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Studies on Topical Antiinflammatory Corticosteroids. II. Synthesis and Vasoconstrictive Activity of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17-Methoxy- and (Methylthio)acetates[1]

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17-Methoxyacetate (**3a**) and 17-(methylthio)acetate (**3b**) of 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methylprednisolone, **1**) and their 21-esters (**4a** and **4b**) were synthesized and tested for vasoconstrictive activities. The activities of the 17-(methylthio)acetate derivatives (**3b** and **4b**) were more potent than those of the corresponding 17-methoxyacetates (**3a** and **4a**). The activities of **3b**, $\mathbf{4a}_2$, $\mathbf{4b}_{1-4}$ and $\mathbf{4b}_5$ were equivalent to that of 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV). The reaction of 6α-methylprednisolone (**1**) with triethyl orthomethoxyacetate afforded a stereoisomeric mixture of 6α-methylprednisolone 17,21-cyclic ortho esters (**2aA** and **2aB**) in a ratio of 22 : 78, while the reaction of **1** with triethyl ortho(methylthio)acetate resulted in the formation of a single isomer (**2bB**) of the isomeric 17,21-cyclic ortho esters (**2b**).

Keywords——corticosteroid; 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione; 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-cyclic ortho ester; diastereoisomer; 11β,21-dihydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione; 11β,21-dihydroxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione; 17α,21-diacyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione; vasoconstrictive activity

In the preceding paper,[1] we reported an efficient and simple synthetic method for 17-esters and 17,21-diesters of 11β,17α,21-trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methylprednisolone, **1**). The vasoconstrictive activities of the products were determined. In the present work, in order to examine whether oxygen and sulfur atoms introduced into the 17-ester chain affect the activity or not, the 17-methoxyacetate (**3a**) and 17-(methylthio)acetate (**3b**) of **1** and their 21-esters (**4a** and **4b**) were synthesized and tested for vasoconstrictive activities.[2] The results are reported here.

Results and Discussion

Synthesis of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17-Methoxyacetate (3a) and 17-(Methylthio)acetate (3b)

In the same manner as described in the previous papers,[1,3] 6α-methylprednisolone 17,21-cyclic orthomethoxyacetate (**2a**) and 6α-methylprednisolone 17,21-cyclic ortho(methylthio)-acetate (**2b**) were prepared by the reaction of **1** with triethyl orthomethoxyacetate[4] and triethyl ortho(methylthio)acetate[5] in 85% and 87.8% yields, respectively. The cyclic ortho ester (**2a**) was a mixture of two diastereoisomers attributable to C17 and the newly

produced asymmetric carbon in the cyclic ortho ester.[6,7] These isomers were separable by silica-gel thin-layer chromatography (TLC, benzene:ethanol=10:1) with *Rf* 0.42 and 0.37. In fact, these isomers could be separated by silica-gel column chromatography (CH_2Cl_2) in a ratio of 22:78.[8] This separation is the first such example to be reported. The less polar isomer and the more polar isomer on TLC were named **2a**A and **2a**B, respectively. The stereochemistry of the cyclic ortho esters (**2a**A and **2a**B) could not be determined. On the other hand, the cyclic ortho ester (**2b**) was a nearly sole product, which corresponded to the more polar isomer (**2b**B) on TLC, and only a trace amount of the less polar isomer (**2b**A) could be observed.

Next, these cyclic ortho esters (**2a** and **2b**) were treated with aqueous oxalic acid in MeOH to give the corresponding 17-methoxyacetate (**3a**) and 17-(methylthio)acetate (**3b**) in 53.5% and 80.9% yields, respectively, after purification by silica-gel preparative thin-layer chromatography (PTLC) (Chart 1).

