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REACTIONS AND DETERMINATION OF STEREOCHEMISTRY OF 3-METHYLENECEPHAM DERIVATIVES

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In the previous communications,[1,2] we reported the facile syntheses of a novel class of cephalosporins, 3-methylenecepham derivatives, by an electrochemical reduction or chromium(II) salts reduction of cephalosporanic acids. This communication describes some aspects of chemical reactions of these compounds and also the establishment of the stereochemistry at position 4.

Esterification of Ia by the conventional treatment with diazomethane gave the 3-methylenecepham methyl ester (Ib), m.p. 145-147°C, IR (KBr): 1765 cm^{-1} (β-lactam), NMR (δ, 100 Mc, $CDCl_3$): 3.17 and 3.68 (two doublets, 2H, 2-C$\underline{H}_2$), 5.10 (singlet, 1H, 4-C$\underline{H}$), 5.21 (broad doublet, 2H, C=C$\underline{H}_2$), 5.39 (doublet, 1H, 6-C$\underline{H}$), 5.69 (doublet of doublet, 1H, 7-C$\underline{H}$). Oxidation of Ib with m-chloroperbenzoic acid in dichloromethane provided a β-sulfoxide* (II), m.p. 188-190°C, IR (KBr): 1770 cm^{-1} (β-lactam), NMR (δ, 100 Mc, $CDCl_3$): 3.67 (doublet, 2H, 2-C$\underline{H}_2$), 5.19 (singlet, 1H, 4-C$\underline{H}$), 5.40 and 5.69 (two singlets, 2H, C=C$\underline{H}_2$), 5.97 (doublet of doublet, 1H, 7-C$\underline{H}$).

The treatment of II with pyridine[1,2] afforded 3-methyl-3-cephem β-sulfoxide (IVa), m.p. 213-215°C, IR (KBr): 1760 cm^{-1} (β-lactam), NMR (δ, 100 Mc, d_6-DMSO): 2.03 (singlet, 3H, 3-C$\underline{H}_3$), 3.71 (singlet, 2H, 2-C$\underline{H}_2$), 4.91 (doublet, 1H, 6-C$\underline{H}$), 5.93 (doublet of doublet, 1H, 7-C$\underline{H}$). The characterization of IVa

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All the new compounds gave satisfactory combustion analyses.

* α-Sulfoxide corresponds to (R)-configuration and β-sulfoxide to (S)-configuration.[3]

was established by the direct comparison with a specimen obtained from the known compound (IVb)[3] by hydrolysis with zinc in acetic acid[4] followed by esterification with diazomethane.

The treatment of Ib with an equimolar amount of N,N-dichlorourethane in THF gave another sulfoxide compound (III), m.p. 158-159°C, IR (KBr): 1775 cm^{-1} (β-lactam), NMR (δ, 100 Mc, $CDCl_3$): 3.60 and 4.00 (two doublets, 2H, 2-C$\underline{H}_2$), 4.76 (doublet, 1H, 6-C$\underline{H}$), 5.04 (singlet, 1H, 4-C$\underline{H}$), 5.46 (doublet of doublet, 1H, 7-C$\underline{H}$), 5.46 (doublet, 2H, C=C$\underline{H}_2$). III was isomerized in pyridine to the 3-methyl-3-cephem sulfoxide (Va), m.p. 161-163°C, IR (KBr): 1790 cm^{-1} (β-lactam), NMR (δ, 100 Mc, $CDCl_3$): 2.21 (singlet, 3H, 3-C$\underline{H}_3$), 3.40 and 4.00 (two doublets, 2H, 2-C$\underline{H}_2$), 4.57 (doublet, 1H, 6-C$\underline{H}$), 5.49 (doublet of doublet, 1H, 7-C$\underline{H}$). Both IVa and Va gave the same sulfone derivative (VI) upon further oxidation with m-chloroperbenzoic acid. The results clearly indicate that III and Va should be assigned α-configuration at position 1. Conversion of the known compound (Vb)[3] to Va confirmed this configuration.

