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Studies on Topical Antiinflammatory Agents. I. Synthesis and Vasoconstrictive Activity of Corticosteroid 17-Succinyl Esters

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A series of 17-succinyl derivatives of four corticosteroids was prepared. They were tested for vasoconstrictive activity in humans, using 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV) as a standard. The activities of the 21-chloro 17-methylsuccinate compounds (6A, 6C and 6D) were greater than that of BV. A structure–activity relationship study showed that the activities of the 21-chloro 17-methylsuccinates were more potent than those of the corresponding 21-esters.

Keywords corticosteroid; antiinflammatory agent; vasoconstrictive activity; 21-chloro-17α-(3-methoxycarbonyl)propanoyloxy corticosteroid; structure–activity relationship

Introduction

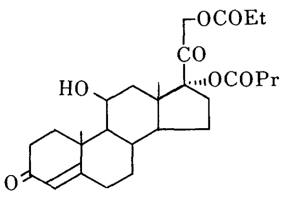
Since the first topical administration of hydrocortisone[1] 21-acetate in the dermatological field,[2] various chemical modifications of corticosteroids have been carried out with the aim of enhancing the antiinflammatory activity.

Many corticosteroids are widely used clinically for a variety of skin diseases. Hydrocortisone 17-butyrate 21-propionate[3] (Fig. 1) was recently introduced by us in this category. We have continued to prepare other novel 17-ester derivatives of corticosteroids, and in this paper we describe the preparation and vasoconstrictive activity of a new series of 17-succinyl derivatives of corticosteroids.

Chemistry The corticosteroid 17-alkylsuccinates listed in Tables I and II were prepared by the route shown in Chart 1. Four 17-ortho-esters (**2A**—**D**) were prepared from the corresponding corticosteroids, namely hydrocortisone (**1A**), prednisolone (**1B**), dexamethasone (**1C**) and betamethasone (**1D**), respectively, by exchange reaction with methyl 3,3,3-trimethoxypropanoate[4] in benzene–dimethylformamide (DMF) according to the method described by Gardi *et al.*[5] Their acid-catalyzed hydrolysis with aqueous acetic acid in MeOH gave the 17-methylsuccinates (**3A**—**D**). The four compounds (**3A**—**D**) were acylated with the appropriate acid anhydride in pyridine to give the corresponding 21-esters (**4A**—**D**).

On the other hand, 21-halo 17-methylsuccinate derivatives (**6**—**8**) were prepared by mesylation with MsCl, followed by halogenation with lithium halides in CH_3CN–DMF. The other 17-alkylsuccinates (**9A**—**D**) were prepared by heating of the 17-methylsuccinates (**6A**—**D**) in the presence of concentrated H_2SO_4 in the corresponding alcohol (Chart 2). The yields, melting points and analytical data for the compounds are summarized in Tables I and II.

Safety of the Compounds Tested Before application to



hydrocortisone 17-butyrate 21-propionate

Fig. 1

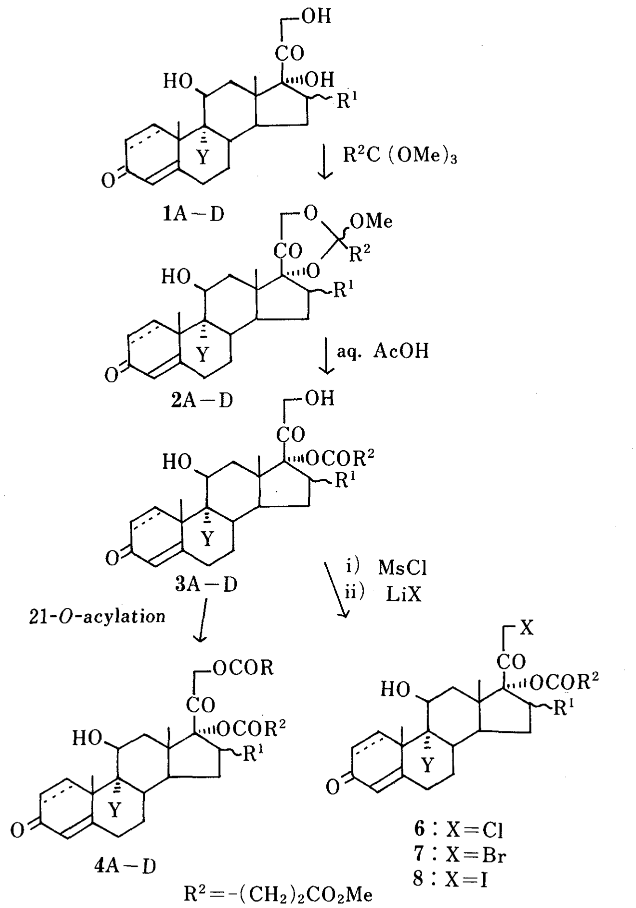
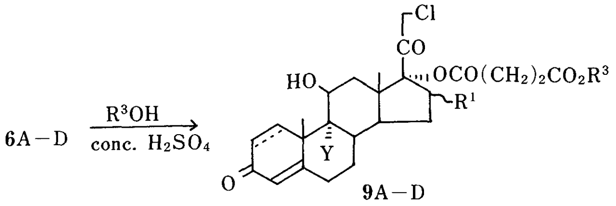


