

[Chem. Pharm. Bull.]
34(4)1607—1612(1986)

Studies on Topical Antiinflammatory Corticosteroids. II. Synthesis and Vasoconstrictive Activity of 11 β ,17 α ,21-Trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione 17-Methoxy- and (Methylthio)acetates¹⁾

SABURO SUGAI,^{*,a} TOKUJI OKAZAKI,^a YOSHIO KAJIWARA,^a TOSHIFUMI KANBARA,^a
YASUO NAITO,^a SEIICHIRO YOSHIDA,^a SANYA AKABOSHI,^a
SHIRO IKEGAMI,^{*,b} and YOSHIKI KAMANO^c

*Research Laboratories, Ohta Pharmaceutical Co., Ltd.,^a Namiki, Kawaguchi, Saitama 332, Japan,
Faculty of Pharmaceutical Sciences, Teikyo University,^b Sagamiko, Kanagawa 199-01,
Japan and Cancer Research Institute, Arizona State University,^c
Tempe, Arizona 85287, U.S.A.*

(Received July 10, 1985)

17-Methoxyacetate (**3a**) and 17-(methylthio)acetate (**3b**) of 11 β ,17 α ,21-trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione (6 α -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**, **4a**₂, **4b**₁₋₄ and **4b**₅ were equivalent to 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). The reaction of 6 α -methylprednisolone (**1**) with triethyl orthomethoxyacetate afforded a stereoisomeric mixture of 6 α -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; 11 β ,17 α ,21-trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 11 β ,17 α ,21-trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione 17,21-cyclic ortho ester; diastereoisomer; 11 β ,21-dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 11 β ,21-dihydroxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione; 17 α ,21-diacyloxy-11 β -hydroxy-6 α -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-diester of 11 β ,17 α ,21-trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione (6 α -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 11 β ,17 α ,21-Trihydroxy-6 α -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)} 6 α -methylprednisolone 17,21-cyclic orthomethoxyacetate (**2a**) and 6 α -methylprednisolone 17,21-cyclic ortho(methylthio)acetate (**2b**) were prepared by the reaction of **1** with triethyl orthomethoxyacetate⁴⁾ and triethyl ortho(methylthio)acetate⁵⁾ 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 R_f 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 **2aA** and **2aB**, respectively. The stereochemistry of the cyclic ortho esters (**2aA** and **2aB**) 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 (**2bB**) on TLC, and only a trace amount of the less polar isomer (**2bA**) 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).

