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C_2-SPIROAZIRIDINO-CEPHALOSPORINS

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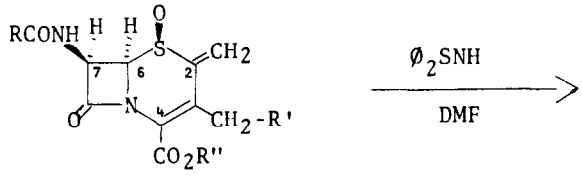
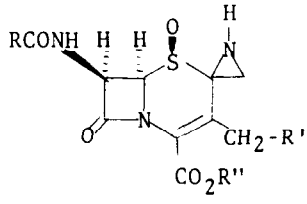
Furukawa and Oae recently reported the Michael type addition of diphenylsulfilimine to α,β-unsaturated ketones and esters to give mixtures of the corresponding aziridine and the enamine[1].

We now report the use of this reagent with the electrophilic C_2-exomethylene cephalosporin[2] 1 to give the C_2-spiroaziridino-cephalosporin 2. Thus a cooled (0°) solution of the diene sulfoxide (1.0 equiv) in DMF was treated with 1.1 equiv of diphenylsulfilimine[3]. After 30 min without cooling the reaction was diluted with ethyl acetate, washed with water, brine, dried, and chromatographed on silica gel to give the corresponding spiroaziridine.



1



2

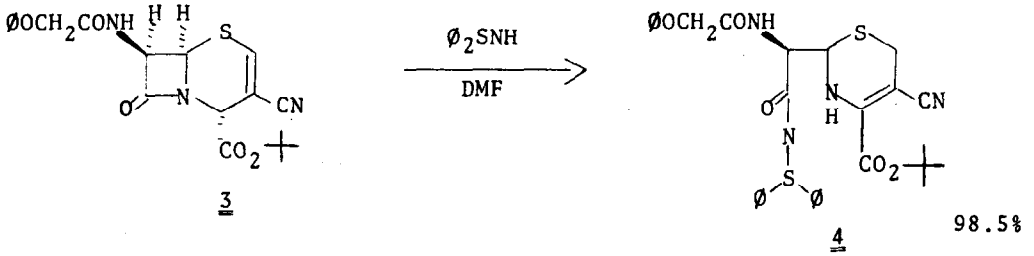
Where	R	R'	R"	%2	mp (acetone/CH_2Cl_2-hexane)
	V	H	PNB	52-63	174-175°
	CH_3	H	TCE	56-63	180°
		OAc	$CH\emptyset_2$	50	

PNB = P-nitrobenzyl
TCE = trichloroethyl
V = $C_6H_5OCH_2$

Evidence for the spiroaziridine was provided by loss of the vinyl protons in the NMR ($DMSOd_6$) and the presence of a multiplet at 2.6-3.0δ for the aziridine methylene and a replaceable proton at 3.4-3.8δ. Physical data implies one of two possible geometric isomers for the spiroaziridine. However, the reaction of

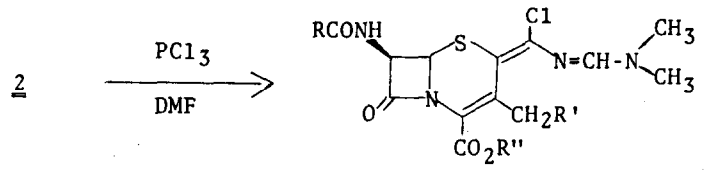
the N-acetyl diene sulfone [R(Me), R'(H), R''(CH_2CCl_3)] with diphenylsulfilimine gave a mixture of isomers[4].

Treatment of other cephem double bonds with $\emptyset_2SNH$ indicates that under these conditions the Δ^3-double bond is inert when the C_3-substituent is methyl or acetoxymethyl. Δ^2-Cephem, with acetoxymethyl at C_3 gave mixtures of Δ^2-Δ^3, while Δ^2-derivatives with electron withdrawing substituents at C_3 resulted in shifting of the double bond and attack of the β-lactam to give the corresponding N-acyl-sulfilimine[5].



3 4 98.5%

Attempts to reduce the sulfoxide of 2 using PCl_3-DMF[6] gave the chloramidine 5.



