SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 7β-[2-(2-AMINOTHIAZOL-4-YL)ACETAMIDO]-CEPHALOSPORIN DERIVATIVES

II. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7β-[2-(2-AMINOTHIAZOL-4-YL)ACETAMIDO]-7α-METHOXYCEPHALOSPORINS*

MICHIHIKO OCHIAI, AKIRA MORIMOTO, YOSHIHIRO MATSUSHITA and MAKOTO KIDA

Central Research Division, Takeda Chemical Ind., Ltd., Juso, Yodogawa-ku, Osaka 532, Japan

(Received for publication June 27, 1980)

7β-[2-(2-Aminothiazol-4-yl)acetamido]-7α-methoxycephalosporins were synthesized both by acylation of the 7β-amino-7α-methoxycephalosporin compound (**VIII**) and a new direct acyl-exchange reaction of 7α-methoxy-7β-phosphoramido compound (**VII**). Some of these compounds (**IXa, IXb**) showed higher antibacterial activity than the 7α-unsubstituted compound against β-lactamase-producing strains of *Serratia marcescens* and *Proteus vulgaris*.

In the preceding paper[1] the synthesis and the antibacterial activity of 7β-[2-(2-aminothiazol-4-yl)-2-(substituted)acetamido]cephalosporins were reported, and improvement in activity against β-lactamase-producing strains of bacteria was demonstrated.

Another group of cephalosporins characterized by high antibacterial activity[2] and stability to β-lactamases bear a methoxy substituent at the 7α-position. Therefore, it was interesting to us to synthesize 7α-methoxy derivatives of 7β-[2-(2-aminothiazol-4-yl)acetamido]cephalosporins with the expectation of obtaining further improvement in antibacterial activity.

Chemistry

To introduce a methoxy group into the 7α-position an efficient method *via* an acylimine[3] (or *t*-butyl hypochlorite method) was applied to diphenylmethyl 7β-[2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanate (**IV**) (Chart 1). The reaction of N-(2,2,2-trichloroethoxycarbonyl)thiourea (**I**)[1] and ethyl γ-bromoacetoacetate gave ethyl 2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetate (**IIa**) which was obtained alternatively by the acylation of ethyl 2-(2-aminothiazol-4-yl)acetate[4] with trichloroethoxycarbonyl chloride. Hydrolysis of the ester (**IIa**) to the acid (**IIb**) followed by the action of PCl_5 afforded the acid chloride as the crystalline hydrochloride (**III**). Acylation of 7-aminocephalosporanic acid (7-ACA) with **III** and subsequent esterification with diphenyldiazomethane gave the 7-acylated compound (**IV**).

Application of the acylimine method to compound **IV**, however, did not give rise to the expected 7α-methoxy compound (**V**) but to a chlorinated derivative (**VI**) in poor yield. The structure of **VI** was assigned on the basis of its NMR spectrum and confirmed by comparison with the NMR spectrum of a sample from an alternate synthesis (*vide infra*).

* Part of this paper was presented at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy. Oct. 2, 1978. Atlanta, Ga., U.S.A. (Abstract No. 150).

Chart 1.