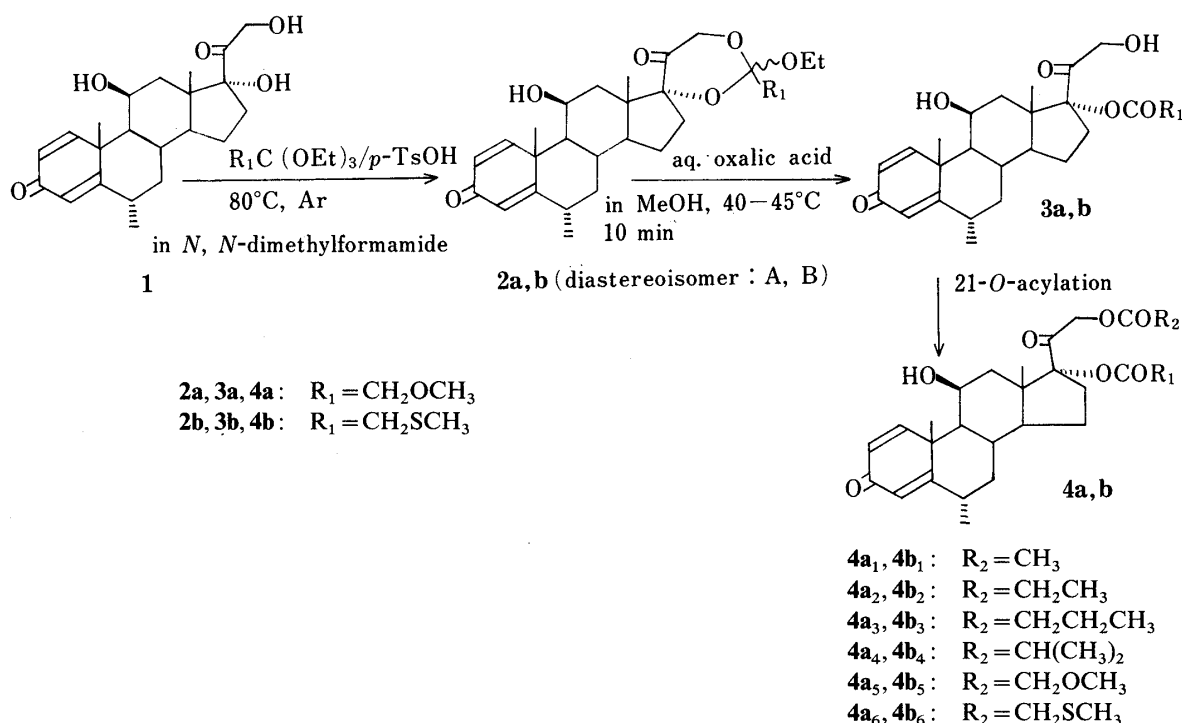


Chart 1

Synthesis of 11 β ,17 α ,21-Trihydroxy-6 α -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 **4a₁** and **4a₄**, 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-diester (**3** and **4**) tested were as active or more active than the mother

TABLE I. Yields, Melting Points and Elementary Analyses of 11 β ,17 α , 21-Trihydroxy-6 α -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 ₈ S	62.67 (62.90)	7.06 (7.16)
4b ₁	66.6	149—151	C ₂₇ H ₃₆ O ₇ S	63.96 (64.26)	7.27 (7.19)
4b ₂	64.2	117—119	C ₂₈ H ₃₈ O ₇ S	64.61 (64.84)	7.29 (7.38)
4b ₃	68.1	126—128	C ₂₉ H ₄₀ O ₇ S	65.22 (65.39)	7.57 (7.57)
4b ₄	68.4	151—152	C ₂₉ H ₄₀ O ₇ S	65.19 (65.39)	7.66 (7.57)
4b ₅	76.6	111—113	C ₂₈ H ₃₈ O ₈ S	63.09 (62.90)	7.39 (7.16)
4b ₆	77.0	175—177	C ₂₈ H ₃₈ O ₇ S 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 9 α -fluoro-11 β ,21-dihydroxy-16 β -methyl-17 α -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 (¹H-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 11 β ,17 α ,21-Trihydroxy-6 α -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 6 α -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 11 β ,17 α ,21-Trihydroxy-6 α -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)}	4a ₅	1.14 ^{g)}	0.64 ^{g)}
3b	1.55 ^{h)}	0.95 ^{g, h)}	4a ₆	1.36 ^{g)}	0.57 ^{g)}
4a ₂	1.60 ^{h)}	0.80 ^{g)}	4b ₁	2.14 ^{h)}	1.29 ^{h)}
4a ₃	1.25 ^{g, h)}	0.80 ^{g)}	4b ₂	2.64 ^{h)}	1.86 ^{h)}
4b ₅	1.45 ^{h)}	1.20 ^{h)}	4b ₃	1.86 ^{h)}	1.21 ^{g, h)}
4b ₆	0.85 ^{g, h)}	0.65 ^{g)}	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-11 β ,17 α -dihydroxy-4-pregnene-3,20-dione (hydrocortisone 21-acetate, 0.1%). d) 11 β ,17 α ,21-Trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione (6 α -methylprednisolone, 1). e) 9 α -Fluoro-11 β ,21-dihydroxy-16 β -methyl-17 α -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% Na₂CO₃ aq. solution (0.5 ml) were added. The ethyl acetate layer was washed with water (30 ml $\times$ 3), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica-gel column chromatography (CH₂Cl₂) 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.

