An Improved Synthesis of 17α-Acyloxy-21-chloro-substituted Corticosteroids using Xanthene-9-carbonyl Chloride

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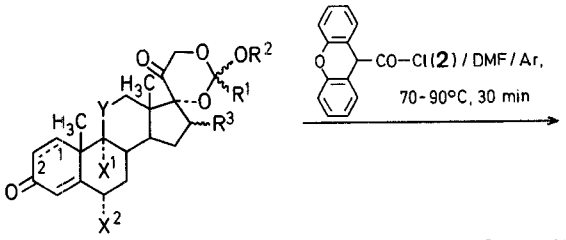
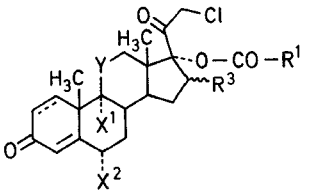
Certain 17α-acyloxy-21-chloro corticosteroids **3** are known to be clinically useful as a potent topical antiinflammatory agent[1]. These corticosteroids **3** have been hitherto synthesized from the corresponding 17α,21-cyclic ortho esters **1** in 3 or 5 steps[2,3,4]. Recently, a direct conversion from **1** to **3** by reaction with acid chlorides has been reported in a patent[5].

However, the yields of compounds **3** are poor (0–28%) since the reaction has to be carried out with reactive acid chlorides such as acetyl chloride at room temperature. With these reagents, decomposition of **1** may occur by the action of hydrochloric acid and/or the carboxylic acid resulting from hydrolysis of the acid chloride. Thus, we found that compounds **1** are decomposed completely on reaction with dry hydrogen chloride. Furthermore, it was stated in the patent that the presence of dimethyl sulfoxide and/or a tertiary amide such as dimethylformamide are essential for the preparation of products **3**.

Because of these practical limitations, we have developed an improved synthesis of products **3** using moisture-stable, crystalline acid chlorides. Thus, xanthene-9-carbonyl chloride **(2)**[6] was found to convert **1** to **3** in good yields within 30 min at 70–90 °C. The presence of a tertiary amide or dimethyl sulfoxide is not necessary. Good yields (40–60%) could also be obtained using 1,2-dichloroethane, benzene, or acetonitrile as solvent.



1a-i



3a-i

1,3	C(1)–C(2)	X¹	X²	Y	R¹	R²	R³
a	Δ¹	H	α-CH₃	CH–OH	C₂H₅	C₂H₅	H
b	Δ¹	H	α-CH₃	CH–OH	n-C₃H₇	C₂H₅	H
c	sat.	H	H	CH–OH	C₂H₅	C₂H₅	H
d	Δ¹	H	H	CH–OH	C₂H₅	C₂H₅	H
e	Δ¹	H	α-CH₃	CH–OH	C₆H₅	CH₃	H
f	Δ¹	F	H	CH–OH	C₂H₅	C₂H₅	α-CH₃
g	Δ¹	Cl	H	CH–OH	C₂H₅	C₂H₅	β-CH₃
h	sat.	H	H	CH₂	C₂H₅	C₂H₅	H
i	Δ¹	H	H	C=O	C₂H₅	C₂H₅	H