Chart 1



	Y	R¹	C¹-C²
A	H	H	—
B	H	H	△
C	F	α-Me	△
D	F	β-Me	△

Chart 2

TABLE I. Physical Data for **3** and **4**

Compd. No.	R	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd F	Found C	Found H	Found F
3A	—	74	86—89	M–O	$C_{26}H_{36}O_8$	65.53	7.61		65.26	7.44	
3B	—	67	173—174	A–I	$C_{26}H_{34}O_8$	65.80	7.22		65.90	7.25	
3C	—	87	147—150	A–P	$C_{27}H_{35}FO_8$	64.02	6.96	3.75	63.89	6.98	3.50
3D	—	83	228—230	M	$C_{27}H_{35}FO_8$	64.02	6.96	3.75	64.12	7.01	3.51
4Aa	Me	80	137	E–O	$C_{28}H_{38}O_9$	64.85	7.39		64.59	7.36	
4Ab	Et	80	88—89	E–O	$C_{29}H_{40}O_9 \cdot 1/2\,H_2O$	64.31	7.63		64.56	7.64	
4Ac	Pr	70	165—167	PhH–H	$C_{30}H_{42}O_9$	65.91	7.75		65.85	7.78	
4Ad	$(CH_2)_2CO_2Me$	40	121—126	E–O	$C_{31}H_{42}O_{11}$	63.03	7.17		62.69	7.17	
4Ba	Me	78	157.5—160	A–I	$C_{28}H_{36}O_9$	65.10	7.03		65.36	7.10	
4Bb	Et	89	76—79	A–I	$C_{29}H_{38}O_9$	65.64	7.22		65.57	7.32	
4Bc	Pr	78	138—139	A–I	$C_{30}H_{40}O_9$	66.16	7.40		66.10	7.60	
4Ca	Me	92	90—93	E–O	$C_{29}H_{37}FO_9 \cdot 1/4\,H_2O$	62.97	6.84	3.44	62.90	6.73	3.34
4Cb	Et	77	94—97	E–O	$C_{30}H_{39}FO_9 \cdot 1/4\,H_2O$	63.53	7.03	3.35	63.37	7.00	3.24
4Cc	Pr	83	96—98	E–O	$C_{31}H_{41}FO_9$	64.57	7.17	3.29	64.47	7.24	3.40
4Da	Me	87	90—92	E–O	$C_{29}H_{37}FO_9 \cdot 1/2\,H_2O$	62.46	6.87	3.41	62.18	6.71	3.49
4Db	Et	85	Amorphous		$C_{30}H_{39}FO_9 \cdot 1/2\,H_2O$	63.03	7.05	3.32	63.15	7.10	3.50
4Dc	Pr	81	Amorphous		$C_{31}H_{41}FO_9 \cdot 1/2\,H_2O$	63.57	7.23	3.24	63.72	7.19	3.42

a) Solvents for recrystallization: A = acetone, E = ethanol, H = hexane, I = isopropyl ether, M = methanol, O = H_2O, P = petroleum ether.

TABLE II. Physical Data for **6**, **7**, **8** and **9**

Compd. No.	R^3	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula	Analysis (%) Calcd C	Calcd H	Calcd Cl	Calcd F	Found C	Found H	Found Cl	Found F
6A	—	72	154—155.5	E	$C_{26}H_{35}ClO_7$	63.09	7.13	7.16		62.92	6.90	7.25	
6B	—	85	221.5—223	E–O	$C_{26}H_{33}ClO_7$	63.34	6.75	7.19		63.20	6.64	7.32	
6C	—	80	213—214	E	$C_{27}H_{34}ClFO_7$	61.77	6.53	6.75	3.62	61.71	6.56	6.48	3.57
6D	—	82	213—215	E	$C_{27}H_{34}ClFO_7$	61.77	6.53	6.75	3.62	61.58	6.42	6.45	3.61
7A	—	73	176—180	E–O	$C_{26}H_{35}BrO_7$	57.89	6.54			58.40	6.59		
7B	—	55	191—194	E–O	$C_{26}H_{33}BrO_7$	58.10	6.19			58.13	6.08		
8A	—	47	137—139	AcOEt–H	$C_{26}H_{35}IO_7 \cdot CH_3CO_2Et$	53.41	6.43			53.82	5.98		
9Aa	Et	88	122—123	E–O	$C_{27}H_{37}ClO_7$	63.71	7.33	6.96		63.53	7.42	6.75	
9Ab	Pr	80	134—136	Et_2O–H	$C_{28}H_{39}ClO_7$	64.30	7.52	6.78		64.17	7.35	6.96	
9Ac	Bu	40	73—76	E–O	$C_{29}H_{41}ClO_7$	64.85	7.70	6.60		64.93	7.71	6.48	
9Ad	Cyclohexyl	39	90—93	E–O	$C_{31}H_{43}ClO_7$	66.11	7.70	6.30		66.27	7.84	6.48	
9Ba	Et	68	120—122	E–O	$C_{27}H_{35}ClO_7$	63.96	6.96	6.99		63.94	6.90	7.03	
9Bb	iso-Pr	65	164—167	E–O	$C_{28}H_{37}ClO_7$	64.54	7.16	6.80		64.60	7.11	6.64	
9Bc	iso-Bu	42	157—160	E–O	$C_{29}H_{39}ClO_7$	65.09	7.35	6.63		64.86	7.20	6.58	
9Bd	Cyclopentyl	38	154—156	E–O	$C_{30}H_{39}ClO_7$	65.86	7.19	6.48		65.55	7.03	6.59	
9Ca	Et	33	143—145	E	$C_{28}H_{36}ClFO_7$	62.38	6.73	6.58	3.52	62.11	6.50	6.23	3.51
9Cb	Bu	30	91	E–O	$C_{30}H_{40}ClFO_7$	63.52	7.11	6.25	3.35	63.83	7.24	6.58	3.29
9Cc	Cyclohexyl	55	117—120	E–O	$C_{32}H_{42}ClFO_7$	64.42	7.04	5.98	3.20	64.34	6.98	6.38	3.15
9Da	Et	72	185—187	E	$C_{28}H_{36}ClFO_7$	62.38	6.73	6.58	3.52	62.28	6.70	6.73	3.71
9Db	Pr	60	92—95	E–O	$C_{29}H_{38}ClFO_7$	62.97	6.92	6.40	3.43	63.20	7.04	6.66	3.45
9Dc	iso-Pr	71	158—161	E	$C_{29}H_{38}ClFO_7$	62.97	6.92	6.40	3.43	63.09	6.93	6.69	3.46
9Dd	Bu	53	87—91	E–O	$C_{30}H_{40}ClFO_7$	63.52	7.11	6.25	3.35	63.38	7.12	6.34	3.45
9De	iso-Bu	81	95—98	E–O	$C_{30}H_{40}ClFO_7$	63.52	7.11	6.25	3.35	63.30	6.89	6.17	3.22
9Df	Cyclopentyl	74	182—185	E	$C_{31}H_{40}ClFO_7$	64.28	6.96	6.12	3.28	64.47	7.04	6.12	2.96
9Dg	Cyclohexyl	21	97—101	E–O	$C_{32}H_{42}ClFO_7$	64.78	7.14	5.98	3.20	64.54	6.87	5.90	3.23

a) See footnote *a*) in Table I.

volunteers, the safety of all the compounds was checked by the method reported previously.[3b)]

Results and Discussion

Primary Skin-Irritating Activity As shown in Table III, the mean score of all the compounds was less than 1.00 in the Draize method.[6)] It was considered that the compounds do not cause primary skin irritation.

