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An unusual dienone-phenol rearrangement product formed during the synthesis of mometasone furoate (Sch 32088)

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*The structure of an unusual dienone-phenol rearrangement product **4** obtained during the synthesis of mometasone furoate (Sch 32088) was assigned on the basis of NMR and x-ray crystallographic data. The mechanism of formation is discussed.* (*Steroids* **63**:135–140, 1998) © *1998 by Elsevier Science Inc.*

Keywords: mometasone furoate; dienone-phenol rearrangement; mechanism; NMR; x-ray

Introduction

Discovered in our laboratories, mometasone furoate, 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2′-furoate),[1] Sch 32088, Elocon®, **2** is a medium potency synthetic corticosteroid anti-inflammatory agent, indicated for the treatment of various steroid responsive dermatoses, such as psoriasis[2] and dermatitis.[3] The drug is characterized by its low potential for systemic activity as measured by its effect on the hypothalamic-pituitary-adrenal axis when applied topically.[4,5]

A synthesis of mometasone furoate from commercially available intermediate has been described[6,7] but we have also prepared mometasone furoate from the 9,11 epoxide **1** as shown in Scheme 1.[8] During the course of hydrogen chloride induced ring opening of the 9,11 epoxide, we observed the formation of a byproduct **3** (Figure 1) whose structure was reported previously,[8] arising via a carbonium ion promoted rearrangement involving the C and D rings. In this paper, we describe the formation, isolation, and characterization of a second unusual byproduct **4**, which emanates from a dienone-phenol rearrangement involving the A and B rings.

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Experimental

*9α,21-Dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2′-furoate) **2** and 11α,21-dichloro-3,17α-dihydroxy-16α-methyl-9(10)-secopregna-1,3,5(10)-triene-9,20-dione 17-(2′-furoate) **4***

Hydrogen chloride gas was slowly bubbled through a solution of 21-chloro-9β,11β-epoxy-17α-hydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2′-furoate) **2** (49.39 g, 0.102 mol) in methylene chloride (300 mL) at R_t for 90 min. The solvent was removed under vacuum and the residue was crystallized from methanol to give pure compound **3**[6] (33.24 g, 62.6%). The mother liquors were concentrated to dryness and the residue column chromatographed (silica-gel, 60 mesh, hexane/ethyl acetate gradient, 250-mL fractions). The contents of fractions 4, 5, and 6 were combined and crystallized from ethyl acetate to afford compound **4** (125 mg), m.p. = 240–242°C, decomp., $[\alpha]_D^{23°C} = +6°$ [c = 0.18, $CHCl_3$]. IR (nujol): 1712 & 1695 cm^{-1} (C═O). Analysis calculated for $C_{27}H_{30}Cl_2O_6$: Cl, 13.60%. Found: Cl, 13.49%. Mass calculated for $C_{27}H_{30}Cl_2O_6$: 520. Found: m/z 520 [EIMS] and 521 [FABMS]. Fraction 12 from the same chromatography contained compound **3**.[8]

Figure 2 shows the reverse phase HPLC (Supelcosil LC-8 column; mobile phase, MeOH/H_2O [77 : 43]; flow rate 1.2 mL/min; UV detection at 254 nM) profile of a mixture of compounds **1, 2, 3,** and **4**.

Results and discussion

*NMR analysis of **4***

Table 1 presents the analysis of 2D (^1H–^1H) COSY, HMBC and other NMR data. By comparison of this NMR data with

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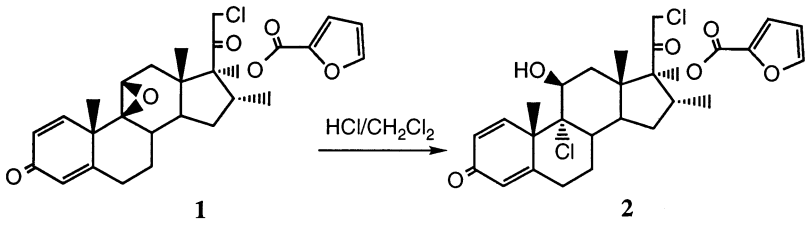


