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An unusual rearrangement product formed during production of mometasone furoate (Sch 32088)

M.S. Puar,* P.A. Thompson,* M. Ruggeri,* D. Beiner,* and A.T. McPhail†

**Schering-Plough Research Institute, Kenilworth, New Jersey; †Department of Chemistry, P.M. Gross Chemical Laboratory, Duke University, Durham, North Carolina, USA*

The structure of an unusual rearrangement product obtained during the production of mometasone furoate (Sch 32088) was assigned on the basis of NMR and X-ray crystallography data. (*Steroids* **60**:612–614, 1995)

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Introduction

During the course of synthesis of mometasone furoate (**1** Sch 32088), we detected minor amounts of a rearranged side product (**2**) (Figure 1). We determined the structure of compound (**2**) in order to propose a mechanism of formation and hence to alter the reaction conditions for its elimination. The latter would improve overall yield of the desired product (**1**). We report here the structure of **2** assigned on the basis of NMR studies and confirmed by the X-ray crystallographic data, and some mechanistic considerations of its formation.

Results and discussion

By column chromatography (silica gel, CH_2Cl_2-EtOAc) of a batch of mometasone furoate, we isolated compound **2** ($C_{27}H_{28}O_5Cl_2$, m/z 502 [EIMS] and 503 [FABMS]). It was crystallized from CH_2Cl_2/MeOH solution (m.p. = 223–224°C, decomp.) and exhibited the following IR spectrum: (nujol, cm^{-1}) 3285 (OH), 3140 (CH furan ring), 1765, 1742 (C=O, OC=O), 1600, 1610 (C=C), 1165 (C−O ester), 1095 (C−O hydroxy). Table 1 presents the analysis of 2D (^1H-^1H) DQF COSY, (^1H-^{13}C) COSY and other NMR data. Comparison of the NMR data with that of compound **1** (not listed) indicated the formation of two double bonds; one tetrasubstituted and the other associated with only a single vinylic proton (δ 6.21, ^{13}C = 107.1 ppm). It also indicated the loss of the 21-methylene protons. In addition, comparison of molar ellipicities from the CD spectra (Figure 2) indicated the loss of C-20 carbonyl absorption at 300 μm with concurrent increase in planarity in the molecule.

Phase-sensitive 2D NOE experiment indicated many cross-peaks depicting through-space interactions (interatomic distances of less than 4Å), for example, between H_1-H_2, H_1-H_{11}, and H_1-H_{19}, as well as H_{19}-11βOH, H_{19}-H_8, H_{19}-H_6, and H_{18}-H_{21}. From the 1D NOE data the most pertinent through-space interactions were between H_{21} and H_{18} (2.4%) and H_{25} and H_{22} (0.8%).

X-ray crystal structure analysis of 2

Crystal data. $C_{27}H_{28}Cl_2O_5$, M = 503.43, monoclinic, a = 8.519(1) Å, b = 20.678(3) Å, c = 7.486(1) Å, β = 111.95(2)°, V = 1223.1(8) Å, Z = 2, D_{calcd} = 1.367 g cm^{-3}, μ(Cu-$K\alpha$ radiation, λ = 1.5418 Å) = 27.2 cm^{-1}. Space group $P2_1(C_2^2)$ from the Laue symmetry and systematic absences, 0k0 when $k \neq 2n$, and **2** is chiral. Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf-Nonius Structure Determination Package (SDP).

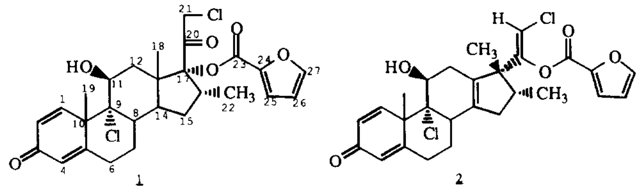

Figure 1 Mometasone furoate (**1**, Sch 32088, 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2′-furoate)) and side product (**2**, (*Z*)-9α,21-dichloro-20-[(2′-furanylcarbonyl)oxyl]-11β-hydroxy-16α,17β-dimethyl-18-norpregna-1,4,13,20-tetraen-3-one).

Address reprint requests to M.S. Puar, Schering-Plough Research Institute, Kenilworth, NJ 07033-0539 USA.