Table 1. Corticosteroid 17α,21-Cyclic Ortho Esters **1a–i** prepared

No.	Name	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p.	I.R. (KBr) ν [cm⁻¹]	M.S. m/e
1a	6α-methylprednisolone-17α,21-ethyl orthopropanoate	91	160–164° (dec)	$C_{27}H_{38}O_6$ (458.6)	3350 (OH); 1720, 1645 (C=O)	459 ($M^+ + 1$); 458 (M^+); 441, 136, 135 (100%)
1b	6α-methylprednisolone-17α,21-ethyl orthobutanoate	91	164–166° (dec)	$C_{28}H_{40}O_6$ (472.6)	3340 (OH); 1720, 1645 (C=O)	473 ($M^+ + 1$); 472 (M^+); 427, 356, 136, 135 (100%)
1c	hydrocortisone-17α,21-ethyl orthopropanoate	90	186–190°	183–185°[5]	—	—
1d	prednisolone-17α,21-ethyl orthopropanoate	93	187–189°	180–184°[5]	—	—
1e	6α-methylprednisolone-17α,21-methyl orthobenzoate	84	amorphous	$C_{30}H_{36}O_6$ (492.6)	3350 (OH); 1715, 1645 (C=O)	493 ($M^+ + 1$); 492 (M^+); 475; 356; 136; 135; 105; 77
1f	dexamethasone-17α,21-ethyl orthopropanoate	85	218–220°	219–221°[5]	—	—
1g	beclomethasone-17α,21-ethyl orthopropanoate	84	146–147°	$C_{27}H_{37}ClO_6$ (493.0)	3340 (OH); 1715, 1655 (C=O)	449 ($M^+ + 2 - OC_2H_5$); 447 ($M^+ - OC_2H_5$); 410; 359; 331 (100%)
1h	11-deoxyhydrocortisone-17α,21-ethyl orthopropanoate	88	180–182°	$C_{26}H_{38}O_5$ (430.6)	1723, 1658 (C=O)	431 ($M^+ + 1$); 430 (M^+); 402; 242; 227; 124; 57 (100%)
1i	prednisone-17α,21-ethyl orthopropanoate	92	188–191°	$C_{26}H_{34}O_6$ (442.6)	1723, 1698, 1658 (C=O)	443 ($M^+ + 1$); 442 (M^+); 414; 368; 242; 121; 57 (100%)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.18, Cl +0.06.

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Table 2. 17α-Acyloxy-21-chloro-corticosteroids **3a–i**

Product	Yield[a] [%]	m.p. [°C]	$[\alpha]_D^{23}$ (C_2H_5OH)	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	M.S. (30 eV) *m/e*
3a	88[c]	147–149°	+63°	$C_{25}H_{33}ClO_5$ (449.0)	3360 (OH); 1720, 1710, 1645 (C=O)	1.0–1.2 (m, 9H); 1.47 (s, 3H); 4.5 (br. s, 1H); 6.0 (br. s, 1H); 6.25 (d, 1H, J=10 Hz); 7.37 (d, 1H, J=10 Hz)	450 (M^++2); 449, 448 (M^+)
3b	57	120–123°	+50°	$C_{26}H_{35}ClO_5$ (463.0)	3400 (OH); 1720, 1715, 1645 (C=O)	0.9 (m, 3H); 1.00 (s, 3H); 1.13 (d, 3H, J=8 Hz); 1.46 (s, 3H); 4.15 (d, 2H, J=1.5 Hz); 4.48 (br. s, 1H); 6.03 (br. s, 1H); 6.26 (d, 1H, J=10 Hz); 7.33 (d, 1H, J=10 Hz)	464 (M^++2); 463, 462 (M^+)
3c	63	240–242°[d]	—	225–227°[5]	3360 (OH); 1725, 1715, 1645 (C=O)	1.00 (s, 3H); 1.14 (t, 3H, J=8 Hz); 1.46 (s, 3H); 4.27 (d, 2H, J=1 Hz); 4.55 (br. s, 1H); 5.71 (s, 1H)	438 (M^++2); 437, 436 (M^+)
3d	71	223–225°	—	225–227°[5]	3360 (OH); 1725, 1715, 1645 (C=O)	—	436 (M^++2); 435, 434 (M^+)
3e	50	157–159°	+17°	$C_{29}H_{33}ClO_5 \cdot 0.5H_2O$ (506.0)	3400 (OH); 1715, 1700, 1650 (C=O)	1.08 (s, 3H); 1.2 (m, 3H); 1.53 (s, 3H); 4.18 (s, 2H); 4.6 (br. s, 1H); 6.1 (br. s, 1H); 6.29 (d, 1H, J=10 Hz); 7.3–8.1 (m, 6H)	498 (M^++2); 497, 496 (M^+)
3f	58	241–243°	—	241–243°[5]	3270 (OH); 1730, 1720, 1655 (C=O)	—	468 (M^++2); 467, 466 (M^+)
3g	41	228–230°[d]	—	202–205°[5]	3400 (OH); 1738, 1730, 1655 (C=O)	1.01 (s, 3H); 1.15 (t, 3H, J=8 Hz); 1.37 (d, 3H, J=8 Hz); 1.66 (s, 3H); 3.99 (s, 2H); 4.56 (br. s, 1H); 6.06 (br. s, 1H); 6.28 (d, 1H, J=10 Hz); 7.23 (d, 1H, 10 Hz)	486 (M^++4); 484 (M^++2); 482 (M^+)
3h	68	177–179°	+63°	$C_{24}H_{33}ClO_5$ (421.0)	1725, 1715, 1660 (C=O)	0.73 (s, 3H); 1.13 (t, 3H, J=8 Hz); 1.18 (s, 3H); 4.12 (d, 2H, J=1.5 Hz); 5.73 (s, 1H)	422 (M^++2); 421, 420 (M^+)
3i	77	amorphous[d]	—	97–100°[4]	1730, 1725, 1700, 1660 (C=O)	0.77 (s, 3H); 1.11 (t, 3H, J=8 Hz); 1.42 (s, 3H); 4.11 (s, 2H); 6.12 (s, 1H); 6.23 (d, 1H, J=10 Hz); 7.66 (d, 1H, J=10 Hz)	434 (M^++2); 433, 432 (M^+)