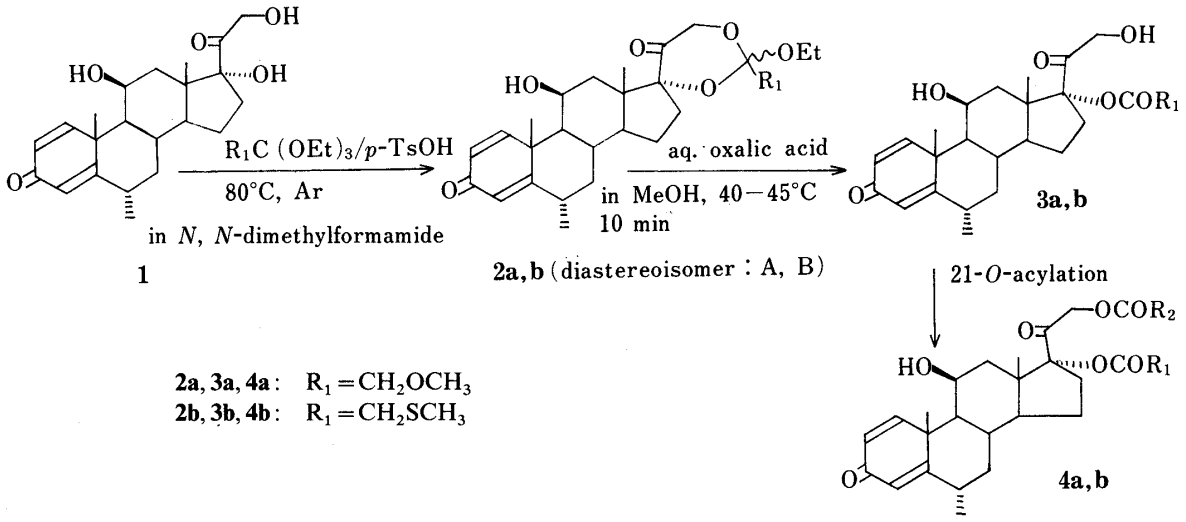

Chart 1

Synthesis of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Diester Derivatives (4a and 4b)

The 17-monoesters (**3a** and **3b**) obtained by the acid-catalyzed ring-opening reaction of **2** as described above were esterified at the C21-hydroxy group without further purification and the desired products were obtained in 22.4—77.0% overall yields from **2** by single recrystallization after PTLC (Chart 1). The results are listed in Table I.

Vasoconstrictive Activities

Twelve compounds of **3** and **4**, except for $\mathbf{4a}_1$ and $\mathbf{4a}_4$, were divided into two groups and tested for vasoconstrictive activities[9,10] in seven or ten healthy male volunteers by the method reported previously.[1a] Since results obtained by this method correlate well with the clinical efficacy for cutaneous disorders, evaluation by this method is recommended as a preclinical study for externally applied corticosteroids.[11,12] Statistical analysis was performed by Wilcoxon's signed-ranks test.[13] The results are summarized in Table II. All of the 17-monoesters and 17,21-diesters (**3** and **4**) tested were as active or more active than the mother

TABLE I. Yields, Melting Points and Elementary Analyses of 11β,17α, 21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Diester Derivatives (**4a** and **4b**)

Compd.	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Found (Calcd)	
				C	H
4a$_1$	38.1	150—152[b]	$C_{27}H_{36}O_8$	66.68 (66.38)	7.55 7.43)
4a$_2$	35.5	115—117	$C_{28}H_{38}O_8$	66.77 (66.91)	7.79 7.62)
4a$_3$	48.4	132—134	$C_{29}H_{40}O_8$	67.71 (67.42)	7.90 7.80)
4a$_4$	39.9	148—150	$C_{29}H_{40}O_8$	67.41 (67.42)	7.97 7.80)
4a$_5$	22.4	Amorphous	$C_{28}H_{38}O_9$	64.72 (64.85)	7.41 7.39)
4a$_6$	31.0	Amorphous	$C_{28}H_{38}O_8S$	62.67 (62.90)	7.06 7.16)
4b$_1$	66.6	149—151	$C_{27}H_{36}O_7S$	63.96 (64.26)	7.27 7.19)
4b$_2$	64.2	117—119	$C_{28}H_{38}O_7S$	64.61 (64.84)	7.29 7.38)
4b$_3$	68.1	126—128	$C_{29}H_{40}O_7S$	65.22 (65.39)	7.57 7.57)
4b$_4$	68.4	151—152	$C_{29}H_{40}O_7S$	65.19 (65.39)	7.66 7.57)
4b$_5$	76.6	111—113	$C_{28}H_{38}O_8S$	63.09 (62.90)	7.39 7.16)
4b$_6$	77.0	175—177	$C_{28}H_{38}O_7S_2$	60.86 (61.07)	7.06 6.95)

a) Overall yield of the isolated compounds from **2** by crystallization after PTLC separation. *b*) Lit.[2] mp 151 °C.