11 β ,17 α ,21-Trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione 17,21-Ethyl Orthomethoxyacetate (2aA)—mp 173.5–175.0°C. $[\alpha]_D^{23} + 73^\circ$ ($c = 1.0$, ethanol). IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3380 (OH), 1725 (C=O), 1660 (C=O). ¹H-NMR (CDCl₃): 0.98–1.28 (9H, m, C₁₈-H, C₆- α CH₃ and CH₂CH₃), 1.46 (3H, s, C₁₉-H), 3.33 (3H, s, OCH₃), 3.51 (2H, s, CH₂OCH₃), 4.45 (1H, br, C₁₁-H), 6.05 (1H, br s, C₄-H), 6.28 (1H, dd, $J = 10$, 2 Hz, C₂-H), 7.32 (1H, d, $J = 10$ Hz, C₁-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 C₂₇H₃₈O₇: C, 68.33; H, 8.07. Found: C, 68.27; H, 8.22.

11 β ,17 α ,21-Trihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione 17,21-Ethyl Orthomethoxyacetate (2aB)—mp 193.5–195.0°C. $[\alpha]_D^{23} + 73^\circ$ ($c = 1.0$, ethanol). IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3510 (OH), 1725 (C=O), 1660 (C=O). ¹H-NMR (CDCl₃): 0.91 (3H, s, C₁₈-H), 1.01–1.25 (6H, m, C₆- α CH₃ and CH₂CH₃), 1.46 (3H, s, C₁₉-H), 3.39 (3H, s, OCH₃), 3.50 (2H, s, CH₂OCH₃), 3.58 (2H, q, $J = 7$ Hz, CH₂CH₃), 3.91, 4.32 (2H, dd, $J = 17$ Hz, C₂₁-H), 4.49 (1H, br, C₁₁-H), 6.01 (1H, br s, C₄-H), 6.25 (1H, dd, $J = 10$, 2 Hz, C₂-H), 7.24 (1H, d, $J = 10$ Hz, C₁-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 C₂₇H₃₈O₇: C, 68.33; H, 8.07. Found: C, 68.25; H, 8.21.

11 β ,17 α ,21-Trihydroxy-6 α -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 2bB. mp 184–186°C. IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3560 (OH), 1715 (C=O), 1660 (C=O). ¹H-NMR (CDCl₃): 0.87 (3H, s, C₁₈-H), 1.10 (3H, t, $J = 7$ Hz, CH₂CH₃), 1.12 (3H, d, $J = 6$ Hz, C₆- α CH₃), 1.47 (3H, s, C₁₉-H), 2.16 (3H, s, SCH₃), 2.84 (2H, s, CH₂SCH₃), 3.57 (2H, q, $J = 7$ Hz, CH₂CH₃), 3.92, 4.30 (2H, dd, $J = 17$ Hz, C₂₁-H), 4.53 (1H, m, C₁₁-H), 6.04 (1H, br s, C₄-H), 6.27 (1H, dd, $J = 10$, 2 Hz, C₂-H), 7.28 (1H, d, $J = 10$ Hz, C₁-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 C₂₇H₃₈O₆S: C, 66.09; H, 7.81; S, 6.53. Found: C, 66.13; H, 7.92; S, 6.41. The less polar isomer, 2bA, showed only a trace on TLC analysis and could not be isolated.

General Procedure for the Preparation of 17 α -Acyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione Derivatives (3a and 3b)—6 α -Methylprednisolone 17,21-ethyl ortho ester (2, 1 mmol) was dissolved in MeOH (8 ml) followed by the addition of 2N 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 $\times$ 3), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The resulting product (3) was isolated by PTLC (CH₂Cl₂: Et₂O = 3:1, twice). Spectral and analytical data are as follows.