Mutagenicity As shown in Table III, all the compounds tested were negative in Ames' spot test.[7)]

Thus, no significant toxic signs were observed in the primary skin irritation or 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 basic of animal studies may be much less potent than expected in

Table III. Primary Skin-Irritating Activity and Mutagenicity of Compounds **3**, **4**, **6**, **7** and **9**

Compd. No.	Primary skin irritation mean value[a]	Mutagenicity *S. typhimurium*		Compd. No.	Primary skin irritation mean value[a]	Mutagenicity *S. typhimurium*	
		TA98	TA100			TA98	TA100
3A	0.29	–	–	**6**B	0.35	–	–
3B	0.51	–	–	**6**C	0.32	–	–
3C	0.25	–	–	**6**D	0.10	–	–
3D	0.50	–	–	**7**A	0.43	–	–
4Aa	0.39	–	–	**7**B	0.47	–	–
4Ab	0.32	–	–	**9**Ab	0.30	–	–
4Ac	0.18	–	–	**9**Ac	0.32	–	–
4Ad	0.25	–	–	**9**Ad	0.57	–	–
4Ba	0.60	–	–	**9**Ba	0.40	–	–
4Bb	0.61	–	–	**9**Bb	0.18	–	–
4Bc	0.89	–	–	**9**Bc	0.43	–	–
4Cb	0.21	–	–	**9**Bd	0.42	–	–
4Cc	0.33	–	–	**9**Da	0.14	–	–
4Da	0.60	–	–	**9**Db	0.17	–	–
4Db	0.71	–	–	**9**Dc	0.17	–	–
4Dc	0.83	–	–	**9**Dd	0.15	–	–
6A	0.28	–	–	**9**De	0.15	–	–
				9Df	0.17	–	–
				9Dg	0.17	–	–
4NQO[b]		+	+	2NF[c]		+	/
				ENNG[d]		/	+

a) The degrees of irritation assessed after 6, 24 and 48 h in rabbits according to Draize's criterion[6] were scored and averaged. *b*) 4-Nitroquinoline-*N*-oxide. *c*) 2-Nitrofluorene. *d*) *N*-Ethyl-*N*′-nitro-*N*-nitrosoguanidine.

humans. Only the vasoconstriction activity test is considered to be reliable for predicting the antiinflammatory potency of topical corticosteroids,[8] because a remarkably good correlation had been found to exist between the result of this test and the topical efficacy in the clinic.[9] Using this method, for instance, clobetasol propionate[10] and betamethasone 17-valerate[11] (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.[8]

Thirty-six selected compounds (**4**, **6**, **7** and **9**) were tested for vasoconstrictive activities in humans. The compounds tested were divided into four groups. Preparations of 0.1% (w/w) vaseline ointment of the compounds were applied at random with the closed patch method (Finn chamber, Epitest Ltd., Oy) to the flexural aspects of both arms of 20 healthy male volunteers for 4 h. The vasoconstriction reading was performed at 2 and 4 h after removal of the ointment. For the grading of blanching phenomenon, a scoring system was used as follows; 0 = no blanching, 1 = slight, 2 = moderate, 3 = marked. The scores were averaged, and the ratios of the compounds to that of BV were calculated. Statistical analysis was performed by using Wilcoxon's rank test.[12] The results are summarized in Table IV.

As shown in Table IV, the 17-methylsuccinates (**3**A—D) were weakly active. Most of the 17, 21-diesters (**4**) showed higher activities than the corresponding 17-monoesters (**3**). Among these compounds, the 21-propionate (**4**Cb) and the 21-butyrates (**4**Cc and **4**Dc) exhibited relatively higher activities, but the activities were still weaker than that of BV.

Table IV. Vasoconstrictive Activity Ratios of Compounds **3**, **4**, **6**, **7** and **9** with Respect to Betamethasone 17-Valerate (BV)

	Compd. **3** and **4** After 2 h	Compd. **3** and **4** After 4 h		Compd. **6**, **7** and **9** After 2 h	Compd. **6**, **7** and **9** After 4 h
3A	24[d]	31[d]	**6**A	136[b]	115
3B	15[d]	21[d]	**6**B	86	85
3C	47[c]	38[d]	**6**C	123	124
3D	41[d]	36[d]	**6**D	141[a]	118
4Aa	35[d]	26[d]	**7**A	91	55[b]
4Ab	18[d]	21[d]	**7**B	54[a]	31[d]
4Ac	29[d]	26[d]	**9**Ab	64	50[d]
4Ad	32[d]	10[d]	**9**Ac	105	100
4Ba	24[d]	33[d]	**9**Ad	57[a]	47[d]
4Bb	29[d]	44[d]	**9**Ba	77	106
4Bc	47[c]	41[d]	**9**Bb	86	73
4Cb	79	38[d]	**9**Bc	79	31[d]
4Cc	71	51[d]	**9**Bd	77	82
4Da	56[b]	41[d]	**9**Da	61	17[d]
4Db	44[d]	36[d]	**9**Db	61	25[d]
4Dc	74	79	**9**Dc	72	33[d]
			9Dd	39[c]	25[d]
			9De	44[b]	33[d]
			9Df	50	29[d]
			9Dg	50	21[d]

Each compound was tested on 20 volunteers. The potency is expressed as the ratio of vasoconstrictive activity to that of BV taken as 100. *a*) $p<0.1$. *b*) $p<0.05$. *c*) $p<0.02$. *d*) $p<0.01$ with respect to BV, using Wilcoxon's rank test.[12]

On the other hand, in the series of 21-halo 17-methylsuccinates, the activities of five compounds, **6**A, **6**C, **6**D, **9**Ac and **9**Ba were equal to or higher than that of BV. The 21-chloro derivatives (**6**A and **6**B) were more active than the corresponding 21-bromo derivatives (**7**A and **7**B). Among the compounds tested, **6**D showed the greatest potency at 2 h. In terms of the activities at 4 h, **6**C was the most potent.

In general, replacement of a 21-acyloxy function with a chlorine atom can lead to more active corticosteroids, such as the clinically used clobetasol propionate[10] or halcinonide.[13] Our results in this series of 21-chloro-17-esters are consistent with this well-known structure–activity relationship.

Conversion of the terminal methyl ester group of **6D** into larger alkyl groups (**9Da**—**9De**) and cycloalkyl groups (**9Df** and **9Dg**) tended to decrease the activity, but the activity of the 17-butyl succinate (**9Ac**) was comparable to that of BV. In the case of prednisolone derivatives (**9Bb**, **9Bc** and **9Bd**), their activities were relatively weak compared with that of BV, the only exception being the 17-ethylsuccinate (**9Ba**), whose activity at 4 h was comparable to that of BV.

