Communications to the Editor

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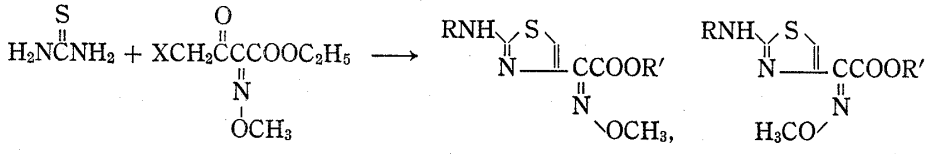
New Cephalosporin Derivatives with High Antibacterial Activities

Syn- and *anti*-isomers of 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-cephalosporins were synthesized selectively. These new cephalosporins exhibited excellent activities against a wide variety of bacteria including those which are resistant to β-lactamase susceptible cephalosporins currently available. The *syn*-isomers showed higher activities than the *anti*-isomers.

Keywords——cephalosporin; 2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid; 2-(2-aminothiazol-4-yl)-(*E*)-2-methoxyiminoacetic acid; 7-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]cephalosporanic acid; 7-[2-(2-aminothiazol-4-yl)-(*E*)-2-methoxyiminoacetamido]cephalosporanic acid; β-lactamase

During the course of our extensive research on modified cephalosporins, our efforts have been focused on synthesizing new cephalosporins with enhanced activities against β-lactamase-producing strains of bacteria. The excellent properties of 7-[2-(2-aminothiazol-4-ylacetamido)]-cephalosporins found in this division[1] and of cefuroxime[2] prompted us to synthesize 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins.[3] In this communication we describe the selective synthesis of stereoisomeric 7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]cephalosporins which possess not only high activities against a wide variety of bacteria, but also excellent efficacy against β-lactamase-producing strains which are generally resistant to currently available cephalosporins.

When thiourea and ethyl 2-methoxyimino-3-oxo-4-halogeno-butyrate[4] were refluxed in ethanol ethyl 2-(2-aminothiazole-4-yl)-(*E*)-2-methoxyiminoacetate (**2a**) was obtained selectively. The selective synthesis of the *syn*-isomer (**1a**) was achieved successfully by conducting the reaction in aqueous tetrahydrofuran in the presence of sodium acetate at room temperature. Hydrolysis after protection of the amino group of each isomer gave 2-(2-chloroacetamidothiazol-4-yl)-2-methoxyiminoacetic acids (**1c** and **2c**) with complete retention of the configuration at the methoxyimino moiety. Some of the physical constants of these compounds are given in Table I.



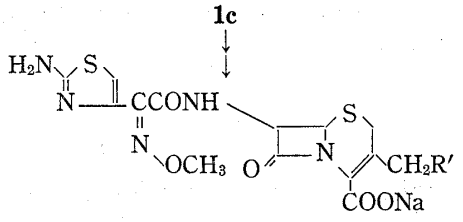
1a, **2a**: R=H, R′=C_2H_5
1b, **2b**: R=$ClCH_2CO$, R′=C_2H_5
1c, **2c**: R=$ClCH_2CO$, R′=H

1 *syn* (*Z*) **2** *anti* (*E*)

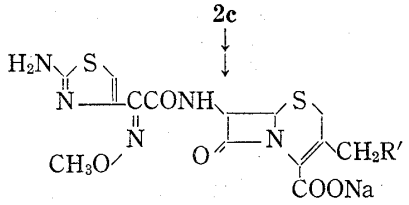
1) M. Numata, I. Minamida, M. Yamaoka, M. Shiraishi, and T. Miyawaki, Japan Patent Application, 49-20752 (1974); Dutch Patent 7416609.
2) C.H. O'Callaghan, R.B. Sykes, D.M. Ryan, R.D. Foord, and P.W. Muggleton, *J. Antibiotics*, **29**, 29 (1976); C.H. O'Callaghan, R.B. Sykes, A. Griffiths, and J.E. Thornton, *Antimicrob. Agents Chemother.*, **9**, 511 (1976).
3) 2-Aminothiazole form is used in this paper to represent possible tautomerism between 2-aminothiazole and 2-iminothiazoline forms.
4) Obtained by methylating ethyl 2-hydroxyimino-3-oxobutyrate[5] with dimethyl sulfate followed by halogenation in chloroform.
5) H. Kawasaki, *J. Chem. Soc. Japan*, **78**, 1254 (1957); H. Adkins and E.W. Reeve, *J. Am. Chem. Soc.*, **60**, 1328 (1938).