11 β ,21-Dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione (3a)—Amorphous. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420 (OH), 1740 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.10 (3H, s, $\text{C}_{18}\text{-H}$), 1.26 (3H, d, $J=6$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.47 (3H, s, $\text{C}_{19}\text{-H}$), 3.39 (3H, s, OCH_3), 4.00 (2H, s, CH_2OCH_3), 4.35 (2H, s, $\text{C}_{21}\text{-H}$), 4.51 (1H, br, $\text{C}_{11}\text{-H}$), 6.08 (1H, br s, $\text{C}_4\text{-H}$), 6.33 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.26 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 446 (M^+), 428, 357, 298, 240, 161, 136 (base peak), 135, 121, 91, 45. Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_7$: C, 67.25; H, 7.67. Found: C, 67.02; H, 7.83.

11 β ,21-Dihydroxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (3b)—Amorphous. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3440 (OH), 1720 (C=O), 1715 (C=O), 1650 (C=O). $^1\text{H-NMR}$ (CDCl_3): 0.98 (3H, s, $\text{C}_{18}\text{-H}$), 1.12 (3H, d, $J=6$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.48 (3H, s, $\text{C}_{19}\text{-H}$), 2.16 (3H, s, SCH_3), 3.15 (2H, s, COCH_2S), 4.32 (2H, s, $\text{C}_{21}\text{-H}$), 4.52 (1H, br s, $\text{C}_{11}\text{-H}$), 6.05 (1H, br s, $\text{C}_4\text{-H}$), 6.28 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.32 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 462 (M^+), 444, 431, 356, 327, 325, 281, 279, 161, 136, 135, 121, 106, 91, 61 (base peak, $\text{CH}_2=\text{SCH}_3$). Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_6\text{S}$: 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 17 α ,21-Diacyloxy-11 β -hydroxy-6 α -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 $\times$ 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 17 α ,21-diacyloxy compounds (4) are as follows.

21-Acetoxy-11 β -hydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione (4a₁)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3320 (OH), 1760 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.05 (3H, s, $\text{C}_{18}\text{-H}$), 1.13 (3H, d, $J=6$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.48 (3H, s, $\text{C}_{19}\text{-H}$), 2.14 (3H, s, COCH_3), 3.42 (3H, s, OCH_3), 3.99 (2H, s, COCH_2), 4.47 (1H, br s, $\text{C}_{11}\text{-H}$), 4.65, 4.96 (2H, dd, $J=17$ Hz, $\text{C}_{21}\text{-H}$), 6.04 (1H, br s, $\text{C}_4\text{-H}$), 6.27 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.33 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 488 (M^+), 470, 398, 325, 297, 279, 263, 161, 136 (base peak), 135, 121, 91, 45, 43.

11 β -Hydroxy-17 α -methoxyacetoxy-6 α -methyl-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4a₂)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.06 (3H, s, $\text{C}_{18}\text{-H}$), 1.17 (3H, m, CH_2CH_3), 1.22 (3H, d, $J=6$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.47 (3H, s, $\text{C}_{19}\text{-H}$), 3.40 (3H, s, OCH_3), 4.00 (2H, s, COCH_2), 4.52 (1H, br s, $\text{C}_{11}\text{-H}$), 4.66, 4.99 (2H, dd, $J=16$ Hz, $\text{C}_{21}\text{-H}$), 6.03 (1H, br s, $\text{C}_4\text{-H}$), 6.25 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.30 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 502 (M^+), 484, 412, 398, 325, 297, 279, 277, 161, 136 (base peak), 135, 121, 91, 57, 45.

21-Butanoyloxy-11 β -hydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione (4a₃)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3440 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.10 (3H, s, $\text{C}_{18}\text{-H}$), 1.15 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.47 (3H, s, $\text{C}_{19}\text{-H}$), 3.42 (3H, s, OCH_3), 4.00 (2H, s, COCH_2), 4.47 (1H, m, $\text{C}_{11}\text{-H}$), 4.63, 4.97 (2H, dd, $J=17$ Hz, $\text{C}_{21}\text{-H}$), 6.08 (1H, br s, $\text{C}_4\text{-H}$), 6.30 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.27 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 516 (M^+), 498, 426, 412, 356, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71, 45.

