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C_2-ALKOXY CEPHALOSPORINS

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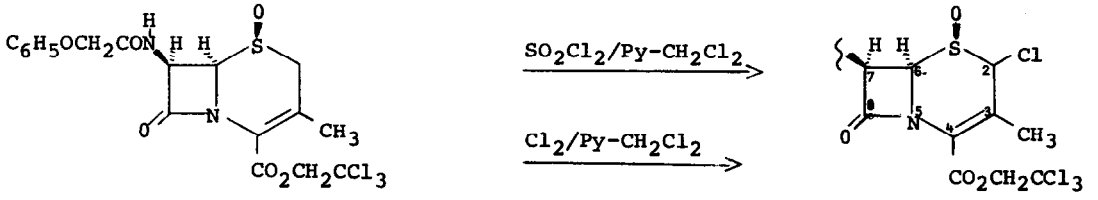
Recent interest in α-chloro sulfides[1] and sulfoxides[2,3] has prompted us to investigate such chemistry as a possible route to C_2-substituted cephalosporins.

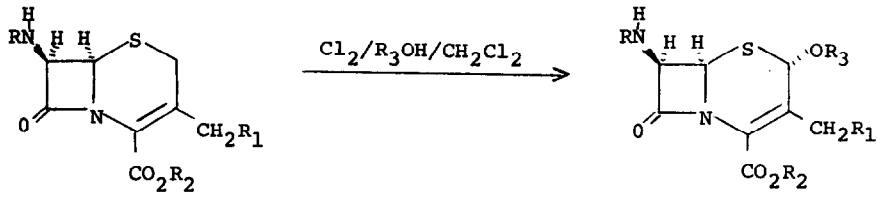
Treatment of 1 with sulfuryl chloride[2] in pyridine-methylene chloride resulted in the α-chloro sulfoxide 2 (one isomer). The same isomer was obtained when 1 was treated with chlorine[3] under similar conditions.



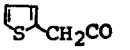
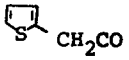
1 2

Treatment of 2 with Grignard reagents[4] or with refluxing methanol failed to cause any reaction at C_2. This is, perhaps, not surprising since Loeppky and Chang have shown that α-chloro sulfoxides are unreactive with nucleophiles.[5] Attempts to reduce the α-chloro sulfoxide to the more reactive α-chloro sulfide failed using the acetyl chloride-stannous chloride procedure.[6]

Since α-chloro sulfides are quite reactive and in some cases unstable, we chose to trap it or its intermediate with an alcohol. Treatment of 3 with one equivalent of chlorine in alcohol-methylene chloride solution resulted in a rapid conversion to the corresponding 2-alkoxy derivative 4. Although the yields of 4 are low (8-40%) the reaction is quite clean, the only product being the alkoxy derivative, with the exception of sulfoxide formation, particularly in the case of t-butanol.



3 4

Where R	R_1	R_2	R_3	%4
$C_6H_5OCH_2CO$	H	$CH_2C_6H_4NO_2$(p)	CH_3	40
"	"	"	CH_3CH_2	30
"	"	"	$CH(CH_3)_2$	33
"	"	"	$C(CH_3)_3$	16
"	OAc	CH_2CCl_3	CH_3	17
	OAc	"	CH_3	20
	OAc	"	CH_3CH_2	8
H·TSA	OAc	$C(CH_3)_3$	CH_3	10