Scheme 1

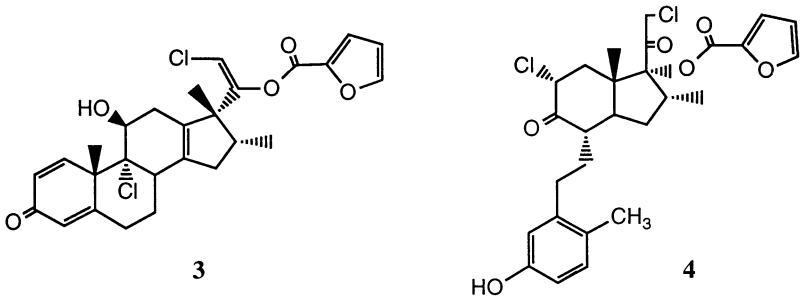


Figure 1 Byproducts **3** & **4** of mometasone furoate synthesis.

that of compounds **3**[8] and **2** (not listed), it is evident that the original A-ring dienone system has been replaced by a methyl substituted phenolic ring and a new ketone function at δ 202.2. The proton resonance of the 19-methyl group was shifted significantly downfield to δ 2.20. The 2D (^{1}H–^{1}H) COSY spectrum provided important structural information about ring C; an A_2X pattern ($C_{(11)}$–$C_{(12)}$) at δ 5.20 (CH) and δ 2.41 (center, m, CH_2) and a correlation of the δ 2.71 (CH) resonance with the δ 1.45 and δ 1.80 multiplets (CH_2) ($C_{(8)}$–$C_{(7)}$) and δ 2.46 (CH) resonance ($C_{(8)}$–$C_{(14)}$). 1D NOE NMR data gave positive NOE's between 18-CH_3 and 12β-H, as well as between 11β-H and 18-CH_3 and 11β-H and 12β-H. A phase sensitive 2D NOE experiment indicated many cross-peaks depicting through space interactions. HMBC correlation confirmed the position of the new ketone function at $C_{(9)}$. These observations led us to assign the 9-keto-11α-chloro-9,10-seco structure **4**, which was confirmed unequivocally by x-ray crystallographic analysis.

*X-ray crystal structure analysis of **4***

Crystal data. $C_{27}H_{30}Cl_2O_6$, M = 521.44, orthorhombic, a = 12.167(1) Å, b = 27.947(3) Å, c = 7.580(1) Å, V = 2577.4(8) Å^3, Z = 4, D_{calcd} = 1.344 g cm^{-3}, μ(Cu–$K\alpha$ radiation, λ = 1.5418 Å) = 26.2 cm^{-1}. Space group $P2_12_12_1$(D_2^4) uniquely from the Laue symmetry and systematic absences: h00 when $h \neq 2n$, 0k0 when $k \neq 2n$, 00l when $l \neq 2n$. Crystallographic calculations were performed

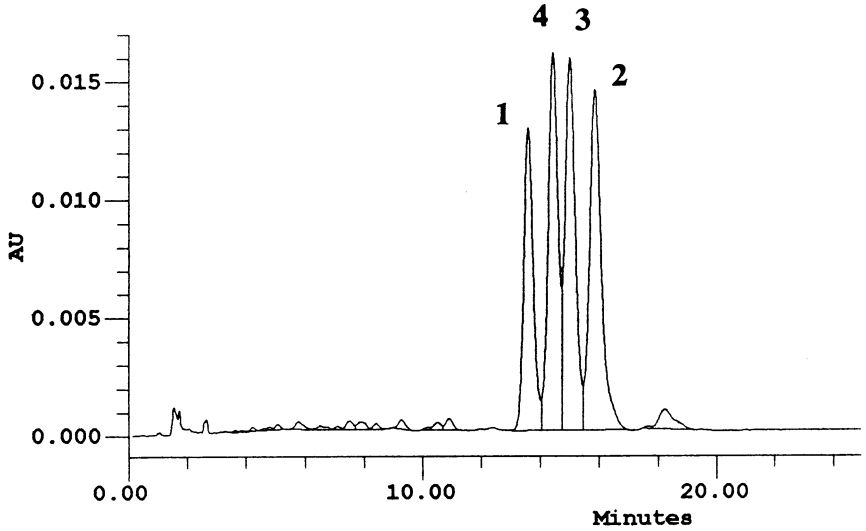


Figure 2 High-performance liquid chromatography profile of a mixture of compounds **1, 2, 3,** and **4**.