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655 Avenue of the Americas, New York, NY 10010

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Table 1 ^{13}C and ^{1}H NMR spectral data of compound 2 in DMSO-d_6[a]

C	^{13}C, δ	^{1}H, δ in ppm, J in Hz
C-1	152.3	7.27 (d, 10)
C-2	127.5	6.16 (dd, 10,1)
C-3	184.3	
C-4	124.2	5.94 (broad s)
C-5	165.5	
C-6	30.9	2.62 (m), 2.32 (m)
C-7	24.3	1.90 (m), 1.35 (m)
C-8	34.4	3.30 (dd, 10,1)
C-9	80.1	
C-10	49.0	
C-11	68.2	4.44 (m)
C-12	39.4	2.42 (dd, 16,1), 1.95 (dd, 16, 1)
C-13	136.0	
C-14	131.5	
C-15	30.3	2.32 (m), 2.04 (m)
C-16	44.8	2.05 (m)
C-17	55.9	
C-18	21.1	1.16 (s)
C-19	24.3	1.52 (s)
C-20	150.7	
C-21	107.1	6.21 (s)
C-22	14.1	1.05 (d, 6.5)
C-23	152.0	
C-24	142.6	
C-25	118.7	7.26 (m)
C-26	111.9	6.68 (m)
C-27	147.7	7.98 (m)

[a] Assignments based upon APT, 2D (H-H) DQF COSY and (H-^{13}C) COSY experiments. (δ11-OH = 5.34 [d, 4])

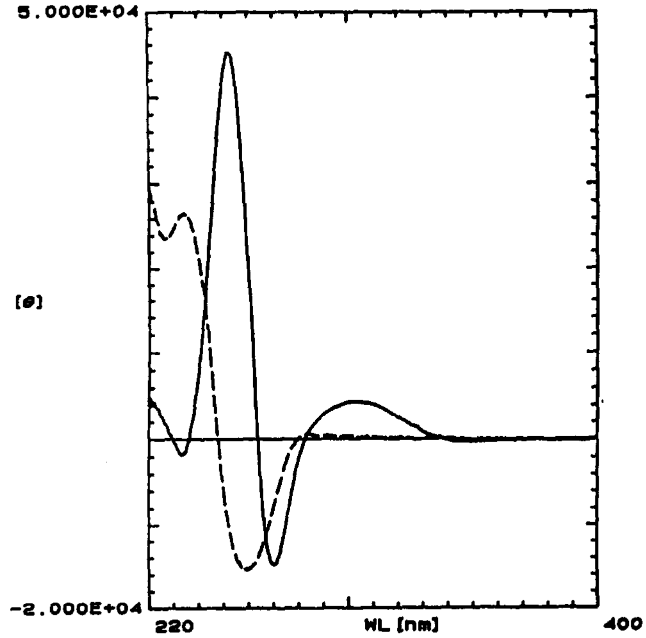


Figure 2 CD spectra of *1* (solid line) and *2* (broken line).

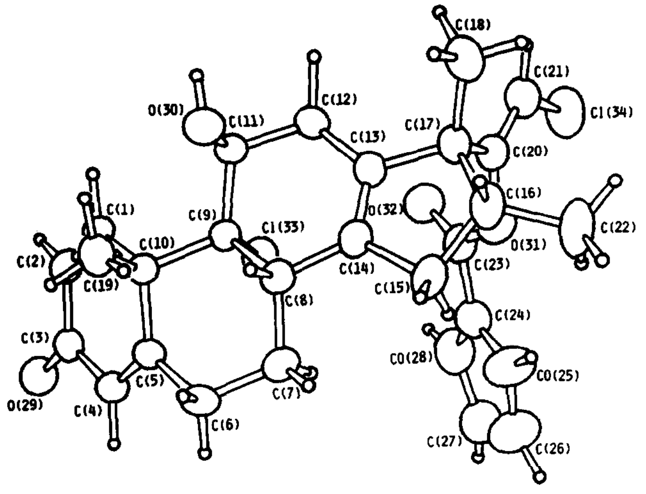


Figure 3 ORTEP diagram showing the structure and solid-state conformation of *2;* small circles represent hydrogen atoms.