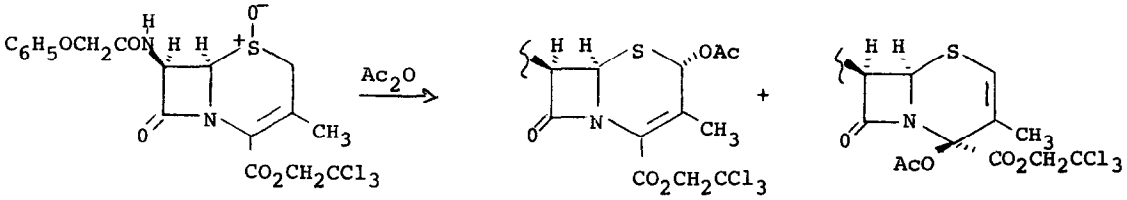
Thus to a stirred solution of p-nitrobenzyl 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (0.50 g, 1.0 mmoles) in 50 ml 1/1 methanol-methylene chloride was added dropwise 1.1 equivalents chlorine in methylene chloride. The reaction mixture was allowed to stir at room temperature for 1 hr; however, TLC showed that the reaction was instantaneous. The mixture was washed with brine, dried with sodium sulfate and chromatographed on silica gel to give 0.22 g starting material and 0.22 g product (40% yield, 69% corr. yield). Crystallization from acetone-hexane gave pure 2-methoxy ester, mp 171.5-172.0°, ir ($CHCl_3$), 1783 cm^{-1} (β-lactam); mass spec 513, nmr ($CDCl_3$) δ 2.19 (s,3,vinyl Me), 3.47 (s,3,OMe), 4.82 (bs,1,H_2), 5.11 (d,J=5.0Hz,1,H_6), 5.95 (q with fine split, J=9.0/5.0/0.5Hz,1,H_7). The compound gave correct elemental analysis.

Ester cleavage, either with zinc-acetic acid or by hydrogenolysis, yields the corresponding 2-alkoxy cephalosporanic acids which have antibacterial activity.

In all cases alkoxylation results in formation of only one of the two possible isomers at C_2, the isomer being assigned the α-configuration on the basis of nmr studies. Thus we observed a nuclear Overhauser effect (12-16%)

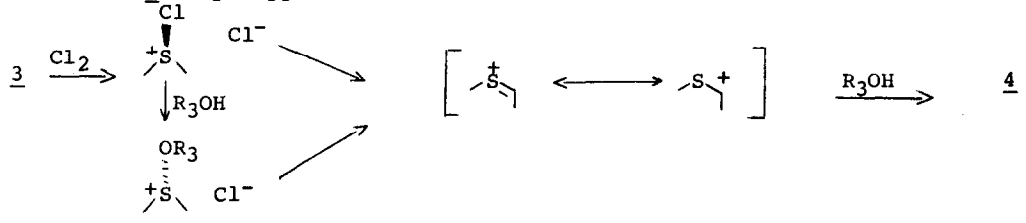
between the C_2-methine and the C_3-vinyl methyl. Benzene shielding studies[7] on the C_2-isopropoxy sulfide and β-sulfoxide derivatives showed no shielding of the C_2-methine. This data implies that the H_2 proton is β equatorial and thus the alkoxy configuration is α axial. In all cases we observed a 5 bonded coupling (0.5-1.0 cps) of the H_2 proton across sulfur to H_7.

Results of this reaction sequence using nucleophiles other than alcohols have been discouraging. Acetate adds, however, to give the C_2-α-acetoxy derivative 5, which was also obtained via the Pummerer rearrangement of 6 (α- or β-sulfoxide) using acetic anhydride. The product (5) compared favorably with known material.[8] The 5 bonded coupling (H_2-H_7) being barely detectable in 5 with the phenoxyacetamido side chain, however, is quite prominent with the phthalimido side chain as a substituent.



6 5 7

The reaction is believed to proceed via the β-chlorosulfonium chloride[9] and is analogous to that reported by Skattebøl *et al*[10] for the reaction of sulfides with t-butyl hypochlorite in alcohols.



The alkaline methanolysis of N-p-toluenesulfonyl sulfilimine to yield α-methoxy sulfides has been described recently and is believed to proceed through a similar mechanism.[11]

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9. Replacing the alcohol by bicarbonate solution in the experimental resulted in the stereospecific formation of the α-sulfoxide (55%), mp 188-189°, identical to known material (Unpublished results of I. G. Wright) obtained from the peracid oxidation in 5.5% yield.

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