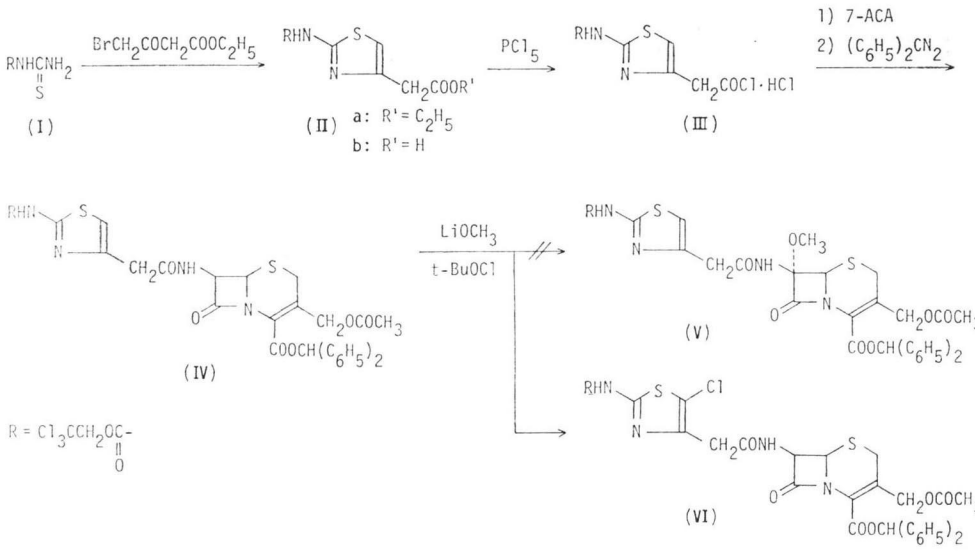
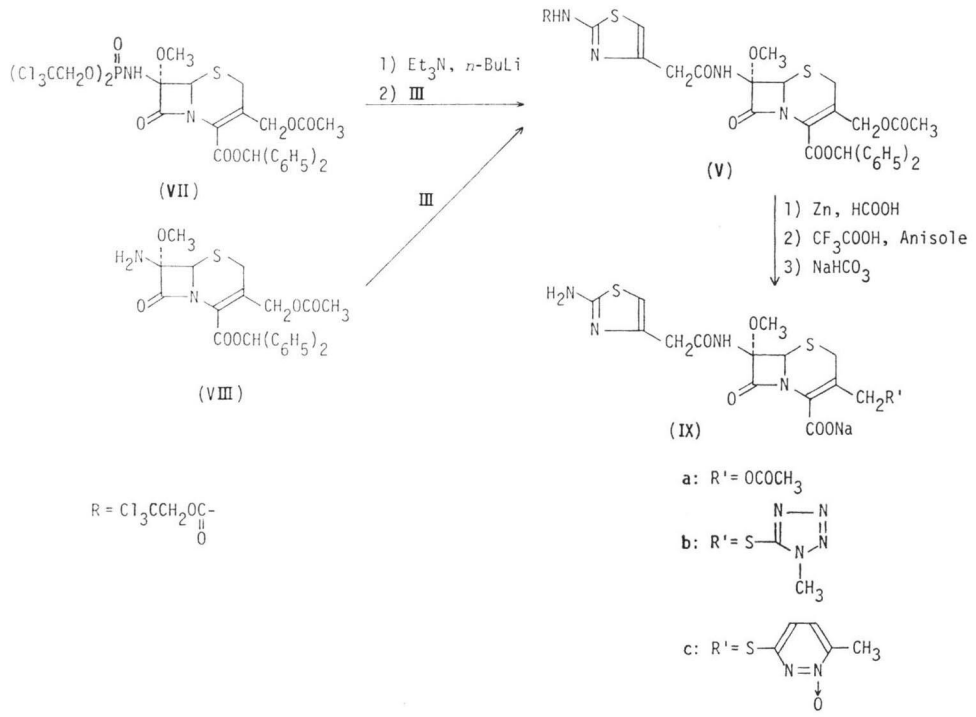
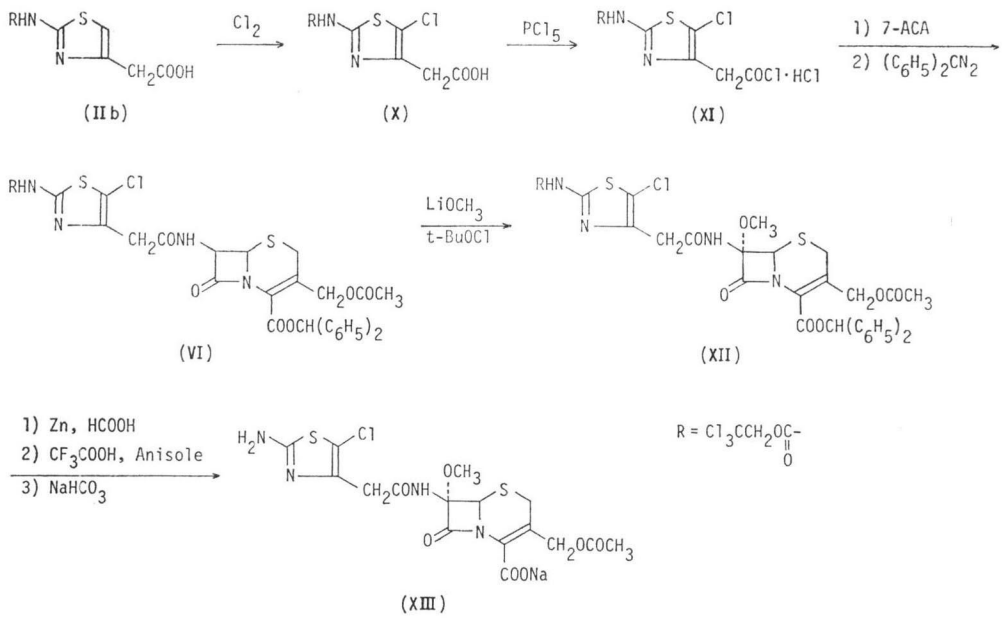


