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Reactions of Cephalosporin Sulphones 1. Rearrangement of the β-Lactam Ring to a Triazole Derivative

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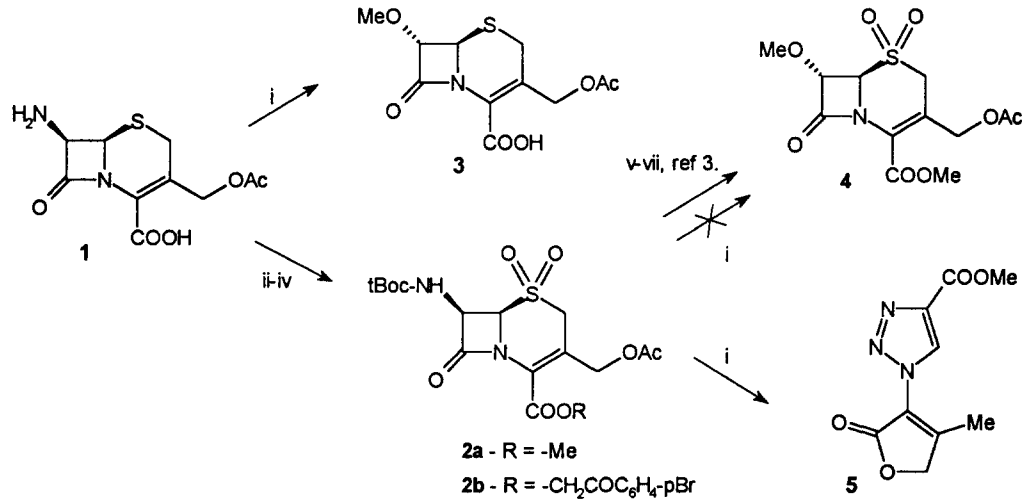
Abstract: The 7β-amino-cephalosporin sulphones, generated *in situ* from the appropriate 7β-tBoc-amino derivative and diazotized in a one-pot reaction in aq. $HClO_4$ - MeOH - $NaNO_2$, rearrange exclusively to the triazoles **5** in a multistep reaction.

Several 7α-alkyloxy- or halogenocephalosporin sulphone derivatives are known to possess β-lactamase[1] or human leukocyte elastase[2] inhibitory properties. The main route to these 7α-derivatives involves diazotisation of the corresponding amine and exchange of the diazo function under appropriate conditions and subsequent oxidation of the sulphur. This is usually a one-pot reaction of inadequate yield, and several attempts have been made recently to optimize this process (see ref. 3 and the literature cited therein). In our approach we have chosen oxidation prior to diazotisation, assuming that the sulphone is more resistant to the reaction conditions of diazotisation. In a previous paper[3] we described the conversion of **2a** to **4** by using distinct steps for removing the tBoc protecting group, diazotisation and rhodium(II)-catalysed exchange



i) $HClO_4$/MeOH, $NaNO_2$; ii) Boc_2O; iii) CH_2N_2 or pBr-$C_6H_4COCH_2Br$; iv) H_2O_2/$NaWO_4$; v) TFA, anisole; vi) i-amyl nitrite, cat. TFA; vii) MeOH, $Rh_2(OAc)_4$