These results indicate that the size of the terminal substituent at the 17-position influences vasoconstrictive activity. The optimal size was that of the methyl group in this series. In addition, there might be rather severe structural requirements interdependently at the 17- and 21-positions of corticosteroids for the activity.

However, introduction of the methylsuccinate function into the 17-position of corticosteroids resulted in significant enhancement of the activity. Among the compounds tested in this study, the most active, **6A**, **6C** and **6D**, were selected for further pharmacological studies.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained with a Hitachi Perkin-Elmer R-20 or a Varian XL-200 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. The mass spectra (MS) were taken with a Hitachi M-80A spectrometer for secondary ionization (SI), and a JEOL DX-303 for fast atom bombardment (FAB). The extracted organic solutions were dried over Na_2SO_4. Column chromatography was carried out on Wakogel C-200.

11β-Hydroxy-17α,21-(1-methoxy-3-methoxycarbonylpropylidenedioxy)-4-pregnene-3,20-dione (2A) Methyl 3,3,3-trimethoxypropanoate (20 g) was added to a stirred mixture of hydrocortisone (**1A**, 30 g) in benzene (250 ml) and DMF (25 ml) followed by the addition of *p*-toluenesulfonic acid (0.2 g), and the mixture was refluxed for 4 h. After the addition of pyridine (1 ml), the mixture was concentrated and the residue was recrystallized from MeOH to give colorless needles (35 g, 86%). mp 153—155 °C. IR (KBr): 3460, 1730, 1710, 1665 cm^{-1}. NMR δ: 0.88 (3H, s), 1.43 (3H, s), 3.23 (3H, s), 3.68 (3H, s), 3.96, 4.16 (2H, each d, J=16), 4.50 (1H, m), 5.71 (1H, s). FAB-MS m/z: 491 (M^++1). *Anal.* Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 66.27; H, 7.93.

Compounds **2B**, **2C** and **2D** were similarly prepared.

11β-Hydroxy-17α,21-(1-methoxy-3-methoxycarbonylpropylidenedioxy)-1,4-pregnadiene-3,20-dione (**2B**): Amorphous. Yield 99%. IR (KBr): 3420, 1730, 1650 cm^{-1}. NMR δ: 0.92 (3H, s), 1.46 (3H, s), 3.24 (3H, s), 3.66 (3H, s), 3.96, 4.16 (2H, each d, J=16), 4.54 (1H, m), 6.05 (1H, s), 6.32 (1H, dd, J=10,2), 7.30 (1H, d, J=10). FAB-MS m/z: 489 (M^++1). *Anal.* Calcd for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43. Found: C, 66.45; H, 7.29.

9α-Fluoro-11β-hydroxy-17α,21-(1-methoxy-3-methoxycarbonylpropylidenedioxy)-16α-methyl-1,4-pregnadiene-3,20-dione (**2C**): mp 209—212 °C (from MeOH). Yield 76%. IR (KBr): 3280, 1740, 1725, 1655 cm^{-1}. NMR δ: 0.90 (3H, d, J=7), 0.97 (3H, s), 1.55 (3H, s), 3.24 (3H, s), 3.67 (3H, s), 3.95, 4.08 (2H, each d, J=16), 4.45 (1H, m), 6.15 (1H, s), 6.38 (1H, dd, J=10, 2), 7.25 (1H, d, J=10). FAB-MS m/z: 521 (M^++1). *Anal.* Calcd for $C_{28}H_{37}FO_8$: C, 64.60; H, 7.17; F, 3.65. Found: C, 64.52; H, 7.21; F, 3.70.

9α-Fluoro-11β-hydroxy-17α,21-(1-methoxy-3-methoxycarbonylpropylidenedioxy)-16β-methyl-1,4-pregnadiene-3,20-dione (**2D**): mp 199—201.5 °C (from MeOH). Yield 87%. IR (KBr): 3280, 1730, 1660 cm^{-1}. NMR δ: 0.98 (3H, s), 1.14 (3H, d, J=7), 1.53 (3H, s), 3.23 (3H, s), 3.63 (3H, s), 3.94 (2H, br s), 4.36 (1H, m), 6.10 (1H, s), 6.32 (1H, d, J=10), 7.20 (1H, d, J=10). FAB-MS m/z: 521 (M^++1). *Anal.* Calcd for $C_{28}H_{37}FO_8$: C, 64.60; H, 7.17; F, 3.65. Found: C, 64.73; H, 6.97; F, 3.68.

11β,21-Dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (3A) A 5% aqueous AcOH (65 ml) was added to a solution of **2A** (35 g) in MeOH (250 ml). The mixture was refluxed for 6 h and concentrated *in vacuo*. The residue was extracted with AcOEt. The extract was washed with H_2O, dried and concentrated. The residual oil was chromatographed with $CHCl_3$–MeOH (10:1) and the product was recrystallized from aqueous MeOH to give **3A** (29 g) as colorless needles. IR (KBr): 3440, 1735, 1660 cm^{-1}. NMR δ: 0.94 (3H, s), 1.45 (3H, s), 2.62 (4H, s), 3.69 (3H, s), 4.31 (2H, d, J=4), 4.52 (1H, m), 5.72 (1H, s). FAB-MS m/z: 477 (M^++1).

Compounds **3B**, **3C** and **3D** were similarly prepared.

11β,21-Dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**3B**): IR (KBr): 3450, 1735, 1650 cm^{-1}. NMR δ: 0.96 (3H, s), 1.46 (3H, s), 2.60 (4H, s), 3.68 (3H, s), 4.30 (2H, s), 4.55 (1H, m), 6.06 (1H, s), 6.32 (1H, dd, J=10, 2), 7.31 (1H, d, J=10). SI-MS m/z: 475 (M^++1).

9α-Fluoro-11β,21-dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (**3C**): IR (KBr): 3400, 1730, 1660 cm^{-1}. NMR δ: 0.97 (3H, d, J=7), 1.02 (3H, s), 1.55 (3H, s), 3.66 (3H, s), 4.30 (2H, s), 4.42 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, J=10, 2), 7.27 (1H, d, J=10). SI-MS m/z: 507 (M^++1).

9α-Fluoro-11β,21-dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**3D**): IR (KBr): 3430, 1725, 1660 cm^{-1}. NMR δ: 0.96 (3H, s), 1.40 (3H, d, J=7), 1.56 (3H, s), 3.68 (3H, s), 4.03, 4.18 (2H, each dd, J=16, 4), 4.44 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.24 (1H, d, J=10). SI-MS m/z: 507 (M^++1).