compound (**1**) ($p<0.05$). In particular, the activities of seven compounds (**3b**, **4a**$_2$, **4b**$_{1-4}$ and **4b**$_5$) at 2 h were equal to that of 9α-fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate, BV). In terms of the activities at 2 and 6 h, the 17-(methylthio)acetate derivatives (**3b** and **4b**) except **4b**$_6$ were more potent than the corresponding 17-methoxyacetates (**3a** and **4a**). The activities after 6 h of **3a** and **4a** were markedly reduced as compared with those of **3b** and **4b**. It could be considered that the higher activities of the sulfur-containing compounds (**3b** and **4b**) were attributable to the higher lipophilicity[6,14] of the sulfur atom as compared with the corresponding oxygen atom. It seems likely that introduction of a suitable ester chain containing a sulfur atom at the 17-position of a corticosteroid could be effective to enhance the antiinflammatory activity.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken with a JASCO IRA-1 spectrophotometer and mass spectra (MS) were recorded on a Hitachi RM-50 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a Hitachi R-24 (60 MHz) spectrometer using tetramethylsilane as an internal standard and chemical shifts are shown in δ (ppm). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

General Procedure for the Preparation of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Cyclic Ortho Esters (2a and 2b)——Ethyl orthomethoxyacetate or ethyl ortho(methylthio)acetate (2 mmol) and *p*-toluenesulfonic acid (0.05—0.1 mmol) were added to a solution of 6α-methylprednisolone (**1**, 1 mmol) in *N*,*N*-dimethylformamide (4 ml) and the reaction mixture was heated at 70—80 °C with stirring for 30 min—2 h under an

TABLE II. Vasoconstrictive Activities of 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17-Ester and 17,21-Diester Derivatives (**3** and **4**)

Compd.	Vasoconstrictive activity[a]		Compd.	Vasoconstrictive activity[a]	
	After 2 h	After 6 h		After 2 h	After 6 h
Experiment 1[b]			Experiment 2[f]		
3a	0.70[g]	0.35[g]	$\mathbf{4a}_5$	1.14[g]	0.64[g]
3b	1.55[h]	0.95[g,h]	$\mathbf{4a}_6$	1.36[g]	0.57[g]
$\mathbf{4a}_2$	1.60[h]	0.80[g]	$\mathbf{4b}_1$	2.14[h]	1.29[h]
$\mathbf{4a}_3$	1.25[g,h]	0.80[g]	$\mathbf{4b}_2$	2.64[h]	1.86[h]
$\mathbf{4b}_5$	1.45[h]	1.20[h]	$\mathbf{4b}_3$	1.86[h]	1.21[g,h]
$\mathbf{4b}_6$	0.85[g,h]	0.65[g]	$\mathbf{4b}_4$	2.50[h]	1.71[h]
Control			Control		
HC[c]	0.65	0.45	HC[c]	1.29	0.57
MP[d]	0.40	0.35	MP[d]	0.71	0.29
BV[e]	1.70	1.65	BV[e]	2.21	2.00

a) Vaseline ointment (0.01%) was used. The activity is shown as averaged scores (maximal value, 3.00). The blanching scores are as follows: 3 for the most potent blanching; 2 for moderate effect; 1 for slight effect; 0 for no effect. *b*) Ten volunteers were used. *c*) 21-Acetoxy-11β,17α-dihydroxy-4-pregnene-3,20-dione (hydrocortisone 21-acetate, 0.1%). *d*) 11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (6α-methylprednisolone, **1**). *e*) 9α-Fluoro-11β,21-dihydroxy-16β-methyl-17α-valeroyloxy-1,4-pregnadiene-3,20-dione (betamethasone 17-valerate). *f*) Seven volunteers were used. *g*) $p<0.05$ for BV. *h*) $p<0.05$ for MP.

argon atmosphere. Then, the reaction mixture was cooled to room temperature and ethyl acetate (50 ml) and 10% Na_2CO_3 aq. solution (0.5 ml) were added. The ethyl acetate layer was washed with water (30 ml × 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography (CH_2Cl_2) followed by recrystallization of the product from ether or ether: *n*-hexane (20—30 : 1). The physical properties, spectral data and elementary analyses are as follows.