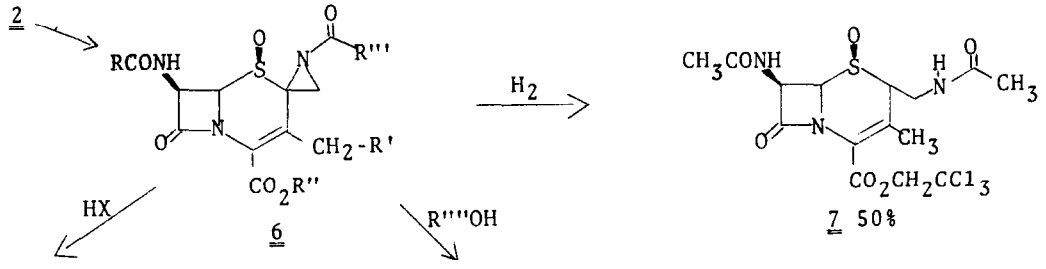
5

Where	R	R'	R''	%5
	V	H	PNB	37
	CH_3	H	TCE	47
		OAc	$CH\emptyset_2$	52

The structure of 5 was evident from the mass spectrum which showed incorporation of chlorine, the IR which showed the β-lactam at 1780 cm^{-1} and a strong -N=C- stretch (1630 cm^{-1}) and from the NMR ($CDCl_3$) which showed a N,N-dimethyl (2.9δ) and an olefinic proton at 7.4δ. The conversion of 2 to 5 can be rationalized as a nucleophilic attack of the aziridine with dimethyl immonium chloride followed by opening of the aziridine and elimination of HCl. The sulfoxide then undergoes a Pummerer reaction with the Vilsmeier reagent to give the sulfide of the chloramidine[7]. The sulfone aziridine reacts under the same conditions to

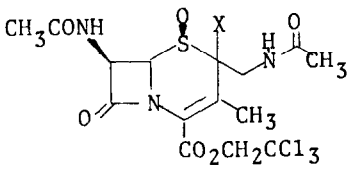
give the 2'-H(deschloro)amidine.

The spiroaziridine 2 can be acylated with various acylating agents (CH_3COCl, ØNCO) to give the spiroacylaziridine 6 (50-60%, 20%). Thus activated the aziridines undergo reactions with hydrogen to give the amide 7, with HX and alcohols to give 2-halo or 2-alkoxy-2-acylaminomethyl derivatives[8] 8 and 9.

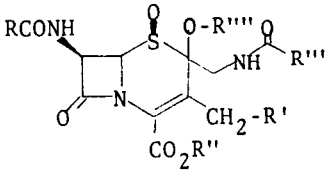


6

7 50%



8



9

X	%
Cl	52
Br	56

9	Where	R	R'	R''	R'''	R''''	%9
		CH_3	H	TCE	CH_3	CH_3	78
		CH_3	H	TCE	CH_3	CH_2CH_3	78
		CH_3	H	TCE	CH_3	$CH(CH_3)_2$	60
		CH_3	H	TCE	CH_3	$C(CH_3)_3$	76
		V	H	PNB	Ø	CH_3	38
		V	H	PNB	NHØ	CH_3	55
		V	H	PNB	CH_3	CH_3	84
			OAc	TCE	CH_3	CH_3	78

Alcoholysis of 6 results in isomers at C_2 which were separated as the sulfides where R(V), R'(H), R''(PNB), R'''(CH_3), R''''(CH_3) following PBr_3-DMF sulfoxide reduction (65%, ratio 4:1).

Both the acid of 5 and the acids of the sulfides of 9 display reduced microbiological activity in comparison to the acid of the corresponding C_2-methylene derivative.

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2. I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, *J. Med. Chem.*, 14, 420 (1971).
3. Diphenylsulfilimine was prepared in 85% from diphenylsulfide and O-mesitylenesulfonylhydroxyamine (MSH). See Y. Tumura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972).
4. One of the isomers was obtained crystalline from acetone/methylene chloride-hexane, mp 188°D.
5. For references on N-acylsulfilimines see: H. Kise, G. F. Whitfield and D. Swern, *Tetrahedron Lett.*, 1761 (1971); A. Kucsman and I. Kapovits, *Phosphorus and Sulfur*, 3, 9 (1977).
6. G. V. Kaiser, I. G. Wright, C. F. Murphy, J. A. Webber, R. D. G. Cooper, and E. M. Van Heyningen, *J. Org. Chem.*, 35, 2430 (1970).
7. This type of Pummerer rearrangement will be discussed further in a future communication. Unpublished results of D. O. Spry.
8. For the synthesis of 2-alkoxycephalosporins see: D. O. Spry, *Tetrahedron Lett.*, 3717 (1972); A. Balsamo, P. Crotti, B. Macchia, F. Macchia, G. Nannini, E. Dradi, and A. Forgioni, *J. Org. Chem.*, 41, 2150 (1976); J. E. Dolfini, U. S. Patent Application No. 499 368.