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C_2-SPIROCYCLOPROPYL CEPHALOSPORINS

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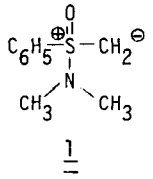
Although sulfonium ylides have been extensively utilized for methylene insertion across double bonds of olefins, to our knowledge there has been no application of such reagents to cephalosporins to give cyclopropyl derivatives. We now wish to report a facile synthesis of C_2-spirocyclopropyl cephalosporins via a sulfonium ylide reaction.

Johnson *et al* have described the synthesis of (dimethylamino)phenyloxosulfonium methylide 1 and its reaction with double bonds of carbonyls or electrophilic olefins to yield oxiranes or cyclopropanes[1].

The C_2-exomethylene of the cephalosporin 2, a product derived from the Mannich reaction on the sulfoxide by Wright[2] and co-workers was anticipated to be electrophilic in nature being doubly activated by the sulfoxide and the conjugated ester.

The reaction of the sulfonium ylide 1 with the diene sulfoxide 2 results in the C_2-spirocyclopropyl cephalosporins 3 in high yield. Thus a cooled (0°) solution of (dimethylamino)methylphenyloxosulfonium fluoroborate (1.06 equiv) in dimethylformamide (DMF) was treated with 1.06 equiv



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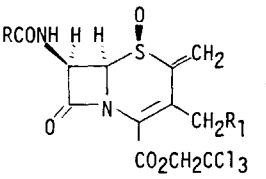

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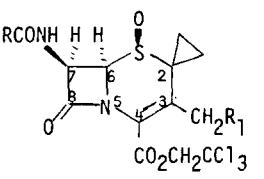
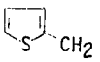


3

Where R	R_1	%3	mp
$C_6H_5OCH_2$	H	80	222-3°/EtOAc
$C_6H_5OCH_2$	OAc	85	187-8°/Acetone-hexane
	OAc	72-88	197-8°/Acetone-hexane
CH_3	OAc	64	---

NaH followed by dropwise addition of a DMF solution of the diene sulfoxide 2 (1.06 equiv). After 1 hr at 0° the reaction was diluted with ethyl acetate and washed with brine, dried, and chromatographed on silica gel to give the product which was crystallized from the appropriate solvent.

Evidence for the spriocyclopropyl group was provided in the loss of the vinyl protons in the nmr spectrum and the presence of a four proton multiplet at approx 0.5 to 2.0δ. The mass spec-

Table I. Chemical Shift Values[a] for Keflin Derivatives

		$OCOCH_3$	OMe		CH_2OAc	H_6	H_7	NH
3 ($DMSOd_6$)	1.0-2.0	1.98	---	3.86	AB,J=13 4.53,4.73	d,J=5.0 5.50	q,J=5.0/8.0 6.00	d,J=8.5 8.46
sulfide of 3 ($CDCl_3$)	0.7-1.8	2.20	---	3.84	AB,J=12 4.52,4.65	d,J=5.0 5.24	q,J=5.0/9.0 5.94	d,J=9.0 6.40
7 ($CDCl_3$)	0.8-1.9	2.00	3.45	3.89	AB,J=13 4.43,4.67	4.83	---	~7.3
sulfide of 7 ($CDCl_3$)	0.9-1.6	2.03	3.48	3.88	AB,J=12 4.50,4.65	5.36	---	6.78

[a]Parts per million; J values in Hertz

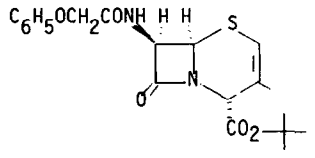
trum showed a gain of 14 mass units, ir ($CHCl_3$) provided evidence for the β-lactam (1800 cm^{-1}) and the compounds gave a correct elemental analysis.

Phosphorous trichloride reduction of the sulfoxide 3 to the sulfide[3,4] followed by ester cleavage[5] provided the corresponding C_2-spirocyclopropyl cephalosporanic acids 4.

4

Although there are several examples of 2,2-dimethyl cephems[6,7] to our knowledge this is the first report of a C_2-spiro cephalosporin.

The reaction of 1 with the 2-cephems 5 and 6 under these conditions failed to give methylene insertion, yielding starting material and the respective Δ^3 isomers.



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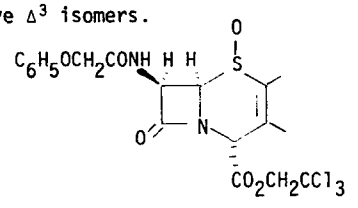
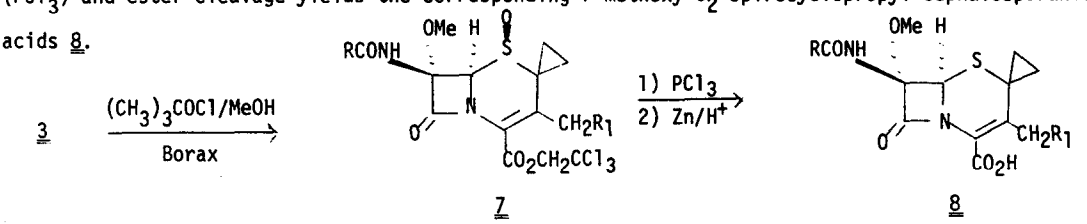


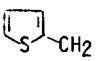
6

Recent interest in 7-methoxy cephalosporins [8a,8b,8c,8d,8e] has prompted us to synthesize the 7-methoxy-C_2-spirocyclopropyl derivatives via the elegant procedure of Baldwin[8e]. Thus

treatment of 3 with *t*-butyl hypochlorite in methanol[9] results in methoxylation at C_7, evident from the appearance of a methoxy methyl in the nmr spectrum, loss of the H_7 quartet, and conversion of the H_6 doublet and NH doublet to singlets (see Table I). Reduction of the sulfoxide 7 (PCl_3) and ester cleavage yields the corresponding 7-methoxy-C_2-spirocyclopropyl cephalosporanic acids 8.



7 8

Where R	R_1	%7
$C_6H_5OCH_2$	OAc	52
	OAc	53
CH_3	OAc	54

Methoxylation of 3 results in only one of two possible isomers at C_7, which was assigned the α-configuration (MeO) on the basis of nmr shielding studies[10]. Thus the amide NH is shielded approx 0.25 ppm in going from the β-sulfoxide to the sulfide, implying hydrogen bonding between the *cis* β-sulfoxide and the amide NH. The fact that the acids 8 are biologically active further corroborates the assignment.

Acknowledgement : We thank I. G. Wright for the Mannich compounds 2.

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