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CHEMICAL TRANSFORMATION OF A CEPHALOSPORIN TO A 6-EPI-1-OXACEPHEM[1a]

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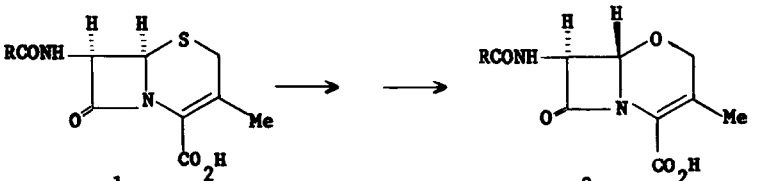
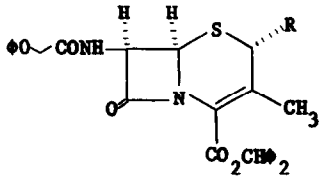
Replacement of the sulfur atom at position 1 of the cephalosporin nucleus with oxygen showed comparable bioactivity to their natural 1-thia counterparts.[1a, 1b] We describe here a very efficient chemical transformation of the dihydrothiazine ring of a cephalosporin 1 into the dihydrooxazine ring (6-epi-1-oxacephem)[1a] 2.



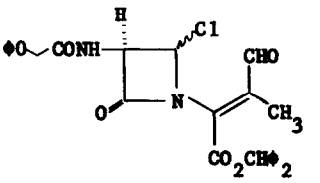
1 2

The reaction of the cephalosporin ester 3 with N-chlorosuccinimide in methanol-methylene chloride (1:1) gave the 2-methoxy cephem 4[2], mp 132-133° in 85% yield after recrystallization from ether. Treatment of 4 with chlorine in carbon tetrachloride (2.5 eq, -20°, 60 min)[3] followed by an aqueous work-up gave a quantitative conversion to the aldehyde 5 as a mixture of cis and trans isomers (α chloro/β chloro ≃ 1/9) [I.R. (KBr) 1795, 1730, 1710 and 1690 cm^{-1}; NMR ($CDCl_3$) of 5b δ 2.20 (s, 3H, methyl), 4.60 (s, 2H, $\phi O\underline{CH}_2$), 5.70 (q, 1H, J=4.2, 11.5 Hz, C-7H), 6.30 (d, 1H, J=4.2Hz, C-6H), 6.8-7.5 (m, 16H), 10.4 (s, 1H, CHO); NMR ($CDCl_3$) of 5a δ 2.10 (s, 3H, methyl), 4.60 (s, 2H, $\phi O\underline{CH}_2$), 5.10 (q, 1H, J=1.2, 10 Hz C-7H), 6.21 (d, 1H, J=1.2Hz, C-6H), 6.8-7.5 (m, 16H) 10.5 (s, 1H, CHO)].