11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Ethyl Orthomethoxyacetate (2aA)——mp 173.5—175.0 °C. $[\alpha]_D^{23}$ +73° (*c*=1.0, ethanol). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1725 (C=O), 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 0.98—1.28 (9H, m, C_{18}-H, C_6-αCH_3 and $CH_2C\underline{H}_3$), 1.46 (3H, s, C_{19}-H), 3.33 (3H, s, OCH_3), 3.51 (2H, s, $C\underline{H}_2OCH_3$), 4.45 (1H, br, C_{11}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, *J*=10, 2 Hz, C_2-H), 7.32 (1H, d, *J*=10 Hz, C_1-H). MS *m/z*: 474 (M^+), 473, 429, 411, 369, 356, 338, 323, 297, 279, 237, 161, 136, 135 (base peak), 121, 45. *Anal.* Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.27; H, 8.22.

11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Ethyl Orthomethoxyacetate (2aB)——mp 193.5—195.0 °C. $[\alpha]_D^{23}$ +73° (*c*=1.0, ethanol). IR ν_{max}^{KBr} cm^{-1}: 3510 (OH), 1725 (C=O), 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 0.91 (3H, s, C_{18}-H), 1.01—1.25 (6H, m, C_6-αCH_3 and $CH_2C\underline{H}_3$), 1.46 (3H, s, C_{19}-H), 3.39 (3H, s, OCH_3), 3.50 (2H, s, $C\underline{H}_2OCH_3$), 3.58 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 3.91, 4.32 (2H, dd, *J*=17 Hz, C_{21}-H), 4.49 (1H, br, C_{11}-H), 6.01 (1H, br s, C_4-H), 6.25 (1H, dd, *J*=10, 2 Hz, C_2-H), 7.24 (1H, d, *J*=10 Hz, C_1-H). MS *m/z*: 474 (M^+), 473, 429, 411, 369, 356, 338, 323, 297, 279, 237, 161, 136, 135 (base peak), 121, 45. *Anal.* Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.25; H, 8.21.

11β,17α,21-Trihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione 17,21-Ethyl Ortho(methylthio)acetate (2bB)—— The title compound is the more polar isomer on TLC and was named **2b**B. mp 184—186 °C. IR ν_{max}^{KBr} cm^{-1}: 3560 (OH), 1715 (C=O), 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 0.87 (3H, s, C_{18}-H), 1.10 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.12 (3H, d, *J*=6 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 2.16 (3H, s, SCH_3), 2.84 (2H, s, $C\underline{H}_2SCH_3$), 3.57 (2H, q, *J*=7 Hz, $C\underline{H}_2CH_3$), 3.92, 4.30 (2H, dd, *J*=17 Hz, C_{21}-H), 4.53 (1H, m, C_{11}-H), 6.04 (1H, br s, C_4-H), 6.27 (1H, dd, *J*=10, 2 Hz, C_2-H), 7.28 (1H, d, *J*=10 Hz, C_1-H). MS *m/z*: 490 (M^+), 446, 445, 429, 411, 357, 321, 297, 279, 237, 161, 136, 135 (base peak), 121, 91, 61, 45. *Anal.* Calcd for $C_{27}H_{38}O_6S$: C, 66.09; H, 7.81; S, 6.53. Found: C, 66.13; H, 7.92; S, 6.41. The less polar isomer, **2b**A, showed only a trace on TLC analysis and could not be isolated.

General Procedure for the Preparation of 17α-Acyloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione Derivatives (3a and 3b)——6α-Methylprednisolone 17,21-ethyl ortho ester (**2**, 1 mmol) was dissolved in MeOH (8 ml) followed by the addition of 2 N oxalic acid (1 ml). Then, the reaction mixture was heated with stirring for 10 min at 40—45 °C. After completion of the reaction, the solution was concentrated *in vacuo* and ethyl acetate (50 ml) was added to the residue. The organic layer was washed with water (30 ml × 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting product (**3**) was isolated by PTLC (CH_2Cl_2: Et_2O=3 : 1, twice). Spectral and analytical data are as follows.