Crystallographic measurements. Weissenberg oscillation and precession photographs yielded preliminary unit-cell parameters and space group information. Intensity data ($+h$, $+k$, $\pm l$; 2236 non-equivalent reflections) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-$K\alpha$ radiation, graphite monochromator; $\omega = 2\theta$ scans, θ_{max} = 67°). The intensities of four reference reflections, remeasured every 2 h during data collection, showed no significant variation (<1%) throughout. The data were corrected for the usual Lorentz and polarization effects, and an empirical absorption correction, based on the ϕ-dependency of the intensities of four reflections with $\chi \sim 90°$, was also applied. Those 2176 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 (56° < θ < 67°) widely separated in reciprocal space.

Structure analysis. The crystal structure was solved by direct methods. Approximate coordinates for the non-hydrogen atoms were derived from an *E*-map. Positional and thermal parameters of these atoms (at first isotropic, then anisotropic) were adjusted by means of several rounds of full-matrix least-squares calculations. During these iterations it became apparent that the furan ring was disordered over two orientations and so for one pair of atoms, CO(25) and CO(28), an average (fo + fc)/2 scattering factor was employed in the later cycles. Hydrogen atoms were located at their expected positions in a difference Fourier synthesis, and their positional and isotropic thermal parameters were included as variables in the subsequent least-squares itera-

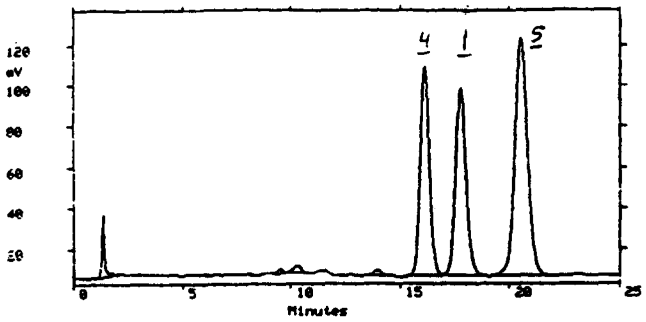


Figure 4 HPLC profile of a mixture of *4, 1,* and *5* detected at 481 nm in CH_3OH-H_2O (65:35) with flow rate of 1.5 ml/min utilizing Dupont Zorbax C-8 30 cm column.

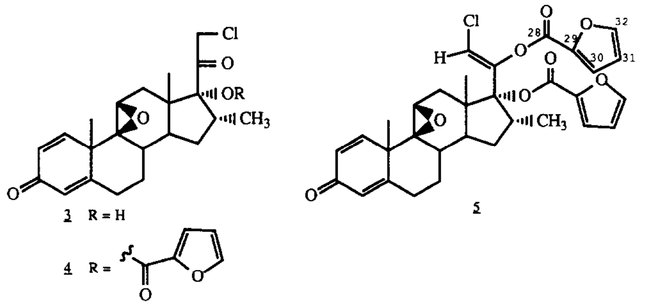


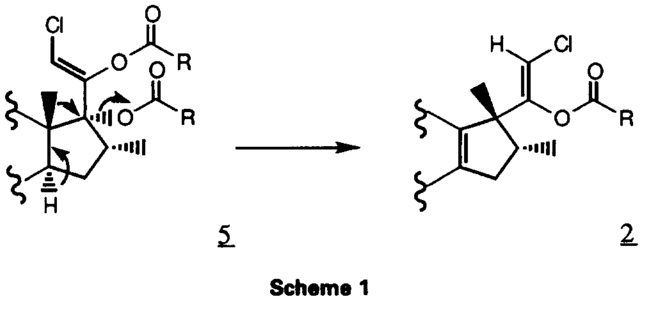
Figure 5 Compounds **3**, **4**, and **5**.

tions; the hydrogen atom associated with disordered CO(25) and CO(28) was incorporated at calculated positions with 50% occupancy of each possible site. A secondary extinction coefficient (g) was also refined during the later least-squares cycles which converged at $R = 0.029$ [$R_w = 0.039$; GOF = 1.54, $g = 2.0(4) \times 10^{-6}$], from equation $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = [\Sigma w(|F_o| - |F_o| - |F_c|)^2/\Sigma_w|F_o|^2]^{1/2}$; GOF $= [\Sigma w\Delta^2/^N\text{observations} - {}^N\text{parameters})]^{1/2}$. A final difference Fourier synthesis contained no unusual features ($\Delta\rho$: max 0.20; min -0.19 e/Å^3). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from the literature.[1] In the least-squares iterations, $\Sigma w\Delta^2[w = 1/\sigma^2(|F_o|), \Delta = (|F_o| - |F_c|)]$ was minimized.