Table 1 ^{13}C and ^{1}H NMR Spectral Data of Compound **4** in DMSO-d_6[a]

C	^{13}C, δ (ppm)	^{1}H, δ (ppm), J (Hz)
C-1	130.6	6.90 (d, 8)
C-2	112.6	6.49 (dd, 8, 1)
C-3	155.1	
C-4	115.2	6.58 (d,1)
C-5	141.4	
C-6	33.0	2.41 (m), 2.60 (m)
C-7	30.6	1.45 (m), 1.80 (m)
C-8	48.1	2.71 (m)
C-9	202.2	
C-10	125.3	
C-11	62.5	5.20 (t, 11, 8.5)
C-12	41.5	2.41 (m)
C-13	49.1	
C-14	48.6	2.46 (m)
C-15	36.1	1.35 (m), 1.95 (m)
C-16	38.5	3.45 (m)
C-17	94.8	
C-18	16.3	1.12 s
C-19	17.8	2.20 s
C-20	196.8	
C-21	47.3	4.63 s
C-22	14.1	0.88 (d, 6.5)
C-23	157.4	
C-24	142.3	
C-25	120.3	7.55 (m)
C-26	112.4	6.74 (m)
C-27	148.6	8.05 (m)

[a]Assignments based upon APT, selective INEPT, 2D (H–H)COSY and HMBC experiments. δ 3-OH = 9.0.

on PDP11/44 and Micro VAX computers by use of the Enraf-Nonius Structure Determination Package.

Crystallographic measurements. Oscillation and Weissenberg photographs yielded preliminary unit-cell parameters and space group information. One octant of intensity data was recorded on an Enraf-Nonius CAD-4 diffractometer (Cu–$K\alpha$ radiation, graphite monochromator; ω-2θ scans, θ_{max} = 75°) from a crystal of dimensions 0.25 × 0.32 × 0.56 mm. The intensities of four strong reference reflections, remeasured every 2 h during data collection, showed insignificant variation (<1% overall). In addition to the usual corrections for Lorentz and polarization effects, an empirical absorption correction, [$T_{max} : T_{min\ (relative)}$ = 1.00 : 0.80] based on the ϕ dependency of the intensities of several reflections with χ ca. 90°, was also applied to the data. From a total of 3,029 nonequivalent measurements, those 2,290 reflections with $I > 3.0\sigma(I)$ were retained for the analysis. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections ($35° < \theta < 40°$) widely separated in reciprocal space.

Structure analysis. The crystal structure was solved by direct methods. Initial non-hydrogen atom coordinates were obtained from an *E*-map. Positional and thermal parameters (first isotropic and then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations during which $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$; $\Delta = (|F_o|-|F_c|)$] was minimized. Hydrogen atoms were then located in a difference Fourier synthesis and incorporated at their calculated positions in the subsequent iterations. A secondary extinction correction, g, was included as a variable during the later iterations which converged at $R = 0.047$ [$R_w = 0.065$, GOF = 1.77, $g = 1.1(2) \times 10^{-6}$], where $R = \Sigma\|F_o|-|F_c\|/\Sigma|F_o|$; $R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|^2]^{1/2}$; GOF = $[\Sigma w\Delta^2/(N_{observations}-N_{parameters})]^{1/2}$. No unusual features were present in a final difference Fourier synthesis ($\Delta\rho$: max 0.30; min −0.28 e/Å^3). For all structure–factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from the literature.[9]

A view of the solid-state conformation, with the crystallographic atom numbering scheme, is provided in Figure 3. Bond lengths all lie close to expected values.[10] The aromatic ring atoms are strictly coplanar ($\Delta \pm 0.001$–0.002 Å) while those of the directly bonded substituents lie close to the least-squares plane through the ring atoms [Δ(Å): C(6) 0.034, C(19) −0.015, O(23) 0.020]; the C(6)-C(7) bond is oriented approximately perpendicular to the ring plane [C(10)-C(5)-C(6)-C(7) torsion angle = 81.0(5)°]. Endocyclic torsion angles, ω_{ij} ($\sigma \pm 0.3$–$0.5°$), about the bonds between atoms i and j in the cyclohexanone moiety [$\omega_{8,9}$