11 β -Hydroxy-21-isobutanoyloxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione (4a₄)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1750 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.10 (3H, s, $\text{C}_{18}\text{-H}$), 1.23 (6H, d, $J=7$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.48 (3H, s, $\text{C}_{19}\text{-H}$), 3.42 (3H, s, OCH_3), 4.01 (2H, s, COCH_2), 4.47 (1H, br, $\text{C}_{11}\text{-H}$), 4.64, 4.96 (2H, dd, $J=15$ Hz, $\text{C}_{21}\text{-H}$), 6.05 (1H, br s, $\text{C}_4\text{-H}$), 6.29 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.30 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 516 (M^+), 498, 426, 412, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 71, 45.

11 β -Hydroxy-17 α ,21-bis(methoxyacetoxy)-6 α -methyl-1,4-pregnadiene-3,20-dione (4a₅)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3440 (OH), 1760 (C=O), 1745 (C=O), 1730 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.06 (3H, s, $\text{C}_{18}\text{-H}$), 1.12 (3H, d, $J=6$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.43 (3H, s, $\text{C}_{19}\text{-H}$), 3.42 (3H, s, $\text{C}_{17}\text{-OCOCH}_2\text{OCH}_3$), 3.49 (3H, s, $\text{C}_{21}\text{-OCOCH}_2\text{OCH}_3$), 4.00 (2H, s, $\text{C}_{17}\text{-OCOCH}_2$), 4.20 (2H, s, $\text{C}_{21}\text{-OCOCH}_2$), 4.50 (1H, br, $\text{C}_{11}\text{-H}$), 4.73, 5.05 (2H, dd, $J=15$ Hz, $\text{C}_{21}\text{-H}$), 6.06 (1H, br s, $\text{C}_4\text{-H}$), 6.29 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.30 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 518 (M^+), 500, 428, 325, 297, 279, 161, 136 (base peak), 135, 121, 91, 60, 45.

11 β -Hydroxy-17 α -methoxyacetoxy-6 α -methyl-21-(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4a₆)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3430 (OH), 1745 (C=O), 1730 (C=O), 1720 (C=O), 1655 (C=O). $^1\text{H-NMR}$ (CDCl_3): 1.10 (3H, s, $\text{C}_{18}\text{-H}$), 1.22 (3H, d, $J=5$ Hz, $\text{C}_6\text{-}\alpha\text{CH}_3$), 1.48 (3H, s, $\text{C}_{19}\text{-H}$), 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, $\text{C}_{11}\text{-H}$), 4.75, 5.09 (2H, dd, $J=16$ Hz, $\text{C}_{21}\text{-H}$), 6.03 (1H, br s, $\text{C}_4\text{-H}$), 6.27 (1H, dd, $J=10$, 2 Hz, $\text{C}_2\text{-H}$), 7.29 (1H, d, $J=10$ Hz, $\text{C}_1\text{-H}$). MS m/z : 534 (M^+), 445, 444, 356, 325, 309, 297, 279, 161, 136, 135, 121, 91, 61, 45 (base peak).

21-Acetoxy-11 β -hydroxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b₁)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 (OH), 1760 (C=O), 1725 (C=O), 1720 (C=O), 1650 (C=O). ¹H-NMR (CDCl₃): 1.03 (3H, s, C₁₈-H), 1.10 (3H, d, $J=8$ Hz, C₆- α CH₃), 1.47 (3H, s, C₁₉-H), 2.15 (3H, s, SCH₃), 2.19 (3H, s, COCH₃), 3.12 (2H, s, COCH₂S), 4.50 (1H, br s, C₁₁-H), 4.69, 4.92 (2H, dd, $J=14$ Hz, C₂₁-H), 6.00 (1H, br s, C₄-H), 6.25 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.32 (1H, d, $J=10$ Hz, C₁-H). MS m/z : 504 (M⁺), 486, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 61 (base peak), 43.