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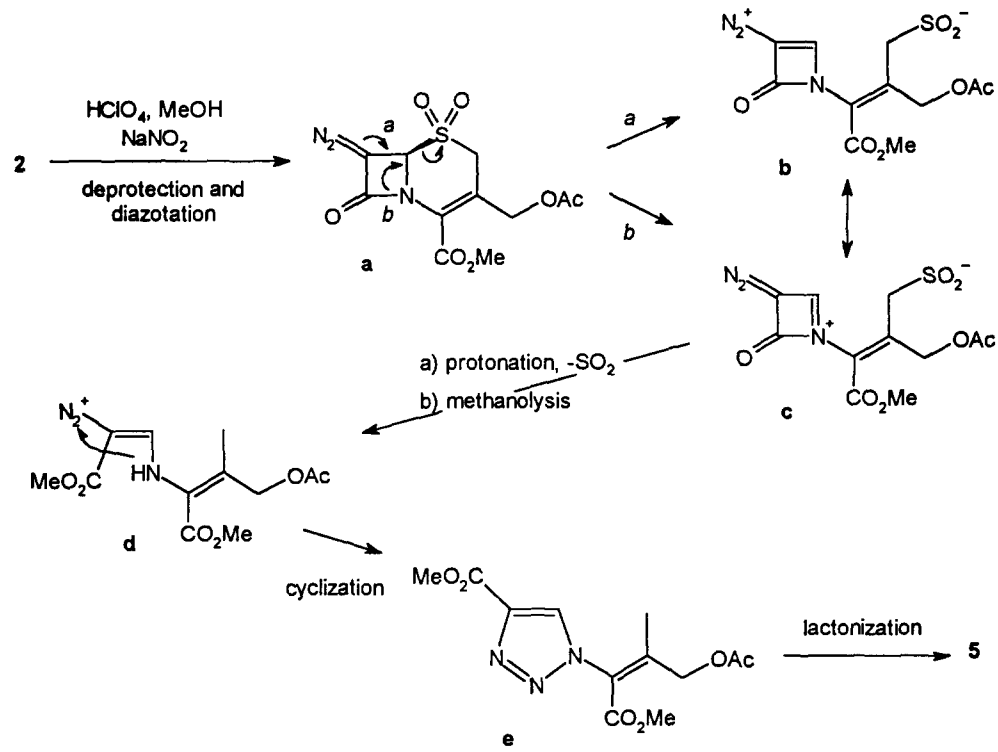
reaction. Our original supposition was that these three steps could be performed in a one-pot operation with a mixture of aq. perchloric acid, methanol and sodium nitrite, because **1** or the corresponding tBoc-sulphide gave the desired 7α-methoxy derivative (**3**) under these conditions, albeit in low overall yield (~10%) together with several unidentified resinous products. Remarkably, under similar conditions **2a** was *in toto* converted to a non-β-lactam product.[6,7] According to preliminary analyses it contained no sulphur, but it exhibited a high nitrogen content. With an X-ray diffraction structure elucidation in mind we aimed at the preparation of the corresponding 4-bromophenacyl ester, but when **2b** was subjected to the same reaction conditions, chromatographic work-up yielded to the same **5** and 1-(4-bromophenyl)-2-hydroxyethanone. Thus, finally **5** was used for X-ray diffraction structure elucidation.

The formation of **5** is the result of several steps of a debatable sequence. First, the tBoc protecting

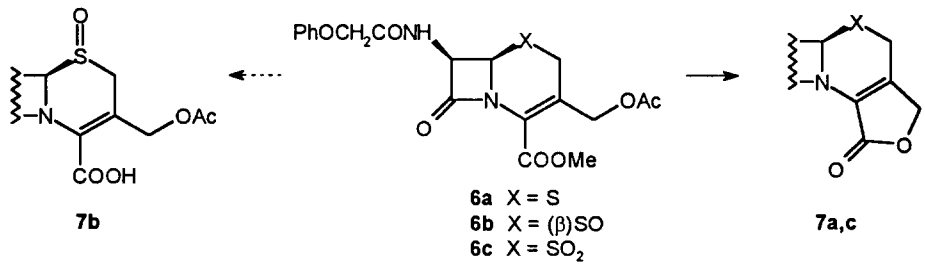


group leaves quickly in the strong acidic milieu and diazotisation occurs (**a**). Most probably the good leaving character of the sulphone is responsible for that instead of the analogous **2** → **4** process the intermediates **b** or **c** are formed. In the penicillin and cephalosporin chemistry several other more or less similar sulphone-related ring opening reactions are known.[4] The ring opening of **a** may formally proceed in two ways: C-6–C-5 elimination leads to the **b** diazonium intermediate, whereas a N–C-5 elimination results in the formation of the **c** immonium intermediate; as **b** and **c** are mutual resonance forms the pathways are indistinguishable. Elimination of SO_2 may happen in this or a later stage.

The reaction of diazonium or diazo compounds with amines, a well known old reaction producing triazenes, is used mostly for obtaining aliphatic triazenes, although cyclic compounds, like benzotriazoles from o-phenylenediamines are available this way too. In the reviews (5a-b) a couple of examples can be found for

the triazole formation of this type. In our case during the **c** → **d** step formation of the new N–N=N bond and the opening of the β-lactam ring are very probably unseparable processes.

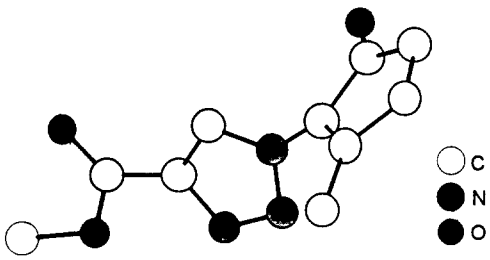
One of the steps of the formation of **5** is the acid-catalysed hydrolysis of the 3-acetoxy and the 4-methyl ester groups. A subsequent lactonization is not surprising, as this is usually a quick process among the 3-hydroxymethyl-cephem-4-carboxylic acids. When the analogue **6c** is subjected to the same reaction conditions (without $NaNO_2$), formation of the lactone derivative **7c** is practically quantitative. However, the oxidation state of the sulphur clearly influences the rate of hydrolysis of the two esters attached to the γ-positions relative to the sulphur: whereas a complete lactone formation took place in the case of the sulphide and sulphone,[9] only the partial hydrolysis of the sulfoxide **6a** occurred giving rise to a mixture of products:



7b

6a X = S
6b X = (β)SO
6c $X = SO_2$

7a,c



Chem3D representation of the X-ray structure of **5**. The dihedral angle of the two rings is 72°.