11β,21-Dihydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione (3a)——Amorphous. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1740 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.10 (3H, s, C_{18}-H), 1.26 (3H, d, J=6 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 3.39 (3H, s, OCH_3), 4.00 (2H, s, CH_2OCH_3), 4.35 (2H, s, C_{21}-H), 4.51 (1H, br, C_{11}-H), 6.08 (1H, br s, C_4-H), 6.33 (1H, dd, J=10, 2 Hz, C_2-H), 7.26 (1H, d, J=10 Hz, C_1-H). MS m/z: 446 (M^+), 428, 357, 298, 240, 161, 136 (base peak), 135, 121, 91, 45. *Anal.* Calcd for $C_{25}H_{34}O_7$: C, 67.25; H, 7.67. Found: C, 67.02; H, 7.83.

11β,21-Dihydroxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (3b)——Amorphous. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1720 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 0.98 (3H, s, C_{18}-H), 1.12 (3H, d, J=6 Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 2.16 (3H, s, SCH_3), 3.15 (2H, s, $COCH_2S$), 4.32 (2H, s, C_{21}-H), 4.52 (1H, br s, C_{11}-H), 6.05 (1H, br s, C_4-H), 6.28 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 462 (M^+), 444, 431, 356, 327, 325, 281, 279, 161, 136, 135, 121, 106, 91, 61 (base peak, $CH_2{=}\overset{+}{S}CH_3$). *Anal.* Calcd for $C_{25}H_{34}O_6S$: C, 64.91; H, 7.44; S, 6.93. Found: C, 64.75; H, 7.67; S, 6.79.

General Procedure for the Preparation of 17α,21-Diacyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione Derivatives (4a and 4b)——An isolated compound (**3**, 1 mmol) or a crude product (**3**) obtained from **2** (1 mmol) by the procedure described above was dissolved in dry dichloromethane (6 ml). Then, a carboxylic anhydride (2—3 mmol) and triethylamine (4—6 mmol) were added to the solution and the reaction mixture was stirred for 30 min to 5 h at room temperature. After completion of the reaction, the reaction mixture was concentrated *in vacuo* and ethyl acetate (50 ml) was added to the resulting residue. The mixture was washed with 0.5% Na_2CO_3 aq. solution (20 ml) and with water (30 ml × 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The product (**4**) was obtained from the resulting residue by PTLC on silica gel (CH_2Cl_2 : Et_2O = 4—5 : 1, twice) and was crystallized from ether or ether : *n*-hexane (20—30 : 1).

Methoxyacetic and (methylthio)acetic anhydrides used were prepared by the following procedure. Methoxyacetic acid or (methylthio)acetic acid (4—6 mmol) was dissolved in dry dichloromethane (6 ml) and then *N*,*N*′-dicyclohexylcarbodiimide (DCC, 2—3 mmol) was added to the solution with stirring. The reaction mixture was stirred for 1 h at room temperature and the precipitated urea compound was filtered off. The filtrate was used directly for esterification without further purification.

Spectra data for the 17α,21-diacyloxy compounds (**4**) are as follows.

21-Acetoxy-11β-hydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_1$)——IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1760 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.05 (3H, s, C_{18}-H), 1.13 (3H, d, J=6 Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 2.14 (3H, s, $COCH_3$), 3.42 (3H, s, OCH_3), 3.99 (2H, s, $COCH_2$), 4.47 (1H, br s, C_{11}-H), 4.65, 4.96 (2H, dd, J=17 Hz, C_{21}-H), 6.04 (1H, br s, C_4-H), 6.27 (1H, dd, J=10, 2 Hz, C_2-H), 7.33 (1H, d, J=10 Hz, C_1-H). MS m/z: 488 (M^+), 470, 398, 325, 297, 279, 263, 161, 136 (base peak), 135, 121, 91, 45, 43.

11β-Hydroxy-17α-methoxyacetoxy-6α-methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione ($4a_2$)——IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.17 (3H, m, CH_2CH_3), 1.22 (3H, d, J=6 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 3.40 (3H, s, OCH_3), 4.00 (2H, s, $COCH_2$), 4.52 (1H, br s, C_{11}-H), 4.66, 4.99 (2H, dd, J=16 Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.25 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-H). MS m/z: 502 (M^+), 484, 412, 398, 325, 297, 279, 277, 161, 136 (base peak), 135, 121, 91, 57, 45.