21-Acetoxy-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (4Aa) Acetic anhydride (0.26 ml) was added to **3A** (1.0 g) in dry pyridine (5 ml) under ice-cooling. The reaction mixture was allowed to stand overnight at room temperature and then poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% HCl, H_2O and brine, then dried and concentrated *in vacuo*. The residue was chromatographed with $CHCl_3$–MeOH (10:1) and the product was recrystallized from aqueous EtOH to give **4Aa** (0.87 g) as a colorless powder. IR (KBr): 3460, 1730, 1660, 1650 cm^{-1}. NMR δ: 1.00 (3H, s), 1.45 (3H, s), 2.17 (3H, s), 3.69 (3H, s), 4.51 (1H, m), 4.69, 4.90 (2H, each d, J=16), 5.71 (1H, s). FAB-MS m/z: 519 (M^++1).

Other compounds (**4**) were similarly prepared.

11β-Hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-21-propanoyloxy-4-pregnene-3,20-dione (**4Ab**): IR (KBr): 3400, 1730, 1655 cm^{-1}. NMR δ: 1.01 (3H, s), 1.18 (3H, t, J=7), 1.45 (3H, s), 2.48 (2H, q, J=7), 3.69 (3H, s), 4.51 (1H, m), 4.69, 4.93 (2H, each d, J=16), 5.71 (1H, s). FAB-MS m/z: 533 (M^++1).

21-Butanoyloxy-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (**4Ac**): IR (KBr): 3360, 1730, 1650 cm^{-1}. NMR δ: 0.98 (3H, t, J=7), 1.01 (3H, s), 1.46 (3H, s), 2.46 (2H, q, J=7), 3.69 (3H, s), 4.51 (1H, m), 4.69, 4.93 (2H, each d, J=17), 5.71 (1H, s). FAB-MS m/z: 547 (M^++1).

11β-Hydroxy-17α,21-bis[(3-methoxycarbonyl)propanoyloxy]-4-pregnene-3,20-dione (4Ad) Compound **3A** was treated with succinic anhydride in pyridine, then the crude product was treated with CH_2N_2 in MeOH under ice-cooling for 1 h to afford the title compound as a colorless powder. IR (KBr): 3500, 1735, 1660 cm^{-1}. NMR δ: 0.99 (3H, s), 1.46 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 4.50 (1H, m), 4.67, 4.96 (2H, each d, J=16), 5.71 (H, s). FAB-MS m/z: 591 (M^++1).

21-Acetoxy-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**4Ba**): IR (KBr): 3380, 1730, 1650 cm^{-1}. NMR δ: 1.02 (3H, s), 1.46 (3H, s), 2.18 (3H, s), 3.67 (3H, s), 4.53 (1H, m), 4.69, 4.91 (2H, each d, J=16), 6.05 (1H, s), 6.31 (1H, dd, J=10, 2), 7.29 (1H, d, J=10). FAB-MS m/z: 517 (M^++1).

11β-Hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-21-propanoyloxy-1,4-pregnadiene-3,20-dione (**4Bb**): IR (KBr): 3400, 1730, 1650 cm^{-1}. NMR δ: 1.03 (3H, s), 1.18 (3H, d, J=7), 1.47 (3H, s), 2.48 (2H, q, J=7), 3.67 (3H, s), 4.53 (1H, m), 4.68, 4.93 (2H, each d, J=16), 6.05 (1H, s), 6.30 (1H, dd, J=10, 2), 7.29 (1H, d, J=10). FAB-MS m/z: 531 (M^++1).

21-Butanoyloxy-11β-hydroxy-17α-(3-methoxycarbonyl) propanoyloxy-1,4-pregnadiene-3,20-dione (**4Bc**): IR (KBr): 3380, 1740, 1650 cm^{-1}. NMR δ: 0.98 (3H, t, J=7), 1.10 (3H, s), 1.55 (3H, s), 2.43 (2H, d, J=7), 3.66 (3H, s), 4.40 (1H, m), 4.84 (2H, s), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.22 (1H, d, J=10). FAB-MS m/z: 545 (M^++1).

21-Acetoxy-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (**4Ca**): IR (KBr): 3380, 1725, 1655 cm^{-1}. NMR δ: 0.96 (3H, d, J=7), 1.09 (3H, s), 1.55 (3H, s), 1.83 (3H, s), 2.19 (3H, s), 3.66 (3H, s), 4.41 (1H, m), 4.84 (2H, s), 6.15 (1H, s), 6.36 (1H, dd, J=10, 2), 7.23 (1H, d, J=10). FAB-MS m/z: 549 (M^++1).

9α-Fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (**4Cb**): IR (KBr): 3420, 1730, 1660 cm^{-1}. NMR δ: 0.97 (3H, d, J=7), 1.11 (3H, s), 1.19 (3H, t, J=7), 1.55 (3H, s), 2.50 (2H, q, J=7), 3.66 (3H, s), 4.42 (1H, m), 4.85

(2H, s), 6.16 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$). FAB-MS m/z: 563 ($M^+ + 1$).

21-Butanoyloxy-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (**4Cc**): IR (KBr): 3360, 1730, 1655 cm^{-1}. NMR δ: 0.98 (3H, t, $J=8$), 1.02 (3H, s), 1.46 (3H, s), 1.70 (2H, q, $J=8$), 2.42 (2H, q, $J=7$), 3.67 (3H, s), 4.52 (1H, m), 4.66, 4.92 (2H, each d, $J=16$), 6.04 (1H, s), 6.30 (1H, dd, $J=10$, 2), 7.29 (1H, d, $J=10$). FAB-MS m/z: 577 ($M^+ + 1$).

21-Acetoxy-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**4Da**): IR (KBr): 3420, 1730, 1660 cm^{-1}. NMR δ: 0.99 (3H, s), 1.34 (3H, d, $J=8$), 1.56 (3H, s), 2.17 (3H, s), 3.68 (3H, s), 4.41 (1H, m), 4.42, 4.88 (2H, each d, $J=16$), 6.15 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$). FAB-MS m/z: 549 ($M^+ + 1$).

9α-Fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (**4Db**): IR (KBr): 3420, 1735, 1660 cm^{-1}. NMR δ: 0.99 (3H, s), 1.17 (3H, t, $J=7$), 1.34 (3H, d, $J=8$), 1.56 (3H, s), 3.68 (3H, s), 4.41 (1H, m), 4.42, 4.88 (2H, each d, $J=16$), 6.15 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$). FAB-MS m/z: 563 ($M^+ + 1$).