Chart 2.



A direct acyl-exchange reaction which we have developed[5] was then successfully extended to the synthesis of the desired compound (V) (Chart 2). The 7α-methoxy-7β-phosphoramido compound (VII) was treated with the acid chloride (III) in the presence of triethylamine and *n*-butyllithium. Purification of the reaction product by silica gel chromatography gave 7β-acylamino compound (V) which was identical with a sample unambigously synthesized by acylation of the known ester (VIII)[6]

Chart 3.



with the acid chloride (**III**). Stepwise removal of the trichloroethoxycarbonyl and diphenylmethyl groups in **V** by conventional methods afforded the anticipated 7α-methoxy compound (**IXa**). **IXa** was further subjected to nucleophilic substitution reaction with thiol compounds to give 3-heterocyclic thiomethyl derivatives (**IXb, IXc**).

The reaction product (**VI**) to which the chlorinated structure was assigned was synthesized alternatively as shown in Chart 3 and was subjected to the acylimine method to afford the 7α-methoxy compound (**XII**). Stepwise removal of the protecting groups gave **XIII**.

Antibacterial Activity

The *in vitro* antibacterial activity of these new compounds against several bacteria, especially β-lactamase-producing strains, is shown in Table 1.

The 7α-methoxy derivatives showed on the whole improved activity when compared with cefotiam and compound **Xb** is comparable in activity to cefoxitin. The 7α-methoxy compounds have, in general, clearly improved activity against *Proteus vulgaris* but less activity against *Enterobacter cloacae* in sharp contrast to the 2-hydroxy- and 2-alkylacyl derivatives reported in our previous paper.[1] Chlorination of the thiazole does not seem to improve the activity.

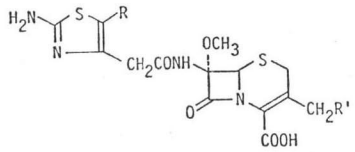
Experimental

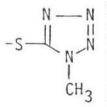
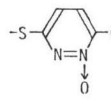
Infrared spectra were measured in a KBr disk using a Hitachi Type 215 spectrophotometer. NMR spectra were done on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as a standard. All melting points are uncorrected.

Ethyl 2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetate (**IIa**)

(a) N-(2,2,2-Trichloroethoxycarbonyl)thiourea (**I**)[1] (500 mg), ethyl γ-bromoacetoacetate[7] (416 mg) and N,N-dimethylaniline (363 mg) were dissolved in EtOH (3 ml), and the solution was stirred for 24 hours at room temperature. After evaporation of the solvent, $CHCl_3$ was added to the residue

Table 1. *In vitro* antibacterial activity of 7α-methoxy derivatives (MIC: μg/ml).



Compound		Cefotiam	Cefazolin	Cefoxitin	IXa	IXb	IXc	XIII
	R				H	H	H	Cl
	R′				$OCOCH_3$			$OCOCH_3$
S. aureus 1840		1.56	0.78	3.13	6.25	3.13	12.5	3.13
E. coli T-7		3.13	100	25	6.25	6.25	50	25
S. marcescens TN 24		100	>100	6.25	12.5	6.25	100	50
P. vulgaris GN 4413		>100	>100	12.5	25	6.25	25	50
E. cloacae TN 1282		100	>100	>100	>100	>100	>100	>100

The MIC_s were determined by a standard dilution method in Trypticase soy agar (BBL).