TABLE I. Physical Constants of 2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetic Acid Derivatives

	1		2	
	NMR of thiazole 5-H δ (ppm)	mp (°C)	NMR of thiazole 5-H δ (ppm)	mp (°C)
a	6.74($CDCl_3$)	163—164	7.43($CDCl_3$)	114—115
b	7.15($CDCl_3$)	111—112	7.94($CDCl_3$)	81— 82
c	7.57(d_6-DMSO)	170—171	8.00(d_6-DMSO)	182—183

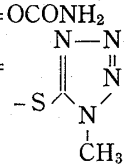


3 *syn*(*Z*)



4 *anti*(*E*)

3a, 4a: R′=$OCOCH_3$
3b, 4b: R′=$OCONH_2$
3c, 4c: R′=



	NMR; thiazole 5-H D_2O, δ (ppm)		
3a	7.01	**4a**	7.58
3b	7.09	**4b**	7.55
3c	7.00	**4c**	7.50

TABLE II. *In Vitro* Activities of 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins

Organism	Minimum inhibitory concentration (μg/ml)								
Compound	**3a**	**4a**	**3b**	**4b**	**3c**	**4c**	CER[a]	CEZ[a]	CXM[a]
Escherichia coli NIHJ[b] JC-2	0.20	3.13	0.10	3.13	0.10	3.13	3.13	1.56	6.25
Escherichia coli T-7	0.78	12.5	0.39	25	0.78	50	>100	100	25
Serratia marcescens IFO 12648	3.13	12.5	1.56	12.5	0.78	25	>100	>100	>100
Serratia marcescens TN 24	0.78	3.13	0.20	3.13	0.20	3.13	>100	>100	>100
Proteus vulgaris IFO 3988[b]	0.024	0.20	≤0.012	0.39	0.024	0.78	6.25	6.25	1.56
Proteus vulgaris GN 4413	0.78	25	1.56	>100	0.39	>100	>100	>100	>100
Proteus morganii IFO 3168	0.20	50	0.39	0.78	0.05	0.78	>100	100	25
Proteus rettgeri GN 4733	0.20	3.13	0.05	0.78	0.20	6.25	>100	100	3.13
Enterobacter cloacae TN 1282	6.25	25	6.25	12.5	1.56	50	>100	>100	>100
Citrobacter freundii GN 1706	0.39	6.25	0.39	6.25	0.20	12.5	>100	>100	6.25

The MICs were determined by a standard agar dilution method in Trypticase soy agar (BBL).
a) Generic name: CER=cephaloridine, CEZ=cefazolin, CXM=cefuroxime.
b) All the organisms except *E. coli* NIHJ JC-2 and *P. vulgaris* IFO 3988 are β-lactamase-producing strains.

7-Aminoceph-3-em-4-carboxylic acids[6] with various substituents at the 3-position were acylated with acid chlorides carefully generated from **1c** and **2c** by the action of PCl_5. Removal of the protecting group with thiourea gave 7-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyimino-acetamido]cephalosporins (**3a**—**c**) and their *anti*-isomers (**4a**—**c**), respectively, in good yields.

The *in vitro* activities of these new compounds against several bacteria including β-lactamase-producing strains are exemplified in Table II. All the *syn*-isomers (**3a**—**c**) exhibit excellent activities [*ca.* 10—250 times as active as the *anti*-isomers (**4a**—**c**)] against those bacteria which are resistant to β-lactamase susceptible cephalosporins currently available.

Further evaluation of these new cephalosporins as chemotherapeutic agents is under way in this division.

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6) G.L. Dunn, J.R.E. Hoover, D.A. Berges, J.J. Taggart, L.D. Davis, E.M. Dietz, D.R. Jakes, N. Yim, P. Actor, J.V. Uri, and J.A. Weisbach, *J. Antibiotics*, **29**, 65 (1965); Glaxo, Brit. Patent 1453049.

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Synthesis of New Cephalosporins with Potent Antibacterial Activities

Cephalosporins bearing (*Z*)- and (*E*)-2-hydroxyimino-2-(2-imino-4-thiazolin-4-yl)-acetamido groups at the 7-position (**5** and **6**) were synthesized. Among them (*Z*)-isomers (**5**) showed superior activities particularly against Gram-negative bacteria to hitherto known cephalosporins.

Keywords——cephalosporin; antibiotics; Gram-negative bacteria; configuration of oxime; 7-[2-hydroxyimino-acetamido]-cephalosporins

Previously,[1] we synthesized a series of cephalosporins bearing the 7-acylamino side chain derived from 2-(2-imino-4-thiazolin-4-yl)acetic acid[2] and various types of substituents at the 3-position (**3**) for the biological screen. Among them SCE-963 (**3d**)[3] showed the most remarkable antibacterial activities together with good pharmacologic properties and thus is currently undergoing clinical trials.

1) M. Numata, I. Minamida, M. Yamaoka, M. Shiraishi, and T. Miyawaki, Japan. Patent Application 49-20752; 49-131381; Dutch Patent Application 7416609 (1975) [*C·A.*, **84**, 74284 (1976)].
2) This form is tautomeric with 2-(2-aminothiazol-4-yl)acetyl form.
3) M. Numata, I. Minamida, M. Yamaoka, M. Shiraishi, T. Miyawaki, and T. Nishimura, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, Oct. 1977, Abstracts, 44. SCE-963: 3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7-[2-(2-imino-4-thiazolin-4-yl)acetamido]-ceph-3-em-4-carboxylic acid.