Acknowledgement

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6. Starting materials: *Methyl 7β-tert.-butoxycarbonyl-cephalosporanic acid 1,1-dioxide* (**2a**): m.p. 179-80 °C; ^{1}H NMR (DMSO-d_6) δ: 1.42 (s, 9H), 2.15 (s, 3H), 3.81 (s, 3H) , 4.18, 4.40 (ABq, 2H, J = 18 Hz), 4.52, 4.98 (ABq, 2H, J = 13.2 Hz), 5.33 (d, H, J = 4.4 Hz), 5.81 (dd, H, J = 4.4, 9.4 Hz), 7.25 (d, H, J = 9.4 Hz); *2-[(4-Bromophenyl)-2-oxo-]ethyl 7β-tert.-butoxycarbonyl-cephalosporanic acid 1,1-dioxide* (**2b**): m.p. 170-1 °C; ^{1}H NMR (DMSO-d_6) δ: 1.42 (s, 9H), 2.09 (s, 3H), 4.23, 4.44 (ABq, 2H, J = 18.4 Hz), 4.84, 4.96 (ABq, 2H, J = 13.0 Hz), 5.40 (d, H, J = 4.6 Hz), 5.84 (dd, H, J = 4.6, 9.4 Hz), 5.70, 5.87, (ABq, 2H, J = 17 Hz), 7.35 (d, H, J = 9.4 Hz), 7.77-7.97 (aromatic, 4H).
7. *Methyl 1-(4-Methyl-2-oxo-2.5-dihydro-furan-3-yl)-1H-[1.2.3]triazole-4-carboxylic acid* (**5**): 1 g of **2a** was dissolved in a mixture of 60 ml methanol and 20 ml 70% aq. $HClO_4$, and the solution was cooled 0-5 °C. 0.66 g of $NaNO_2$, dissolved in 5 ml of H_2O was added dropwise while stirring the mixture. It was allowed to stand for 3 hours in the cold, then it was poured into 200 ml of 10% $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was separated, washed with 10% $NaHCO_3$ and water, dried, evaporated, and the residue was recrystallized twice from EtOAc-Et_2O, yielding to 0.27 g of **5**, m.p. 126-8 °C. ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H), 3.90 (s, 3H), 5.20 (s, 2H), 9.07 (s, H); ^{13}C NMR (DMSO-d_6) δ: 12.5 (CH_3), 52.0 (OCH_3), 72.1 (CH_2), 121.5 (C), 128.6 (CH), 138.9 (C), 158.1 (C), 160.2 (CO), 167.1 (CO).

   Crystal data: $C_9H_9N_3O_4$, M = 223.19, monocline C2/c, a = 25,805(6), b = 5,722(3), c = 13,194(3) Å, β = 93,91(1)°, V = 1943(1) Å^3, Z =8, T = 293 K, μ = 0,123 mm^{-1}; wR(F^2) = 0.2449 (145 parameters); the data collection was performed with an Enraf-Nonius Mach3 diffractometer, the collection, calculation and refinement of the data were made by the programs CAD-4 Express, SIR-92 and SHELXL93.[8]
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9. **7a**: m.p.: 157-8 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 3.50, 3.75 (ABq, 2H, *J* = 18.1 Hz), 4.54 (s, 2H), 4.92 (s, 2H), 5.09 (H, d, *J* = 5.2 Hz), 6.04 (H, dd, *J* = 5.2, 9.2 Hz), 6.89-7.41 (6H, m). **7c**: m.p.: 244-5 °C (acetone-EtOH); ^{1}H NMR (DMSO-d_6) δ: 4.62 (2H, s), 4.64, 4.74 (2H, ABq, *J* = 14 Hz), 4.99, 5.08 (2H, ABq, *J* = 14.5 Hz), 5.35 (H, d, *J* = 5.1 Hz), 6.24 (H, dd, *J* = 5.1, 8.8 Hz), 6.89-7.35 (5H, m), 8.70 (H, d, *J* = 8.8 Hz)