11 β -Hydroxy-6 α -methyl-17 α -(methylthio)acetoxy-21-propanoyloxy-1,4-pregnadiene-3,20-dione (4b₂)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ¹H-NMR (CDCl₃): 1.02 (3H, s, C₁₈-H), 1.15 (3H, t, $J=8$ Hz, CH₂CH₃), 1.45 (3H, s, C₁₉-H), 2.16 (3H, s, SCH₃), 3.12 (2H, s, COCH₂S), 4.50 (1H, br s, C₁₁-H), 4.69, 4.93 (2H, dd, $J=14$ Hz, C₂₁-H), 5.94 (1H, br s, C₄-H), 6.19 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.26 (1H, d, $J=10$ Hz, C₁-H). MS m/z : 518 (M⁺), 500, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 61 (base peak), 57.

21-Butanoyloxy-11 β -hydroxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b₃)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3380 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ¹H-NMR (CDCl₃): 1.00 (3H, s, C₁₈-H), 1.02 (3H, t, $J=8$ Hz, CH₂CH₂CH₃), 1.44 (3H, s, C₁₉-H), 2.18 (3H, s, SCH₃), 3.10 (2H, s, COCH₂S), 4.45 (1H, br s, C₁₁-H), 4.55, 4.92 (2H, dd, $J=15$ Hz, C₂₁-H), 5.94 (1H, br s, C₄-H), 6.18 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.25 (1H, d, $J=10$ Hz, C₁-H). MS m/z : 532 (M⁺), 514, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

11 β -Hydroxy-21-isobutanoyloxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b₄)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360 (OH), 1745 (C=O), 1725 (C=O), 1715 (C=O), 1650 (C=O). ¹H-NMR (CDCl₃): 1.02 (3H, s, C₁₈-H), 1.22 (6H, d, $J=7$ Hz, CH(CH₃)₂), 1.44 (3H, s, C₁₉-H), 2.18 (3H, s, SCH₃), 3.10 (2H, s, COCH₂S), 4.45 (1H, br s, C₁₁-H), 4.60, 4.86 (2H, dd, $J=15$ Hz, C₂₁-H), 5.90 (1H, br s, C₄-H), 6.18 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.20 (1H, d, $J=10$ Hz, C₁-H). MS m/z : 532 (M⁺), 514, 426, 412, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak).

11 β -Hydroxy-21-methoxyacetoxy-6 α -methyl-17 α -(methylthio)acetoxy-1,4-pregnadiene-3,20-dione (4b₅)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360 (OH), 1760 (C=O), 1720 (C=O), 1715 (C=O), 1650 (C=O). ¹H-NMR (CDCl₃): 1.07 (3H, s, C₁₈-H), 1.28 (3H, d, $J=6.5$ Hz, C₆- α CH₃), 1.49 (3H, s, C₁₉-H), 2.18 (3H, s, SCH₃), 3.13 (2H, s, COCH₂S), 3.47 (3H, s, OCH₃), 4.20 (2H, s, COCH₂), 4.54 (1H, br, C₁₁-H), 4.75, 5.12 (2H, dd, $J=15$ Hz, C₂₁-H), 6.08 (1H, br s, C₄-H), 6.32 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.33 (1H, d, $J=10$ Hz, C₁-H). MS m/z : 534 (M⁺), 517, 516, 427, 413, 325, 297, 279, 161, 136, 135, 121, 106, 91, 61 (base peak), 45.