21-Butanoyloxy-11β-hydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_3$)——IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.10 (3H, s, C_{18}-H), 1.15 (3H, m, $CH_2CH_2CH_3$), 1.47 (3H, s, C_{19}-H), 3.42 (3H, s, OCH_3), 4.00 (2H, s, $COCH_2$), 4.47 (1H, m, C_{11}-H), 4.63, 4.97 (2H, dd, J=17 Hz, C_{21}-H), 6.08 (1H, br s, C_4-H), 6.30 (1H, dd, J=10, 2 Hz, C_2-H), 7.27 (1H, d, J=10 Hz, C_1-H). MS m/z: 516 (M^+), 498, 426, 412, 356, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71, 45.

11β-Hydroxy-21-isobutanoyloxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_4$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.10 (3H, s, C_{18}-H), 1.23 (6H, d, J=7 Hz, $CH(CH_3)_2$), 1.48 (3H, s, C_{19}-H), 3.42 (3H, s, OCH_3), 4.01 (2H, s, $COCH_2$), 4.47 (1H, br, C_{11}-H), 4.64, 4.96 (2H, dd, J=15 Hz, C_{21}-H), 6.05 (1H, br s, C_4-H), 6.29 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-H). MS m/z: 516 (M^+), 498, 426, 412, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71, 45.

11β-Hydroxy-17α,21-bis(methoxyacetoxy)-6α-methyl-1,4-pregnadiene-3,20-dione ($4a_5$)——IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1760 (C=O), 1745 (C=O), 1730 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.12 (3H, d, J=6 Hz, C_6-αCH_3), 1.43 (3H, s, C_{19}-H), 3.42 (3H, s, C_{17}-$OCOCH_2OCH_3$), 3.49 (3H, s, C_{21}-$OCOCH_2OCH_3$), 4.00 (2H, s, C_{17}-$OCOCH_2$), 4.20 (2H, s, C_{21}-$OCOCH_2$), 4.50 (1H, br, C_{11}-H), 4.73, 5.05 (2H, dd, J=15 Hz, C_{21}-H), 6.06 (1H, br s, C_4-H), 6.29 (1H, dd, J=10, 2 Hz, C_2-H), 7.30 (1H, d, J=10 Hz, C_1-H). MS m/z: 518 (M^+), 500, 428, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 60, 45.

11β-Hydroxy-17α-methoxyacetoxy-6α-methyl-21-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione ($4a_6$)——IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 1745 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.10 (3H, s, C_{18}-H), 1.22 (3H, d, J=5 Hz, C_6-αCH_3), 1.48 (3H, s, C_{19}-H), 2.28 (3H, s, SCH_3), 3.37 (2H, s, $COCH_2S$), 3.46 (3H, s, OCH_3), 4.03 (2H, s, $COCH_2O$), 4.50 (1H, br, C_{11}-H), 4.75, 5.09 (2H, dd, J=16 Hz, C_{21}-H), 6.03 (1H, br s, C_4-H), 6.27 (1H, dd, J=10, 2 Hz, C_2-H), 7.29 (1H, d, J=10 Hz, C_1-H). MS m/z: 534 (M^+), 445, 444, 356, 325, 309, 297, 279, 161, 136, 135, 121, 91, 61, 45 (base peak).

21-Acetoxy-11β-hydroxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b$_1$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1760 (C=O), 1725 (C=O), 1720 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.03 (3H, s, C_{18}-H), 1.10 (3H, d, J=8 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 2.15 (3H, s, SCH_3), 2.19 (3H, s, $COCH_3$), 3.12 (2H, s, $COCH_2S$), 4.50 (1H, br s, C_{11}-H), 4.69, 4.92 (2H, dd, J=14 Hz, C_{21}-H), 6.00 (1H, br s, C_4-H), 6.25 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 504 (M^+), 486, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 61 (base peak), 43.