21-Butanoyloxy-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**4Dc**): IR (KBr): 3420, 1730, 1660 cm^{-1}. NMR δ: 0.98 (3H, s), 0.99 (3H, t, $J=8$), 1.34 (3H, d, $J=8$), 1.56 (3H, s), 1.70 (2H, q, $J=8$), 3.68 (3H, s), 4.40, 4.90 (2H, each d, $J=16$), 4.41 (1H, m), 6.14 (1H, s), 6.37 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$). FAB-MS m/z: 577 ($M^+ + 1$).

11β,21-Dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione 21-Methanesulfonate (5A) Mesyl chloride (14 g) was added to a solution of compound **3A** (29 g) in dry pyridine (150 ml) under ice-cooling with stirring. The reaction mixture was stirred for 1.5 h and then poured into ice-water and extracted with AcOEt. The extract was washed successively with 10% HCl, H_2O and brine, dried, and concentrated to give the crude product. Recrystallization from acetone–hexane gave colorless needles (28.5 g, 85%). mp 144—145 °C. IR (KBr): 3400, 1730, 1650, 1355 cm^{-1}. NMR δ: 0.98 (3H, s), 1.44 (3H, s), 3.20 (3H, s), 3.70 (3H, s), 4.52 (1H, m), 4.96 (2H, s), 5.72 (1H, s). SI-MS m/z: 555 ($M^+ + 1$).

11β-21-Dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione 21-Methanesulfonate (**5B**): mp 130—132 °C (AcOEt). Yield 74%. IR (KBr): 3360, 1730, 1650, 1355 cm^{-1}. NMR δ: 1.00 (3H, s), 1.46 (3H, s), 3.20 (3H, s), 3.68 (3H, s), 4.55 (1H, m), 4.96 (2H, s), 6.06 (1H, s), 6.32 (1H, dd, $J=10$, 2), 7.30 (1H, d, $J=10$). FAB-MS m/z: 553 ($M^+ + 1$).

9α-Fluoro-11β,21-dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione 21-Methanesulfonate (**5C**): Amorphous. Yield 99%. IR (KBr): 3430, 1735, 1665, 1360 cm^{-1}. NMR δ: 0.93 (3H, d, $J=7$), 1.06 (3H, s), 1.56 (3H, s), 3.21 (3H, s), 3.67 (3H, s), 4.43 (1H, m), 4.88 (2H, s), 6.16 (1H, s), 6.38 (1H, dd, $J=10$, 2), 7.25 (1H, d, $J=10$). SI-MS m/z: 585 ($M^+ + 1$).

9α-Fluoro-11β,21-dihydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione 21-Methanesulfonate (**5D**): Amorphous. Yield 98%. IR (KBr): 3420, 1730, 1660, 1350 cm^{-1}. NMR δ: 1.00 (3H, s), 1.34 (3H, d, $J=7$), 1.55 (3H, s), 2.62 (4H, s), 3.17 (3H, s), 3.65 (3H, s), 4.40 (1H, m), 4.77 (2H, s), 6.12 (1H, s), 6.34 (1H, dd, $J=10$, 2), 7.24 (1H, d, $J=10$). SI-MS m/z: 585 ($M^+ + 1$).

21-Chloro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (6A) Anhydrous lithium chloride (25 g) was added to a solution of **5A** (28 g) in DMF (120 ml) and acetonitrile (140 ml). The mixture was refluxed for 6.5 h, then poured into ice-water, and extracted with AcOEt. The extract was washed with H_2O, dried and concentrated *in vacuo*. The residue was chromatographed with $CHCl_3$–MeOH (10 : 1) and the product was recrystallized from EtOH to give **6A** (17.9 g) as colorless needles. IR (KBr): 3480, 1730, 1720, 1670, 1650 cm^{-1}. NMR δ: 0.97 (3H, s), 1.45 (3H, s), 3.70 (3H, s), 4.16, 4.26 (2H, each d, $J=16$), 4.52 (1H, m), 5.71 (1H, s). SI-MS m/z: 497 ($M^+ + 3$), 496, 495 ($M^+ + 1$).

21-Chloro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**6B**): IR (KBr): 3350, 1740, 1725, 1710, 1640 cm^{-1}. NMR δ: 0.98 (3H, s), 1.48 (3H, s), 2.62 (4H, s), 3.68 (3H, s), 4.19 (2H, s), 4.53 (1H, m), 6.06 (1H, s), 6.30 (1H, dd, $J=10$, 2), 7.35 (1H, d, $J=10$). SI-MS m/z: 495 ($M^+ + 3$), 494, 493 ($M^+ + 1$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16α-methyl-1,4-pregnadiene-3,20-dione (**6C**): IR (KBr): 3410, 1730, 1660, 1650 cm^{-1}. NMR δ: 0.90 (3H, d, $J=8$), 1.05 (3H, s), 1.58 (3H, s), 2.70 (4H, s), 3.70 (3H, s), 4.12 (2H, s), 4.50 (1H, m), 6.21 (1H, d, $J=2$), 6.40 (1H, dd, $J=10$, 2), 7.37 (1H, d, $J=10$). SI-MS m/z: 528 ($M^+ + 4$), 527, 526, 525 ($M^+ + 1$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**6D**): IR (KBr): 3480, 1725, 1660, 1635 cm^{-1}. NMR δ: 1.01 (3H, s), 1.39 (3H, d, $J=7$), 1.57 (3H, s), 3.68 (3H, s), 4.08 (2H, s), 4.44 (1H, m), 6.15 (1H, d, $J=2$), 6.35 (1H, dd, $J=10$, 2), 7.23 (1H, d, $J=10$). SI-MS m/z: 527 ($M^+ + 3$), 526, 525 ($M^+ + 1$).

The following compounds were similarly prepared using the corresponding, lithium halides instead of the chloride.

21-Bromo-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (**7A**): IR (KBr): 3380, 1730, 1710, 1640 cm^{-1}. NMR δ: 0.97 (3H, s), 1.45 (3H, s), 2.65 (4H, s), 3.70 (3H, s), 4.05 (2H, s), 4.50 (1H, m), 5.73 (1H, s). SI-MS m/z: 541 ($M^+ + 3$), 539 ($M^+ + 1$).

21-Bromo-11β-hydroxy-17α-(3-methoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**7B**): IR (KBr): 3350, 1740, 1710, 1640 cm^{-1}. NMR δ: 0.98 (3H, s), 1.47 (3H, s), 2.62 (4H, s), 3.66 (3H, s), 4.01 (2H, s), 4.53 (1H, m), 6.03 (1H, s), 6.28 (1H, dd, $J=10$, 2), 7.30 (1H, d, $J=10$). SI-MS m/z: 540 ($M^+ + 4$), 539, 538, 537 ($M^+ + 1$).

