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Base catalysed rearrangement of fluocinolone acetonide to a 17α-pregnane-21,16α-carbolactone

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Abstract

Treatment of fluocinolone acetonide with sodium hydride in DMF gave the 6α,9α-difluoro-11β,20β-dihydroxy-3-oxo-17α-pregnane-1,4-diene-21,16α-carbolactone in high yield.

Keywords: steroid; rearrangement.

As part of an anti-inflammatory steroid project we were interested in reacting fluocinolone acetonide (**1**) with electrophiles in the presence of sodium hydride in DMF, to obtain 21-substituted derivatives. 21-Ether derivatives of glucocorticoids have been reported by the Syntex group[1,2] and these were prepared by treating 21-hydroxy steroids with silver oxide and alkyl halides in toluene. When **1** was reacted with 1.1 equiv. NaH in the presence or absence of electrophiles, a novel product was obtained in 81% yield. The new product (HPLCt_R 5.19 min, fluocinolone acetonidet_R 6.10 min),[3] $[\alpha]_D^{20}$=+35.8 (*c* 0.95 in DMSO), had a molecular formula of $C_{21}H_{24}F_2O_5$, determined from its high resolution mass spectrum,[4] and the ^{1}H and ^{13}C NMR spectra. The IR spectrum indicated the presence of hydroxy groups (3450 cm^{-1}), the dienone (1668, 1629 and 1610 cm^{-1}) and a γ-lactone moiety (1770 cm^{-1}). The 400 MHz ^{1}H NMR spectrum in DMSO-d_6 indicated the loss of the isopropylidene group, the loss of the ABX system associated with the 21-protons and the appearance of an additional secondary hydroxy group at δ 4.01 (t, *J* 7 Hz, C*H*OH) and 5.89 (d, *J* 7 Hz, CHO*H*). The ^{13}C NMR spectrum confirmed the loss of the 20-keto group (210 ppm) and the presence of an additional secondary alcohol (66.3 ppm) and γ-lactone carbonyl (177.5 ppm). From the above data and with the aid of a COSY and a series of decoupling experiments, all the protons of the product were identified, and structure **2** was proposed (NMR data is shown in Table 1). The 16,17-ring junction stereochemistry was established based on NOE experiments. In particular NOE effects were observed from 18-H to 16-H and 17-H, from 17-H to 16-H and 20-H, and from 16-H to 17-H. These are consistent with 16-H and 17-H being β. Finally the configuration of 20-OH was established as 20β based on the observed NOE between 17-H and 20-OH. Additionally, the 20-propionate ester **3**

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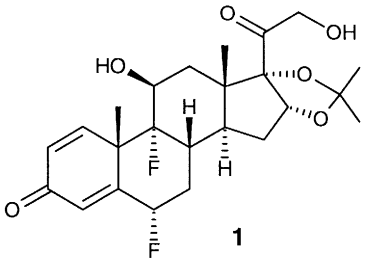
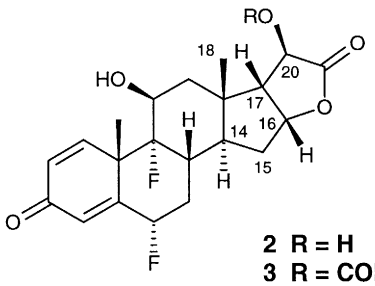
Table 1
NMR data for **2**

Position	δ_H	δ_C
1	7.27 (dd, *J* 10, 1 Hz, 1H)	151.7
2	6.29 (dd, *J* 10, 2 Hz, 1H)	129.0
3	-	184.3
4	6.11 (br.s, 1H)	119.4 (dd, *J* 12, 6 Hz)
5	-	162.7 (dd, *J* 14, 2 Hz)
6	5.62 (dddd, *J* 49, 11, 7, 1 Hz,1H)	86.7
7	2.24 (m, 1 H), 1.55 (m, 1H)	33.8 (d, *J* 18 Hz)
8	2.50 (m, 1H)	31.9 (dd, *J* 18, 12 Hz)
9	-	100.1 (dd, *J* 177, 1 Hz)
10	-	48.0 (dd, *J* 23, 4 Hz)
11	4.18 (m, 1H)	70.0 (dd, *J* 36, 3 Hz)
12	1.86 – 1.60 (m, 2H)	37.6
13	-	41.4
14	1.86 – 1.60 (m, 1H)	42.4
15	1.86 – 1.60 (m, 2H)	32.4
16	5.07 (t, *J* 7.5 Hz, 1H)	79.9
17	2.38 (t, *J* 8 Hz, 1H)	57.4
18	1.05 (s, 3H)	21.7
19	1.50 (s, 3H)	22.6 (d, *J* 5 Hz)
20	4.01 (t, *J* 7 Hz, 1H)	66.3
21	-	177.5
11-OH	5.51 (dd, *J* 5, 1 Hz, 1H)	-
20-OH	5.89 (d, *J* 7 Hz, 1H)	-

was selectively prepared from **2** and propionyl chloride in pyridine indicating that the 20-OH is sterically less hindered than the 11-OH.[5]

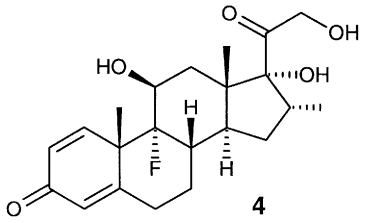


1



2 R = H
3 R = COEt

A search of the literature for novelty of **2** revealed a paper by a group at Syntex describing analytical methods for the determination of impurities of fluocinolone acetonide acetate in a topical formulation.[6] This paper reported a structure similar to that of **2**, however, the configuration at 17 was opposite to the one described herein and that at 16 and 20 was undefined. As there was no data given in the Syntex paper we are not in a position to ascertain whether the two compounds are the same.