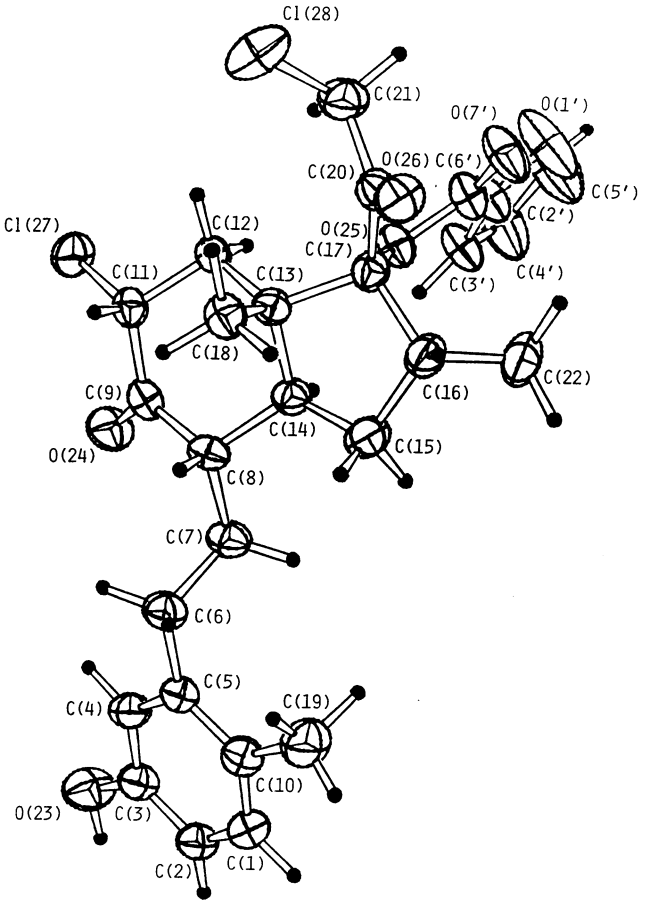
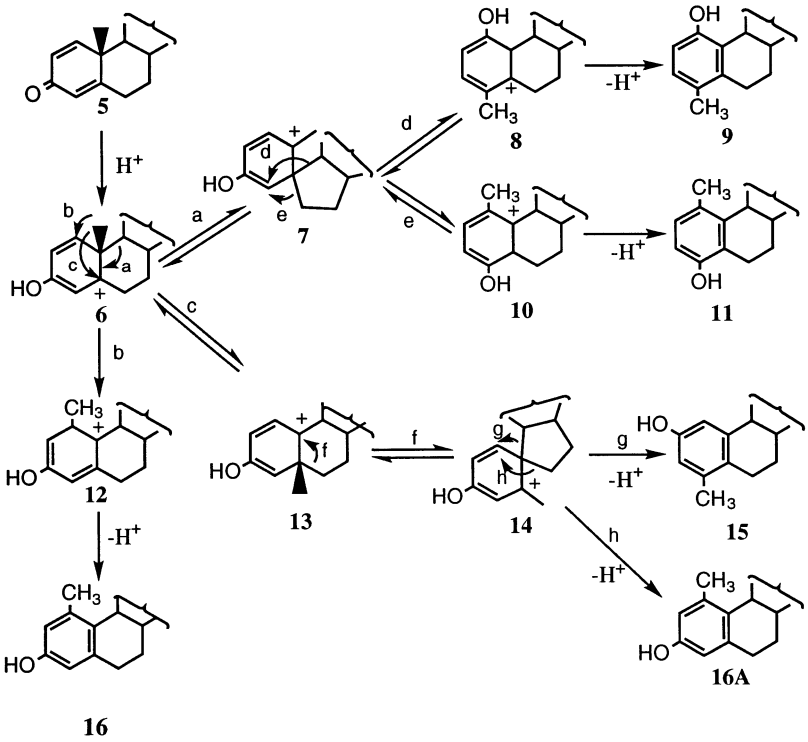
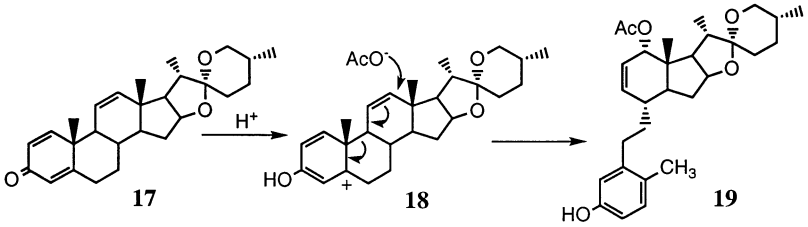


Figure 3 ORTEP diagram (40% probability elipsoids) showing the atom numbering scheme and solid state conformation of **4**; small filled circles represent hydrogen atoms.



