 5.72 (1H, s)
5Aa	3360 1700 1660	541	0.91 (3H, s), 1.17 (3H, s), 1.32 (3H, t, $J=7$), 1.44 (3H, s), 1.54 (3H, s), 3.89, 4.14 (2H, each d, $J=18$), 4.30 (2H, q, $J=7$), 4.45 (1H, m), 5.05 (1H, d, $J=4$), 5.40 (1H, dm, $J=48$), 6.40 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.14 (1H, d, $J=10$)
5Ab	3360 1710 1660	569	0.91 (3H, s), 0.94 (3H, t, $J=8$), 1.17 (3H, s), 1.44 (3H, s), 1.53 (3H, s), 3.88, 4.24 (2H, each d, $J=18$), 4.45 (1H, m), 5.05 (1H, d, $J=5$), 5.40 (1H, dm, $J=48$), 6.39 (1H, dd, $J=10, 2$), 6.46 (1H, s), 7.14 (1H, dd, $J=10, 2$)
5Ba	3330 1715 1645	447	0.95 (3H, s), 1.15 (3H, s), 1.42 (3H, s), 2.18 (3H, s), 3.52, 3.54 (2H, each d, $J=16$), 4.51 (1H, m), 5.03 (1H, d, $J=4$), 6.04 (1H, brs), 6.29 (1H, dd, $J=10, 2$), 7.27 (1H, d, $J=10$)
5Bb	3360 1715 1652	461	0.93 (3H, s), 1.13 (3H, s), 1.25 (3H, t, $J=7$), 1.40 (3H, s), 1.43 (3H, s), 2.50–2.70 (2H, m), 3.48, 3.59 (2H, each d, $J=16$), 4.50 (1H, m), 5.00 (1H, d, $J=4$), 6.02 (1H, brs), 6.27 (1H, dd, $J=10, 2$), 7.23 (1H, d, $J=10$)
5Bc	3320 1707 1650	491	0.91 (3H, s), 1.16 (3H, s), 1.43 (3H, s), 1.45 (3H, s), 3.83 (3H, s), 3.86, 4.17 (2H, each d, $J=18$), 4.52 (1H, m), 5.03 (1H, d, $J=4$), 6.04 (1H, brs), 6.29 (1H, dd, $J=10, 2$), 7.26 (1H, d, $J=10$)
5Bd	3330 1710 1685 1645	505	0.90 (3H, s), 1.15 (3H, s), 1.30 (3H, t, $J=6$), 1.42 (3H, s), 1.44 (3H, s), 3.84, 4.16 (2H, each d, $J=18$), 4.28 (2H, q, $J=6$), 4.46–4.58 (1H, m), 5.03 (1H, d, $J=4$), 6.04 (1H, brs), 6.28 (1H, dd, $J=10, 2$), 7.27 (1H, d, $J=10$)
5Ca	3400 1715 1650	449	0.93 (3H, s), 1.16 (3H, s), 1.44 (3H, s), 1.45 (3H, s), 2.19 (3H, s), 3.49, 3.60 (2H, each d, $J=16$), 4.50 (1H, m), 5.05 (1H, d, $J=4$), 5.71 (1H, s)
5Cb	3380 1715 1705 1650	493	0.90 (3H, s), 1.18 (3H, s), 1.45 (3H, s), 1.47 (3H, s), 3.84 (3H, s), 3.87, 4.21 (2H, each d, $J=18$), 4.51 (1H, m), 5.06 (1H, d, $J=4$), 5.71 (1H, s)

The physical properties of **4** are summarized in Tables II and VII.

21-Ethoxycarbonylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (5Aa) *N,N*-Diisopropylethylamine (0.24 ml) was added to a solution of **4A** (200 mg) in dry CH_2Cl_2 (60 ml) under ice-cooling. After 10 min, ethyl chloroformate (0.13 ml) was added to the mixture. The resulting solution was stirred under ice-cooling for an additional 0.5 h. The separated organic layer was washed successively with 1% HCl, saturated NaHCO_3 and brine, dried and concentrated. The residual solid was recrystallized from CH_2Cl_2 –hexane to give **5Aa** (220 mg) as colorless leaflets.