[a] Non-optimized yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.26, H ±0.19, Cl ±0.14.
[c] In 1,2-dichloroethane 49% yield, in benzene 59% yield, in acetonitrile 60% yield.
[d] These products are homogeneous by T.L.C. and satisfactory microanalyses were obtained (C ±0.26, H ±0.16, Cl ±0.12).

Other aroyl chlorides proved to be less suitable than **2**. Acid chloride **2** can be recovered easily as its ethyl or methyl ester from the reaction mixture and recycled if desired. The starting materials **1** were obtained in 84–93% yield from the corresponding corticosteroids and ethyl or methyl ortho esters.

Corticosteroid 17α,21-Cyclic Ortho Esters 1a–i; General Procedure:
To a stirred solution of the corticosteroid (2 mmol) in dimethylformamide (4 ml) are added the ethyl or methyl ortho ester (4 mmol) and anhydrous *p*-toluenesulfonic acid (0.1 mmol) under argon. The mixture is heated at 85 °C for 1.5 h, 10% sodium carbonate solution (0.5 ml) and ethyl acetate (50 ml) are added at room temperature. The resultant mixture is washed with water (3×30 ml), dried with sodium sulfate, and filtered. The solvents are evaporated and the residual product isolated by recrystallization from ether/hexane to afford the product **1**; yield: 84–93% (Table 1).

Xanthene-9-carbonyl Chloride (2)[6]:
Prepared from commercially available xanthene-9-carboxylic acid (2.26 g, 10 mmol) and thionyl chloride (1.58 g, 13.3 mmol) in dry dichloromethane (12 ml) under reflux for 7 h; yield: 92%; m.p. 86–88 °C; colorless needles from hexane.

I.R. (KBr): ν=1775 cm^{-1} (CO).

17α-Acyloxy-21-chloro-corticosteroids 3a–i; General Procedure:
To a solution of the corticosteroid 17α,21-ethyl or methyl ortho ester **1** (1 mmol) in dimethylformamide (3 ml) heated at 80 °C under argon is added xanthene-9-carbonyl chloride (**2**; 0.37 g, 1.5 mmol). The mixture is stirred for 30 min, cooled to room temperature and ethyl acetate (50 ml) and 10% sodium carbonate solution (1 ml) are added. The resultant mixture is washed with water (3×30 ml), dried with anhydrous sodium sulfate, and evaporated. The residual product is isolated by recrystallization from ether/hexane or by preparative thin layer chromatography on silica gel; yield: 41–88% (Table 2).

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[1] For example, 21-chloro-9α-fluoro-16β-methyl-17α-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione has been used clinically: C. G. Sparkes, L. Wilson, *Br. J. Dermatol.* **90**, 197 (1974).
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