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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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.

In our search for more potent cephalosporins, we found that new compounds (*Z*)- and (*E*)-7-[2-hydroxyimino-2-(2-imino-4-thiazolin-4-yl)acetamido]-cephalosporins (**5** and **6**), which are modified compounds of **3** by introducing the hydroxyimino group at the α-position of the acyl part, exhibited superior activities to hitherto known cephalosporins.

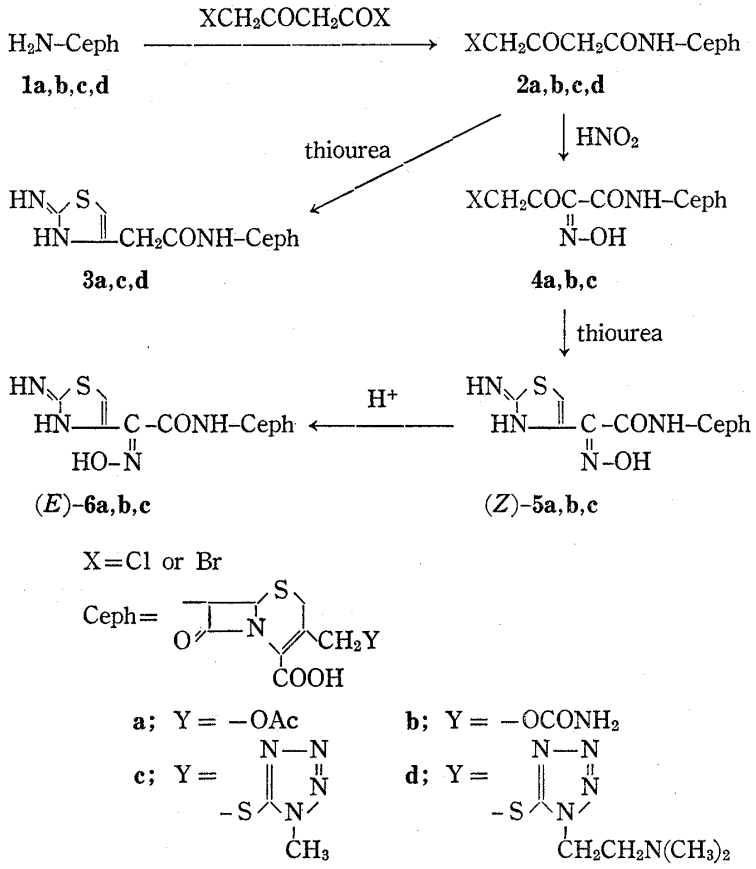

Chart 1

Acylation of 7-aminoceph-3-em-4-carboxylic acids[4] (**1**) with 4-chloro (or bromo)-3-oxobutyryl chloride (or bromide) gave **2**. Nitrosation of **2** with $NaNO_2$/AcOH afforded **4** with a minor by-product, presumably the stereoisomer of **4**. The product, without further purification, was treated with thiourea to obtain **5** and **6** in *ca.* 50:1 judged by the NMR signals. The mixture, after treatment with aq. $NaHCO_3$, was developed on a XAD-2 resin column with water to furnish sodium salts of **5** and **6** each in pure state. **6** was also obtained by isomerization of **5** with HCl.

Table I. NMR Spectra of Sodium Salts of **5** and **6** in d_6-DMSO at 100 MHz (δ in ppm)

Antibiotic	Configuration	Amide	Thiazoline-5-H
5a	*Z*	9.35	6.64
6a	*E*	9.16	7.50
5b	*Z*	9.40	6.72
6b	*E*	9.24	7.52
5c	*Z*	9.38	6.64
6c	*E*	9.22	7.51

4) G.L. Dunn, J.R.E. Hoover, D.A. Berges, J.J. Taggert, L.D. Davis, E.M. Dietz, D.R. Jakas, N. Yim, P. Actor, J.V. Uri, and J.A. Weisbach, *J. Antibiot.* (Tokyo), *Ser. A*, **29**, 65 (1976); Beecham, Belg. Patent 835238 (1976).

The configuration of **5** and **6**, which are geometric isomers to each other at the hydroxyimino group, was determined by comparison of NMR chemical shifts of amide protons of both isomers (Table I). The resonance of amide protons of (*Z*)-isomers (**5**) at lower field than that of corresponding (*E*)-isomers (**6**) is related to the closer proximity of the oxime OH to the amide proton in the former isomers. This trend is in good accord with the similar observations reported on the NMR spectra of Nocardicins.[5] The difference in the NMR spectra due to the geometry of the oxime is also prominent on the signals of the protons at 5-position of thiazoline as shown in Table I.

Table II. Antibacterial Activity of 7-Hydroxyimino-acetamido Cephalosporins (MIC μg/ml)[a]

Organism	Compound						CEZ[b]	CER[b]	CXM[b]
	(*Z*)-Isomer			(*E*)-Isomer					
	5a	**5b**	**5c**	**6a**	**6b**	**6c**			
S. aureus 209P	0.39	0.78	0.39	1.56	6.25	3.13	0.39	0.05	3.13
E. coli NIHJ JC-2	0.024	0.05	0.05	0.20	0.78	0.78	1.56	3.13	0.78
E. coli T-7	0.39	0.39	0.78	3.13	12.5	12.5	100	>100	100
Serr. malcescens TN-24	1.56	1.56	0.39	50	100	100	>100	>100	>100
Pr. vulgaris GN-4413	12.5	50	6.25	>50	>100	100	>100	>100	>100
Ent. cloacae IFO-12937	25	12.5	6.25	>50	50	12.5	>100	>100	100
Cit. freundii GN-1706	0.10	0.10	0.10	0.39	0.78	0.78	>100	>100	6.25

a) MICs were measured by the serial dilution method on Tripticase soy agar (BBL).
b) Generic name: CEZ=cefazolin, CER=cephaloridine, CXM=cefuroxime.

The *in vitro* antibacterial activities of the new compounds were tested by the serial agar dilution method, whereupon they showed marked activities not only against a wide variety of bacteria but also against bacteria resistant to hitherto known cephalosporins.

From the data of Table II, it is apparent that (*Z*)-isomers (**5a, b, c**) have more potent antibacterial activities than (*E*)-isomers (**6a, b, c**). The difference in activities caused by the (*Z*)- and (*E*)-configurations of 7-(2-hydroxyiminoacetamido) side chains was also reported on other series of cephalosporins.[6]

Extensive survey on the properties of **5** and **6** is now in progress.

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