3 R = H

4 R = OMe

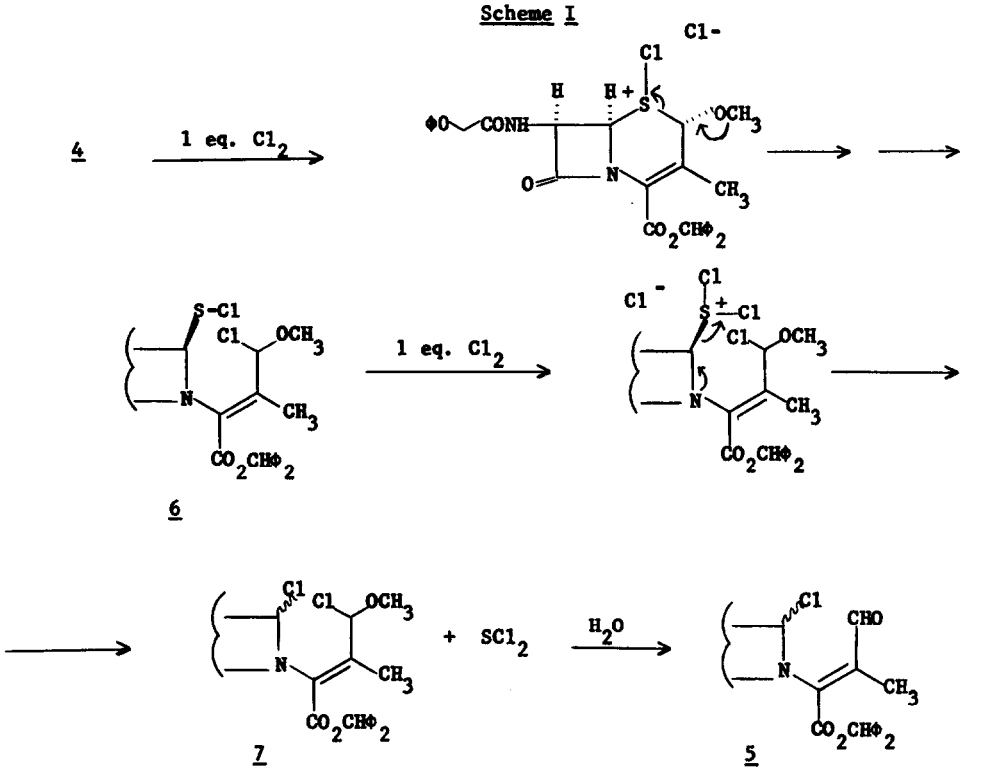


5 a = α chloro

b = β chloro

Presumably the chlorinolysis includes initial S-chlorination to give the sulfenyl chloride 6 followed by further chlorinolysis to the dichloride 7 and subsequent hydrolysis to the aldehyde 5. In fact, intermediate 7 could be isolated by anhydrous work-up and quantitatively converted into the aldehyde 5 by contact with water. It is not clear why the thermodynamically less stable β-chloro isomer 5b is predominant in the reaction mixture.

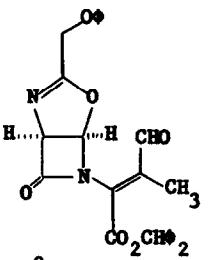
Scheme I



The reaction of the isomeric mixture 5 with $AgBF_4$-Ag_2O (1:1)[1a] in methylene chloride gave the oxazolone 8 in 85% yield [I.R. (KBr) 1780, 1720 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3H, methyl) 4.81 (broad s, 2H, $\phi O\underline{CH_2}$), 5.40 (d, 1H, J=4.5 Hz, C-7H), 6.30 (d, 1H, J=4.5 Hz, C-6H), 6.9-7.8 (m, 16H)]. Treatment of a methylene chloride solution of 8 with HCl gas at 0° gave quantitatively the α-chloro isomer 5a by a stereospecific ring opening.[4] Reduction of aldehyde 5 with sodium cyanoborohydride[5] in THF-acetic acid produced the alcohol 9 in over 90% yield [I.R. (KBr) 1785, 1700 and 1685 cm^{-1}; NMR ($CDCl_3$) of 9b δ 2.35 (s, 3H, methyl), 4.21 (d, 1H, J=12Hz, $\underline{CH_2}OH$) 4.40 (d, 1H, J=12Hz, $\underline{CH_2}OH$), 4.51 (s, 2H, $\phi O\underline{CH_2}$),

5.62 (q, 1H, J=3.9, 9.5Hz, C-7H), 5.90 (d, 1H, J=3.9Hz, C-6H), 6.7-7.5 (m, 16H)]. Ring closure of 9a or a mixture of 9a and 9b with $AgBF_4$-Ag_2O (1:1) in methylene chloride[1a] gave the 6-epi-1-oxacephem 10b in 87% yield after silica gel chromatography [I.R. (KBr) 1785, 1735 and 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (s, 3H, methyl), 4.42 (broad s, 2H, C-2H), 4.65 (s, 2H, $\phi O\underline{CH}_2$), 4.80 (q, 1H, J=0.8, 8.7Hz, C-7H), 5.20 (d, 1H, J=0.8Hz, C-6H), 6.9-7.8 (m, 17H)]. No trace of the cis isomer 10a was detected in the reaction products by examination with 100 MHz nmr. This indicates that the intermediate ion 11[6] generated by Ag^+ cyclizes only from the less sterically hindered α-side and produces exclusively the trans isomer.

Hydrogenation of 10b over Pd/C in dioxane-water gave the free acid 12b, mp 139-141° [I.R. (KBr) 1785, 1720 and 1670 cm^{-1}], which displayed significantly diminished antibacterial activity when compared with 1 (R = ϕOCH_2).



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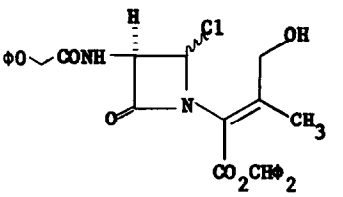
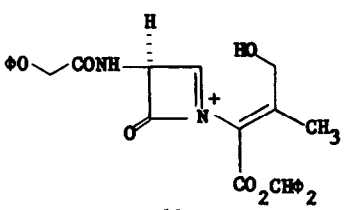


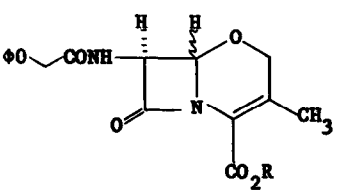
9

a = α chloro

b = β chloro



11



10a R = $CH\Phi_2$ (α 6H)

10b R = $CH\Phi_2$ (β 6H)

12a R = H (α 6H)

12b R = H (β 6H)

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   c. Also see references 1a, 3, and 4b.