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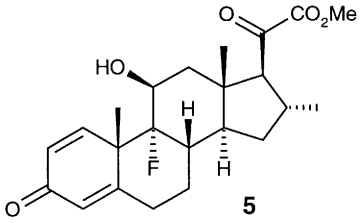

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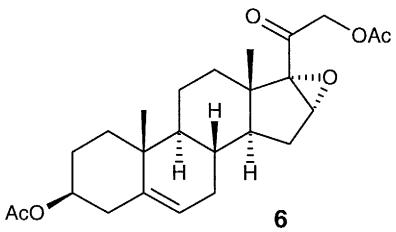

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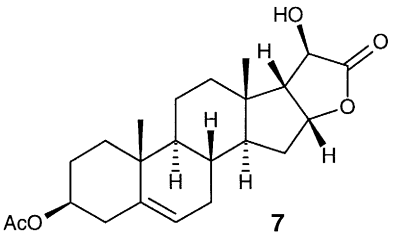

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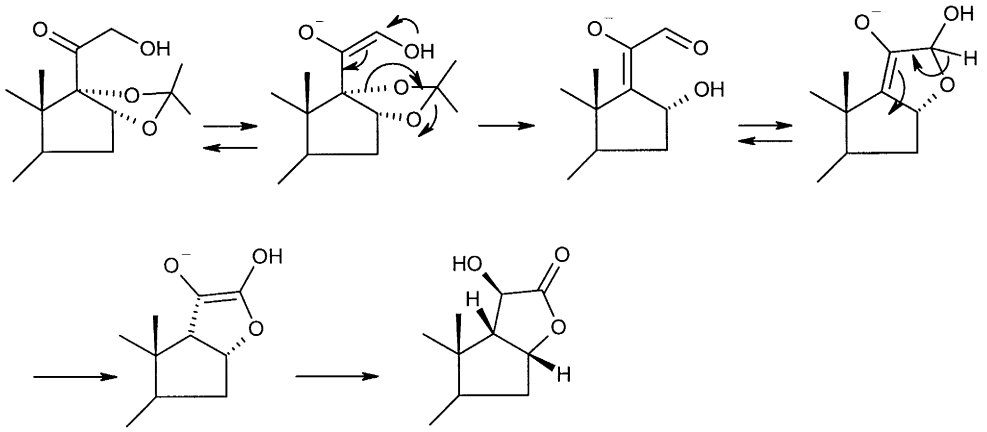
The methanolic hydrogen chloride catalysed rearrangement of the 17-dihydroxyacetone side chain of steroids to 17-glyoxal derivatives is known as the Mattox rearrangement.[7,8] More recently, it was shown that *N*,*N*-dimethylformamide dimethyl acetal rearranged dexamethasone (**4**) to the methyl ester **5**.[9] Finally a Schering group has reported[10] the treatment of epoxypregnenone **6** with *t*-BuOK in *t*-BuOH–CH_2Cl_2 to give the lactone **7** in 46% after heating to 80°C for 1 h. The rearrangement reported herein, and the above mentioned literature rearrangements, are rationalised by enolisation of the 20-keto group, followed by elimination of the 17α-substituent (Scheme 1). Cyclisation of the unmasked 16α-OH on to the newly generated aldehyde carbonyl gives a lactol, which undergoes a proton shift establishing the *cis* ring junction at 16 and 17. Protonation upon work up provides the α-hydroxy-ɣ-lactone. The isolation of only the 20β-OH diastereoisomer may be a result of thermodynamic equilibration.

In summary we have demonstrated the formation of the novel lactone **2** from **1** by simply using 1.1 equiv. NaH in DMF at room temperature and in high yield. A plausible mechanism for the formation



Scheme 1.

of the above lactone and of related rearrangements of steroids with the 17-dihydroxyacetone chain is presented.

References

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3. Analytical HPLC conducted on 15 cm×0.46 cm Phenomenex Prodigy ODS-2 column, eluting with 0.05% aqueous TFA–MeCN using a gradient (15–95% MeCN) over 16 min, with a flow rate of 1.5 ml/min.
4. Mass spectrum: ES+ve *m/z* 395 $(M+H)^+$ and 789 $(2M+H)^+$. HRMS found: 395.1668 $C_{21}H_{25}F_2O_5$ requires 395.1670.
5. Data for **3**: HPLC t_R 7.02 min; IR (KBr) 3470, 1764, 1747, 1669, 1632 cm^{-1}; NMR δ (250 MHz, DMSO-d_6) 7.27 (1H, d, *J* 10 Hz), 6.29 (1H, d, *J* 10 Hz), 6.11 (1H, s), 5.72 and 5.56 (1H, 2m), 5.57 (1H, m), 5.22 (2H, m), 4.17 (1H, m), 2.67 (1H, t, *J* 7 Hz), 2.39 (2H, q, *J* 7 Hz), 1.49 (3H, s), 1.05 (6H, s and t, *J* 7 Hz); MS(ES+ve) *m/z* 451 $(M+H)^+$, 901 $(2M+H)^+$. Found: C, 63.61; H, 6.51 $C_{24}H_{28}F_2O_6$ requires C, 63.99; H, 6.27%.
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