11β-Hydroxy-6α-methyl-17α-(methylthio)acetoxy-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4b$_2$)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.02 (3H, s, C_{18}-H), 1.15 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$), 1.45 (3H, s, C_{19}-H), 2.16 (3H, s, SCH_3), 3.12 (2H, s, $COCH_2S$), 4.50 (1H, br s, C_{11}-H), 4.69, 4.93 (2H, dd, J=14 Hz, C_{21}-H), 5.94 (1H, br s, C_4-H), 6.19 (1H, dd, J=10, 2 Hz, C_2-H), 7.26 (1H, d, J=10 Hz, C_1-H). MS m/z: 518 (M^+), 500, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 61 (base peak), 57.

21-Butanoyloxy-11β-hydroxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b$_3$)——IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.00 (3H, s, C_{18}-H), 1.02 (3H, t, J=8 Hz, $CH_2CH_2C\underline{H}_3$), 1.44 (3H, s, C_{19}-H), 2.18 (3H, s, SCH_3), 3.10 (2H, s, $COCH_2S$), 4.45 (1H, br s, C_{11}-H), 4.55, 4.92 (2H, dd, J=15 Hz, C_{21}-H), 5.94 (1H, br s, C_4-H), 6.18 (1H, dd, J=10, 2 Hz, C_2-H), 7.25 (1H, d, J=10 Hz, C_1-H). MS m/z: 532 (M^+), 514, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

11β-Hydroxy-21-isobutanoyloxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b$_4$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.02 (3H, s, C_{18}-H), 1.22 (6H, d, J=7 Hz, $CH(C\underline{H}_3)_2$), 1.44 (3H, s, C_{19}-H), 2.18 (3H, s, SCH_3), 3.10 (2H, s, $COCH_2S$), 4.45 (1H, br s, C_{11}-H), 4.60, 4.86 (2H, dd, J=15 Hz, C_{21}-H), 5.90 (1H, br s, C_4-H), 6.18 (1H, dd, J=10, 2 Hz, C_2-H), 7.20 (1H, d, J=10 Hz, C_1-H). MS m/z: 532 (M^+), 514, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

11β-Hydroxy-21-methoxyacetoxy-6α-methyl-17α-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b$_5$)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1760 (C=O), 1720 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$): 1.07 (3H, s, C_{18}-H), 1.28 (3H, d, J=6.5 Hz, C_6-αCH_3), 1.49 (3H, s, C_{19}-H), 2.18 (3H, s, SCH_3), 3.13 (2H, s, $COCH_2S$), 3.47 (3H, s, OCH_3), 4.20 (2H, s, $COCH_2$), 4.54 (1H, br, C_{11}-H), 4.75, 5.12 (2H, dd, J=15 Hz, C_{21}-H), 6.08 (1H, br s, C_4-H), 6.32 (1H, dd, J=10, 2 Hz, C_2-H), 7.33 (1H, d, J=10 Hz, C_1-H). MS m/z: 534 (M^+), 517, 516, 427, 413, 325, 297, 279, 161, 136, 135, 121, 106, 91, 61 (base peak), 45.

11β-Hydroxy-6α-methyl-17α,21-bis[(methylthio)acetoxy]-1,4-pregnadiene-3,20-dione (4b$_6$)——IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1740 (C=O), 1720 (C=O), 1715 (C=O), 1655 (C=O). ^{1}H-NMR ($CDCl_3$): 1.06 (3H, s, C_{18}-H), 1.15 (3H, d, J=4 Hz, C_6-αCH_3), 1.47 (3H, s, C_{19}-H), 2.19 (3H, s, C_{17}-$OCOCH_2SC\underline{H}_3$), 2.25 (3H, s, C_{21}-$OCOCH_2SCH_3$), 3.12 (2H, s, C_{17}-$OCOCH_2$), 3.33 (2H, s, C_{21}-$OCOCH_2$), 4.52 (1H, br, C_{11}-H), 4.73, 5.03 (2H, dd, J=15 Hz, C_{21}-H), 6.08 (1H, br s, C_4-H), 6.32 (1H, dd, J=10, 2 Hz, C_2-H), 7.32 (1H, d, J=10 Hz, C_1-H). MS m/z: 550 (M^+), 445, 444, 426, 408, 356, 325, 309, 297, 281, 279, 161, 136, 135, 121, 105, 91, 61 (base peak).

References and Notes

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