11 β -Hydroxy-6 α -methyl-17 α ,21-bis[(methylthio)acetoxy]-1,4-pregnadiene-3,20-dione (4b₆)—IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3370 (OH), 1740 (C=O), 1720 (C=O), 1715 (C=O), 1655 (C=O). ¹H-NMR (CDCl₃): 1.06 (3H, s, C₁₈-H), 1.15 (3H, d, $J=4$ Hz, C₆- α CH₃), 1.47 (3H, s, C₁₉-H), 2.19 (3H, s, C₁₇-OCOCH₂SCH₃), 2.25 (3H, s, C₂₁-OCOCH₂SCH₃), 3.12 (2H, s, C₁₇-OCOCH₂), 3.33 (2H, s, C₂₁-OCOCH₂), 4.52 (1H, br, C₁₁-H), 4.73, 5.03 (2H, dd, $J=15$ Hz, C₂₁-H), 6.08 (1H, br s, C₄-H), 6.32 (1H, dd, $J=10$, 2 Hz, C₂-H), 7.32 (1H, d, $J=10$ Hz, C₁-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

- 1) a) Part I: S. Sugai, T. Okazaki, Y. Kajiwara, T. Kanbara, Y. Naito, S. Yoshida, S. Akaboshi, S. Ikegami and Y. Kamano, *Chem. Pharm. Bull.*, **33**, 1889 (1985); b) Y. Kamano, S. Sugai, T. Okazaki, S. Yoshida and S. Akaboshi, Japan Patent Appl. 83-66872 (1983) [*Chem. Abstr.*, **100**, 210264y (1984)].
- 2) Recently, a preparation of 4a₁ by the acyl migration of 6 α -methylprednisolone 21-methoxyacetate followed by acetylation of the C₂₁-hydroxy group has been reported in a patent. Schering A.-G., Japan Kokai Tokkyo Koho 83-74699 (1983) [*Chem. Abstr.*, **99**, 38714t (1983)].
- 3) S. Sugai, S. Akaboshi and S. Ikegami, *Chem. Pharm. Bull.*, **31**, 12 (1983).
- 4) E. T. Stiller, U.S. patent 2422598 (1947) [*Chem. Abstr.*, **41**, P5904a (1947)].
- 5) A. I. Kiprianov, Z. P. Suitnikov and E. D. Suich, *J. Gen. Chem. USSR*, **6**, 576 (1936) [*Chem. Abstr.*, **30**, 5583⁸ (1936)].
- 6) M. J. Green, H.-J. Shue, R. Tibiri, J. Berkenkopf, X. Fernandez, M. Monahan and B. N. Lutsky, *Arzneim.-Forsch./Drug Res.*, **30**, 1618 (1980).
- 7) R. Gardi, R. Vitali and A. Ercoli, *Tetrahedron Lett.*, **1961**, 448.
- 8) Usually, corticosteroid 17,21-cyclic ortho ester is obtained as a nearly sole product.
- 9) A. W. McKenzie and R. B. Stoughton, *Arch. Dermatol.*, **86**, 608 (1962).
- 10) Before application to the volunteers, the safety of the compounds (3 and 4) was checked by means of acute toxicity (in mice) and cutaneous irritation (in rabbits) tests.
- 11) M. Ishihara, *Nishinohon J. Dermatol.* (Japan), **37**, 86 (1975). The compounds used were applied at random and the activities were examined according to double blind procedure.
- 12) a) M. Ishihara, *Clinical Evaluation*, **4**, 323 (1976); b) *Idem*, *Nishinohon J. Dermatol.* (Japan), **38**, 286 (1976); c) K. Takeda, *Dermatologic Therapy*, **26**, 631 (1984).
- 13) F. Wilcoxon, *Biometrics*, **1**, 80 (1945).
- 14) a) B. Shroot, J. C. Caron and M. Poncet, *Brit. J. Dermatol.*, **107**, Suppl. **23**, 30 (1982); b) S. Otomo, Y. Tarumoto, H. Yasui, Y. Tachi, K. Sota, S. Omura, M. Sasajima, M. Washitake and J. Sawada, *Oyo Yakuri*, **23**, 455 (1982); c) A. W. McKenzie and R. M. Atkinson, *Arch. Dermatol.*, **89**, 741 (1964).