Scheme 2

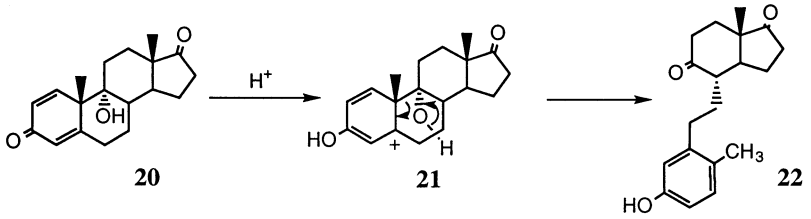


Scheme 3

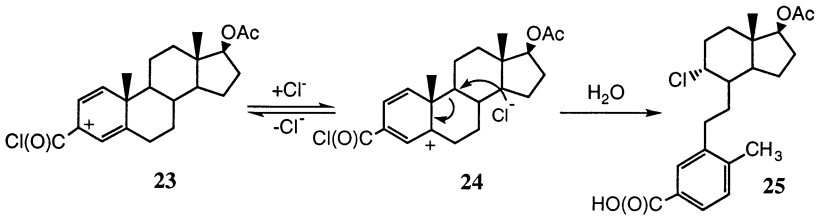
-47.9, $\omega_{9,11}$ 47.1, $\omega_{11,12}$ -51.0, $\omega_{12,13}$ 58.5, $\omega_{13,14}$ -65.3, $\omega_{14,8}$ 57.5°] show that the ring has a chair conformation flattened around C(9); the α-oriented Cl substituent is equatorial. Torsion angles ($\sigma \pm 0.3$–0.5°) in the cyclopentane ring [$\omega_{13,14}$ 46.4, $\omega_{14,15}$ -34.3, $\omega_{15,16}$ 7.9, $\omega_{16,17}$ 20.9, $\omega_{13,17}$ -41.4°] indicate that it lies intermediate between an envelope form, with C(13) as the out-of-plane atom, and a half-chair form in which the C_2-symmetry axis passes through C(16) and bisects the C(13)-C(17) bond. The furan ring atoms are coplanar ($\Delta \pm 0.003$–0.007 Å), and C(6′) lies in the ring plane (Δ 0.001 Å). The dihedral angle between the least-squares plane through C(2′), C(6′), O(7′), O(25) of the ester group at C(17) (Δ 0.319 Å) and that through the furan ring atoms is 10.8°; torsion angles characterizing the arrangement around the O(25)-C(6′) and C(2′)-C(6′) bonds are: C(17)-O(25)-C(6′)-O(7′) -14.7(6)°, O(1′)-C(2′)-C(6′)-O(7′) -11.4(8)°. In crystals of **4**, molecules related by the 2_1 screw axis along *a* are linked by an O-H . . . O hydrogen bond [O(23) . . . O(24) = 2.931(5) Å].