A view of the solid-state conformation, with the crystallographic atom numbering scheme, is provided in Figure 3. Ring A is fairly flat, ring B has a chair conformation slightly flattened as expected around C-5, ring C approximates to a half-chair form, and ring D is in an envelope conformation. Endocyclic torsion angles $w_{ij}(\sigma \pm 0.2–0.5°)$ about the bond between atoms i and j as follows: $\omega_{1,2}$ -0.5, $\omega_{2,3}$ -3.1, $\omega_{3,4}$ 1.5, $\omega_{4,5}$ 3.7, $\omega_{5,10}$ $-6.7°$ in ring A; $\omega_{5,6}$ -51.9, $\omega_{6,7}$ 50.6, $\omega_{7,8}$ -54.4, $\omega_{8,9}$ 57.7, $\omega_{9,10}$ -54.5, $\omega_{10,5}$ 52.5° in ring B; $\omega_{8,9}$ -43.2, $\omega_{9,11}$ 58.6, $\omega_{11,12}$ -44.4, $\omega_{12,13}$ 17.7, $\omega_{13,14}$ -4.2, $\omega_{14,8}$ 17.3° in ring C; $\omega_{13,14}$ -0.2, $\omega_{14,15}$ 14.4, $\omega_{15,16}$ -22.1, $\omega_{16,17}$ 21.7, $\omega_{17,13}$ $-13.7°$ in ring D. Bond lengths are in accord with expectations.[2] In the crystal, molecules of Sch 32088 are associated by an O–H . . . O hydrogen bond [O(30) . . . O(29) + 2.782(3) Å].

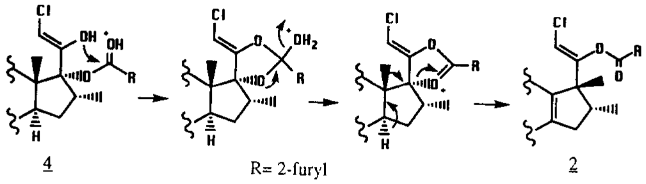
Mechanistic considerations

We observed that during the formation of **4** from **3** (via esterification with 2-furoyl chloride[3–5] a diester (**5**) was also formed, through enolization of the 20-ketone. Compound **5** ($C_{32}H_{31}O_8Cl$, m/z 577.5/579.5); [^{1}H NMR, $CDCl_3$, δ] 1.05 (d, 6.5, CH_3), 1.20 (s, CH_3), 1.45 (s, Ch_3), 2.84 (m, H_{16}), 3.15 (m, H_{11}), 6.18 (dd, H_2), 6.20 (m, H_4), 6.27 (s, new = CH), 6.48, 6.56, 7.02 (d), 7.13 (d), 7.59, 7.62 (all furan protons), and 6.60 (d, H_1). [^{13}C NMR] 17.1, 17.7, 23.6 (all CH_3's), 19.2, 30.2, 30.6, 34.3 (all CH_2's), 34.6, 37.5, 47.2 (all CH's), 44.1, 49.4, 66.1, 94.4 (all quaternary carbons), 62.6 (CHO), 110.9, 111.9, 112.1, 118.0, 119.8, 125.0, 127.9, 146.5, 147.6, 152.4 (all = CH's) and 143.1, 144.7, 145.1, 152.8, 156.6, 165.2, 186.3 (all = C and C = O carbons).



Scheme 1

Compounds **4** and **5** co-elute on thin-layer chromatography (TLC) and normal phase HPLC. However, reverse-phase HPLC resulted in separation (Figure 4) indicating a 1:1 mixture v/v of **4** and **5**. However, ratios as high as 8:1 have been observed depending upon the reaction conditions (Figure 5).



Scheme 2

We can rationalize the formation of compound *2* as follows. Ring opening of the 9,11-epoxide (concentrated HCl, glacial acetic acid), carried out on the mixture of **4** and **5** led to the formation of **1** along with **2** as a minor impurity. The latter is likely formed from **5** via a carbonium ion mechanism, with the migration of the C-18 methyl to the electron deficient C-17 by either a stepwise or concerted process (Scheme 1). One of the reviewer suggested an alternative mechanism involving acid-catalyzed migration from C-17 to C-20 of acyl moiety (Scheme 2). Such reactions are well documented for the acid catalyzed rearrangement of 17-hydroxy steroids.[6]

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Notes and abbreviations

X-ray crystallographic data for this structure have been deposited with the Director, Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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