This assignment was further corroborated by the hydrogen bonding studies in NMR. As is shown in the Table a change in solvent ($CDCl_3 \rightarrow d_6$-DMSO) induces a down field shift of 1.71 ppm in the resonance of NH in III indicative of an intermolecular hydrogen bonding to DMSO. The β-sulfoxide (II), however, exhibits only a negligible shift. This is in good accord with the phenomena observed with other cephalosporin sulfoxide compounds.[5]

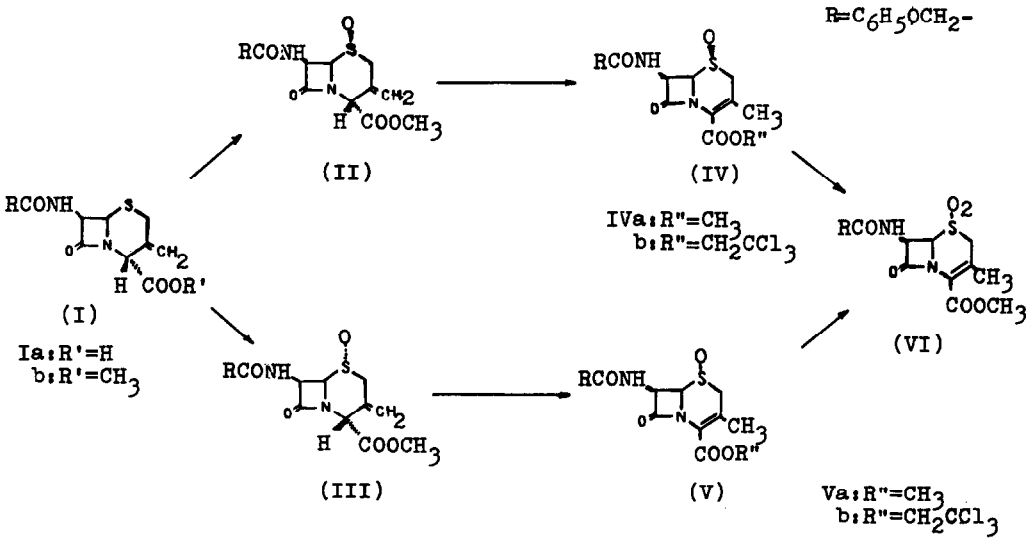
The present stereospecific oxidation of II with N,N-dichlorourethane is of interest because no other method has been known for the stereospecific synthesis of α-sulfoxides of cephalosporins.[6] It is likely that chlorination of Ib might form the (S)-sulfonium chloride (VII) which upon subsequent hydrolysis with inversion would give the (R)-sulfoxide (III).

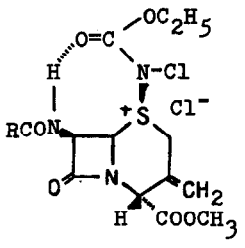
Taking into consideration that the S→O bond has a similar anisotropic effect[7] as an acetylene bond, the anisotropic effect of α-and β-sulfoxides (III, II) on each proton at position 4 was examined. The proton at position 4 is shielded by 0.06 ppm in the α-sulfoxide (III) and deshielded by 0.09 ppm in the β-sulfoxide (II) compared with the sulfide (Ib). There are two conformational possibilities, A and B, for both II and III. The proton

Table Hydrogen Bonding Studies via Solvent Induced Shift

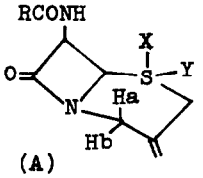
Compound	Solvent	Chemical Shift for NH (δppm)	
II	$CDCl_3$	8.09	Δ=-0.12
	d_6-DMSO	8.21	
III	$CDCl_3$	7.53	Δ=-1.71
	d_6-DMSO	9.24	

Δ : δ($CDCl_3$)-δ(d_6-DMSO)

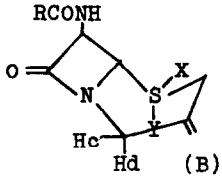




(VII)



(A)



(B)

X = O or lone pair electrons
Y = lone pair electrons or O

at position 4 can take four possible situations (Ha, Hb, Hc, Hd). Examination of a Dreiding model indicated that only the β-configuration (Ha) for the proton at position 4 in the conformation A satisfies the above anisotropy shift values.[8)]

The same stereochemistry was achieved with a 3-methylenecepham derivative by means of lanthanide-induced shifts combined with computer calculation, which will be published elsewhere.[9)]

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References

1. M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asahi, Tetrahedron Letters, in press.
2. M. Ochiai, O. Aki, A. Morimoto, T. Okada, and H. Shimadzu, J. C. S. Chem. Comm., in press.
3. G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, J. Org. Chem., 35, 2430 (1970).
4. R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, J. Am. Chem. Soc., 88, 852 (1966).
5. R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, J. Chem. Soc. (C), 340 (1970).
6. Brief comment of the oxidation of cephalosporins and penicillins is given; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, J. Chem. Soc. (C), 3540 (1971).
7. K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, Chem. Comm., 759 (1966); A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, ibid., 1086 (1968).
8. For analogous discussions, see the reference 5.
9. M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, Tetrahedron Letters, in press.