Mechanistic considerations

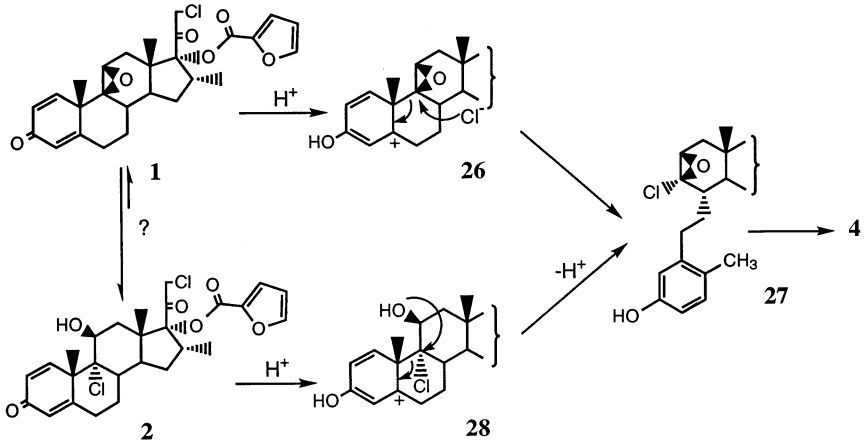
The products of steroid 1,4-diene-3-one-phenol rearrangements are A-ring aromatized compounds, bearing a methyl and phenolic hydroxyl group, either *meta* or *para* to each other which arise through various 1,2 carbon bond shifts, from the carbonium ion **6** produced by protonation of the 3-carbonyl oxygen (Scheme 2).[11] Migration of $C_{(9)}$ to $C_{(5)}$ leads to the spiro cation **7**, which in turn gives rise to the '*para*' phenols **9** and **11** by migration of $C_{(9)}$ to $C_{(4)}$ or $C_{(6)}$ to $C_{(4)}$ respectively, followed by deprotonation. The '*meta*' phenol **16** is generated from cation **6** by migration of the C-19 methyl, from $C_{(10)}$ to $C_{(1)}$ affording cation **12** which aromatizes by loss of a proton. Conversely, shift of the 19-methyl group from $C_{(10)}$ to $C_{(5)}$ affording **13**, followed by a migration of $C_{(6)}$ to $C_{(10)}$ generates a new spiro cation **14** which on suffering a $C_{(9)}$ to $C_{(1)}$ reorganization yields a second '*meta*' phenol **15**. In cation **14**, migration of $C_{(6)}$ to $C_{(1)}$ leads to the '*meta*' phenol **16A** which although structurally identical to **16** has a different ordering of



Scheme 4



Scheme 5



Scheme 6

the original carbon atoms. The particular mechanistic pathway followed in the dienone–phenol rearrangement is dependent upon reaction conditions and the nature of substituents in the substrate.

Steroid carbocations of type **6** and **7** can also be quenched by scission of the $C_{(9,10)}$ bond to produce 9,10-secosteroids. This mechanistic variant is rare, although fragmentation of this bond with concomitant aromatization of the A ring is often observed in certain reductive rearrangements.[12] The rearrangement of the $\Delta^{11,12}$-1,4-diene-3-one **17** with acetic anhydride in acetic acid gave the aromatic 12α-acetoxy-$\Delta^{9,11}$-9,10-secosteroid **19** by the mechanism suggested in Scheme 3[13] and microbiological reduction of 9α-hydroxyandrost-4-ene-3,17-dione was reported[14] to give the aromatic 9,17-diketo-secosteroid **22** via the putative corresponding 1,4-dien-3-one intermediate **20** (Scheme 4). Interestingly, in the reaction of a $\Delta^{1,4}$-3-ketosteroid with phenyl(trichloromethyl)mercury, intermediate carbocations **23** and **24** (Scheme 5) were proposed to justify the formation of the aromatic 9α-chloro-9,10-secosteroid **25**.[15]

We are not aware of any examples of dienone-phenol rearrangements of 9β,11β-epoxysteroids, which are normally protonated on the epoxide oxygen, leading in this case to a chlorohydrin. However, competitive protonation at the 3-carbonyl oxygen would generate carbocation **26** (Scheme 6). By analogy to the precedents cited above, ion **26** can be quenched by chloride attack at C-9α with consequent rupture of the $C_{(9,10)}$ bond to give chloroepoxide **27**. Carbonium ion **26** may undergo bond reorganization via a spirocation of type **7** followed by a $C_{(9)}$ to $C_{(4)}$ shift prior to $C_{(9,10)}$ bond scission which would also lead to the same chloro-epoxide **27**. Steroid chloroepoxides have been reported[16] to readily undergo rearrangement to α-chloroketones by migration of chlorine, with the intermediate being considered an α-ketocarbonium ion chloride in the form of an ion pair.

Intermediate **27** might also arise by an alternative mechanism from mometasone furoate **2**. Protonation of the 3-carbonyl oxygen of **2** would lead to a new carbocation **28** (Scheme 6) which could gain aromaticity by intramolecular attack of the 11β hydroxyl at $C_{(9)}$ to afford the same chloroepoxide **27**. Indeed when mometasone furoate **2** was treated with hydrogen chloride in methylene chloride, a small amount of the same chloroseco compound **4** was observed. We cannot distinguish which or whether both of these mechanisms are operating. It may also be true, that under the conditions of the reaction, an equilibrium exists between chlorohydrin **2** and its precursor epoxide **1** and the chloroseco compound **4** arises only from the latter.

Acknowledgment

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Note

Tables of atomic positional and thermal parameters, bond lengths and angles for compound **4** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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