The following compounds (21-butoxycarbonylthio-6 α ,9 α -difluoro-11 β -hydroxy-16 α ,17 α -isopropylidenedioxy-1,4-pregnadiene-3,20-dione (**5Ab**),

TABLE VIII. Spectral Data for 6

Compd. No.	IR cm ⁻¹	SIMS m/z (MH ⁺)	¹ H-NMR δ (ppm, J=Hz) in CDCl ₃
6Aa	3380 1705 1660	515	0.95 (3H, s), 1.18 (3H, s), 1.44 (3H, s), 1.54 (3H, s), 2.50 (3H, s), 3.77, 4.02 (2H, each d, J=17), 4.44 (1H, m), 5.06 (1H, d, J=7), 5.41 (1H, dm, J=48), 6.37 (1H, dd, J=10, 2), 6.45 (1H, s), 7.14 (1H, dd, J=10, 2)
6Ab	3340 1720 1660	528 ^{a)}	0.95 (3H, s), 1.17 (3H, s), 1.35 (3H, t, J=8), 1.43 (3H, s), 1.53 (3H, s), 2.81 (2H, q, J=8), 3.77, 4.01 (2H, each d, J=16), 4.45 (1H, m), 5.05 (1H, d, J=4), 5.40 (1H, dm, J=48), 6.39 (1H, dd, J=10, 2), 6.47 (1H, s), 7.14 (1H, dd, J=10, 2)
6Ac	3380 1720 1660	542 ^{a)}	0.94 (3H, s), 1.01 (3H, t, J=7), 1.17 (3H, s), 1.43 (3H, s), 1.54 (3H, s), 2.78 (2H, t, J=7), 3.76, 4.00 (2H, each d, J=16), 4.44 (1H, m), 5.05 (1H, d, J=4), 5.40 (1H, dm, J=48), 6.39 (1H, dd, J=10, 2), 6.46 (1H, s), 7.13 (1H, dd, J=10, 2)
6Ad	3380 1660	543	0.94 (3H, s), 1.17 (3H, s), 1.32 (3H, d, J=7), 1.33 (3H, d, J=7), 1.44 (3H, s), 1.53 (3H, s), 3.14 (1H, m), 3.76, 4.00 (2H, each d, J=16), 4.44 (1H, m), 5.05 (1H, d, J=5), 5.40 (1H, dm, J=48), 6.39 (1H, dd, J=10, 2), 6.46 (1H, s), 7.13 (1H, dd, J=10, 2)
6Ca	3380 1710 1650	495	0.92 (3H, s), 1.17 (3H, s), 1.35 (3H, t, J=7), 1.44 (3H, s), 1.45 (3H, s), 2.82 (2H, q, J=7), 3.76, 4.05 (2H, each d, J=16), 4.51 (1H, m), 5.06 (1H, d, J=5), 5.72 (1H, br s)

a) See footnote a in Table VI.

11β-hydroxy-16α,17α-isopropylidenedioxy-21-methylthio-1,4-pregnadiene-3,20-dione (5Ba), 21-ethylthio-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (5Bb), 11β-hydroxy-16α,17α-isopropylidenedioxy-21-methoxycarbonylthio-1,4-pregnadiene-3,20-dione (5Bc), 21-ethoxycarbonylthio-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (5Bd), 11β-hydroxy-16α,17α-isopropylidenedioxy-21-methylthio-4-pregnene-3,20-dione (5Ca) and 11β-hydroxy-16α,17α-isopropylidenedioxy-21-methoxycarbonylthio-4-pregnene-3,20-dione (5Cb) were similarly prepared. The physical properties of 5Aa, 5Ab, 5Ba—d, 5Ca and 5Cb are summarized in Tables II and VII.

6α,9α-Difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-methylthio-1,4-pregnadiene-3,20-dione (6Aa) N-Methylthiophthalimide (400

mg) was added to a solution of 4A (270 mg) in CH₂Cl₂ (60 ml) with stirring. The mixture was stirred at room temperature for 5 h. The reaction mixture was evaporated to give a residue, which was purified by column chromatography using CHCl₃ as an eluent. The product was recrystallized from CH₂Cl₂-hexane to give 6Aa (260 mg) as colorless needles.

The following compounds (21-ethylthio-6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione (6Ab), 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-propyldithio-1,4-pregnadiene-3,20-dione (6Ac), 6α,9α-difluoro-11β-hydroxy-16α,17α-isopropylidenedioxy-21-isopropyldithio-1,4-pregnadiene-3,20-dione (6Ad) and 21-ethylthio-11β-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (6Ca)) were similarly prepared. The physical properties of 6 are summarized in Tables III and VIII.

References and Notes

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