11β-Hydroxy-21-iodo-17α-(3-methoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (**8A**): IR (KBr): 3550, 1730, 1715, 1650 cm^{-1}. NMR δ: 0.98 (3H, s), 1.45 (3H, s), 3.69 (3H, s), 3.93, 4.02 (2H, each d, $J=14$), 4.52 (1H, m), 5.72 (1H, s). SI-MS m/z: 587 ($M^+ + 1$).

21-Chloro-17α-(3-ethoxycarbonyl)propanoyloxy-11β-hydroxy-4-pregnene-3,20-dione (9Aa) A few drops of concentrated H_2SO_4 were added to a solution of **6A** (300 mg) in EtOH (30 ml). The mixture was refluxed for 10 h, and after addition of pyridine (1 ml), the whole was concentrated *in vacuo*. The residue was extracted with AcOEt. The extract was washed with H_2O, dried and concentrated. The residue was chromatographed with $CHCl_3$–MeOH (20 : 1) as the eluent, then recrystallization from EtOH gave **9Aa** as colorless prisms (270 mg). IR (KBr): 3440, 1725, 1715, 1650 cm^{-1}. NMR δ: 0.97 (3H, s), 1.26 (3H, t, $J=7$), 1.45 (3H, s), 4.15 (2H, q, $J=7$), 4.18, 4.25 (2H, each d, $J=15$), 4.52 (1H, m), 5.71 (1H, s). SI-MS m/z: 511 ($M^+ + 3$), 510, 509 ($M^+ + 1$).

The following compounds were similarly prepared.

21-Chloro-11β-hydroxy-17α-(3-propoxycarbonyl)propanoyloxy-4-pregnene-3,20-dione (**9Ab**): IR (KBr): 3480, 1735, 1660 cm^{-1}. NMR δ: 0.94 (3H, t, $J=7$), 0.96 (3H, s), 1.46 (3H, s), 2.65 (4H, s), 4.20 (2H, s), 4.55 (1H, m), 5.73 (1H, s). SI-MS m/z: 525 ($M^+ + 3$), 524, 523 ($M^+ + 1$).

17α-(3-Butoxycarbonyl)propanoyloxy-21-chloro-11β-hydroxy-4-pregnene-3,20-dione (**9Ac**): IR (KBr): 3460, 1735, 1660 cm^{-1}. NMR δ: 0.92 (3H, t, $J=8$), 0.95 (3H, s), 1.47 (3H, s), 2.65 (4H, s), 4.22 (2H, s), 4.55 (1H, m), 4.62 (1H, br s). SI-MS m/z: 537 ($M^+ + 1$).

21-Chloro-17α-(3-ethoxycarbonyl)propanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione (**9Ba**): IR (KBr): 3280, 1720, 1650 cm^{-1}. NMR δ: 0.98 (3H, s), 1.23 (3H, t, $J=7$), 1.47 (3H, s), 2.60 (4H, s), 4.10 (2H, q, $J=7$), 4.18 (2H, s), 4.50 (1H, m), 6.05 (1H, s), 6.29 (1H, dd, $J=10$, 2), 7.30 (1H, d, $J=10$). SI-MS m/z: 510 ($M^+ + 4$), 509, 508, 507 ($M^+ + 1$).

21-Chloro-11β-hydroxy-17α-(3-isopropoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**9Bb**): IR (KBr): 3280, 1720, 1650 cm^{-1}. NMR δ: 0.98 (3H, s), 1.25 (6H, d, $J=7$), 1.47 (3H, s), 2.58 (4H, s), 4.18 (2H, s), 4.57 (1H, m), 5.00 (1H, q, $J=7$), 6.06 (1H, br s), 6.30 (1H, dd, $J=10$, 2), 7.32 (1H, d, $J=10$). SI-MS m/z: 524 ($M^+ + 4$), 522, 521 ($M^+ + 1$).

21-Chloro-11β-hydroxy-17α-(3-isobutoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**9Bc**): IR (KBr): 3280, 1720, 1650 cm^{-1}. NMR δ: 0.94 (6H, d, $J=7$), 0.98 (3H, s), 1.50 (3H, s), 2.64 (4H, s), 3.88 (2H, d, $J=7$), 4.22 (2H, s), 4.60 (1H, m), 6.10 (1H, br s), 6.35 (1H, dd, $J=10$, 2), 7.36 (1H, d, $J=10$). SI-MS m/z: 537 ($M^+ + 3$), 535 ($M^+ + 1$).

21-Chloro-17α-(3-ethoxycarbonyl)propanoyloxy-9α-fluoro-11β-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (**9Ca**): IR (KBr): 3520, 3260, 1725, 1655 cm^{-1}. NMR δ: 0.94 (3H, d, $J=6$), 1.08 (3H, s), 1.15 (3H, t, $J=8$), 1.58 (3H, s), 2.68 (4H, br s), 4.05, 4.14 (2H, each d, $J=14$), 4.25 (1H, m), 6.17 (1H, d, $J=2$), 6.38 (1H, dd, $J=10$, 2), 7.25 (1H, d, $J=10$). SI-MS m/z: 541 ($M^+ + 3$), 539 ($M^+ + 1$).

17α-(3-Butoxycarbonyl)propanoyloxy-21-chloro-9α-fluoro-11β-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (**9Cb**): IR (KBr): 3400, 1725, 1655 cm^{-1}. NMR δ: 0.90 (3H, d, $J=6$), 1.08 (3H, s), 1.15 (3H, t, $J=8$), 1.58 (3H, s), 2.68 (4H, br s), 4.05, 4.14 (2H, each d, $J=14$), 4.25 (1H, m), 6.17 (1H, d, $J=2$), 6.38 (1H, dd, $J=10$, 2), 7.25 (1H, d, $J=10$). SI-MS m/z: 569 ($M^+ + 3$), 567 ($M^+ + 1$).

21-Chloro-17α-(3-ethoxycarbonyl)propanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9Da**); IR (KBr): 3500, 1725, 1665 cm^{-1}. NMR δ: 1.00 (3H, s), 1.24 (3H, t, $J=5$), 1.39 (3H, d, $J=7$), 1.58 (3H, s), 4.09 (2H, s), 4.14 (2H, q, $J=5$), 4.47 (1H, m), 6.16 (1H, br s), 6.38 (1H, dd, $J=10$, 2), 7.30 (1H, d, $J=10$). SI-MS m/z: 541 ($M^+ + 3$), 540, 539 ($M^+ + 1$).

21-Chloro-9α-fluoro-11β-hydroxy-16β-methyl-17α-(3-propoxycarbonyl)propanoyloxy-1,4-pregnadiene-3,20-dione (**9Db**): IR (KBr): 3420, 1730, 1660 cm^{-1}. NMR δ: 0.92 (3H, t, *J*=7), 1.00 (3H, s), 1.38 (3H, d, *J*=7), 1.57 (3H, s), 4.06 (2H, q, *J*=7), 4.07 (2H, s), 4.45 (1H, m), 6.16 (1H, s), 6.37 (1H, dd, *J*=10, 2), 7.23 (1H, d, *J*=10). SI-MS *m/z*: 555 ($M^+ + 3$), 553 ($M^+ + 1$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-isopropoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9Dc**): IR (KBr): 3420, 1725, 1660 cm^{-1}. NMR δ: 1.01 (3H, s), 1.23 (6H, d, *J*=6), 1.39 (3H, d, *J*=6), 1.57 (3H, s), 4.09 (2H, s), 4.45 (1H, m), 4.99 (1H, septet, *J*=6), 6.15 (1H, d, *J*=2), 6.27 (1H, dd, *J*=10, 2), 7.21 (1H, d, *J*=10). SI-MS *m/z*: 555 ($M^+ + 3$), 553 ($M^+ + 1$).

17α-(3-Butoxycarbonyl)propanoyloxy-21-chloro-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9Dd**): IR (KBr): 3400, 1730, 1660 cm^{-1}. NMR δ: 0.93 (3H, t, *J*=7), 1.38 (3H, d, *J*=7), 1.56 (3H, s), 4.08 (4H, s and q, *J*=7), 4.46 (1H, m), 6.17 (1H, s), 6.38 (1H, dd, *J*=10, 2), 7.23 (1H, d, *J*=10). SI-MS *m/z*: 567 ($M^+ + 1$).

21-Chloro-9α-fluoro-11β-hydroxy-17α-(3-isobutoxycarbonyl)propanoyloxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9De**): IR (KBr): 3400, 1725, 1655 cm^{-1}. NMR δ: 0.90 (6H, d, *J*=7), 1.00 (3H, s), 1.37 (3H, d, *J*=7), 1.56 (3H, s), 3.85 (2H, d, *J*=7), 4.06 (3H, m), 4.43 (1H, m), 6.14 (1H, s), 6.36 (1H, dd, *J*=10, 2), 7.18 (1H, d, *J*=10). SI-MS *m/z*: 569 ($M^+ + 3$), 567 ($M^+ + 1$).

21-Chloro-17α-(3-cyclohexyloxycarbonyl)propanoyloxy-11β-hydroxy-4-pregnene-3,20-dione (9Ad) A mixture of **6**A (500 mg), cyclohexanol (3.5 ml), dry benzene (35 ml) and a few drops of concentrated H_2SO_4 was refluxed for 15 h. The mixture was washed with H_2O, dried and concentrated. The residue was chromatographed with hexane–AcOEt (2 : 1) as the eluent to give **9**Ad (220 mg) as colorless needles. IR (KBr): 3420, 1725, 1655 cm^{-1}. NMR δ: 0.96 (3H, s), 1.62 (3H, s), 2.58 (4H, s), 4.18 (2H, s), 4.47 (1H, m), 5.68 (1H, s). SI-MS *m/z*: 565 ($M^+ + 3$), 564, 563 ($M^+ + 1$).

The following compounds were similarly prepared.

21-Chloro-17α-(3-cyclopentyloxycarbonyl)propanoyloxy-11β-hydroxy-1,4-pregnadiene-3,20-dione (**9Bd**): IR (KBr): 3270, 1715, 1650 cm^{-1}. NMR δ: 0.99 (3H, s), 1.48 (3H, s), 2.58 (4H, s), 4.21 (2H, s), 4.57 (1H, m), 5.20 (1H, m), 6.08 (1H, s), 6.36 (1H, dd, *J*=10, 2), 7.34 (1H, d, *J*=10). SI-MS *m/z*: 549 ($M^+ + 3$), 548, 547 ($M^+ + 1$).

21-Chloro-17α-(3-cyclohexyloxycarbonyl)propanoyloxy-9α-fluoro-11β-hydroxy-16α-methyl-1,4-pregnadiene-3,20-dione (**9Cc**): IR (KBr): 3420, 1725, 1660 cm^{-1}. NMR δ: 0.90 (3H, d, *J*=6), 1.06 (3H, s), 1.56 (3H, s), 4.08 (2H, s), 4.22 (1H, m), 6.17 (1H, d, *J*=2), 6.38 (1H, dd, *J*=10, 2), 7.25 (1H, d, *J*=10). SI-MS *m/z*: 593 ($M^+ + 1$).

21-Chloro-17α-(3-cyclopentyloxycarbonyl)propanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9Df**): IR (KBr): 3400, 1725, 1660 cm^{-1}. NMR δ: 1.00 (3H, s), 1.38 (3H, d, *J*=7), 1.56 (3H, s), 4.07 (2H, s), 4.43 (1H, m), 5.12 (1H, m), 6.15 (1H, s), 6.36 (1H, dd, *J*=10, 2), 7.21 (1H, d, *J*=10). SI-MS *m/z*: 579 ($M^+ + 1$).

21-Chloro-17α-(3-cyclohexyloxycarbonyl)propanoyloxy-9α-fluoro-11β-hydroxy-16β-methyl-1,4-pregnadiene-3,20-dione (**9Dg**): IR (KBr): 3400, 1720, 1655 cm^{-1}. NMR δ: 1.00 (3H, s), 1.38 (3H, d, *J*=7), 1.55 (3H, s), 4.02, 4.10 (2H, each d, *J*=16), 4.43 (1H, m), 4.72 (1H, m), 6.15 (1H, s), 6.37 (1H, dd, *J*=10, 2), 7.20 (1H, d, *J*=10). SI-MS *m/z*: 595 ($M^+ + 3$), 594, 593 ($M^+ + 1$).

References and Notes

1) Trivial names employed are hydrocortisone (11β,17α,21-trihydroxy-4-pregnene-3,20-dione), prednisolone (11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione), dexamethasone (9α-fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione) and betamethasone (9α-fluoro-11β,21-dihydroxy-16β-methyl-1,4-pregnadiene-3,20-dione).

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