Cefotiam: generic name of 7β-[2-(2-aminothiazol-4-yl)acetamido]-3-[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thiomethyl]ceph-3-em-4-carboxylic acid.

and the solution was washed with 10% aqueous HCl and then with water. An oily product obtained by evaporation of the dried $CHCl_3$ layer was chromatographed on silica gel using benzene - $CHCl_3$ (1 : 1) as eluent to give **IIa** as yellowish crystals (540 mg), mp 91~92°C.

Anal. Calcd. for $C_{10}H_{11}Cl_3N_2O_4S$: C, 33.21; H, 3.07; N, 7.75.
Found: C, 33.38; H, 2.85; N, 7.73.

(**b**) To an ice-cooled solution of ethyl 2-(2-aminothiazol-4-yl)acetate[4] (18.6 g) and Et_3N (11.1 g) in $CHCl_3$ (100 ml) was added 2,2,2-trichloroethoxycarbonyl chloride (23.3 g) dropwise with stirring. After stirring for 2 hours at room temperature, the mixture was poured into water and extracted with AcOEt. The residue obtained by evaporation of the dried AcOEt layer was treated with a small amount of EtOH to crystallize the unreacted ethyl 2-(2-aminothiazol-4-yl)acetate which was removed by filtration. The filtrate was concentrated and chromatographed as described in section (**a**) to afford **IIa** (12.2 g). Comparison of IR and NMR spectra confirmed the identity of the product with the sample obtained in section (**a**).

2-[2-(2,2,2-Trichloroethoxycarbonylamino)thiazol-4-yl]acetic acid (**IIb**)

IIa (5.9 g) and KOH (1.3 g) were dissolved in a mixture of water (50 ml) and MeOH (50 ml) and the mixture was stirred for 4 hours at room temperature. After the MeOH was distilled off under reduced pressure, the aqueous solution was washed with AcOEt, acidified with 10% aqueous HCl, and then extracted with Et_2O. Evaporation of the solvent from the dried extract gave **IIb** as colorless crystals (3.1 g), mp 164~165°C.

Anal. Calcd. for $C_8H_7Cl_3N_2O_4S$: C, 28.81; H, 2.12; N, 8.40.
Found: C, 28.92; H, 2.20; N, 8.44.

2-[2-(2,2,2-Trichloroethoxycarbonylamino)thiazol-4-yl]acetyl chloride hydrochloride (**III**)

To a suspension of **IIb** (6.67 g) in $CHCl_3$ (20 ml) was added PCl_5 (4.15 g) under ice-cooling. **IIb** gradually went into solution and after about 5 minutes solids separated from the reaction solution. After stirring for 1 hour at room temperature, the separated solid was collected by suction and washed with petroleum ether to give **III** as colorless needles (6.59 g), mp 109.7°C (dec.).

Anal. Calcd. for $C_8H_6Cl_4N_2O_3S \cdot HCl$: C, 24.73; H, 1.81; N, 7.21.
Found: C, 24.40; H, 1.63; N, 6.94.

Diphenylmethyl 7β-[2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanate (**IV**)

To a suspension of 7-ACA (3.04 g) in DMA (15 ml) was added **III** (4.13 g) with stirring and the mixture was stirred for 1 hour at room temperature. The reaction mixture was poured into water and extracted with AcOEt. From the dried extract was obtained crude 7β-[2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanic acid as yellowish powder (3.30 g). The crude acid (1 g) was dissolved in THF (40 ml) and treated with diphenyldiazomethane[8] (stirred for 4 hours at room temperature). The reaction mixture was poured into water and extracted with AcOEt. The AcOEt extract was washed with 0.5 N HCl and water and dried over $MgSO_4$. The residue obtained by condensation of the extract was chromatographed on silica gel using $CHCl_3$ as eluent to afford **IV** as yellowish powder (1.54 g). NMR ($CDCl_3$): δ 1.94 (3H, s, $OCOCH_3$), 3.30 (2H, s, 2-CH_2), 3.64 (2H, s, CH_2CO), 4.84 (1H, d, 6-CH), 4.88 (4H, q, CCl_3CH_2- and 3-CH_2), 5.66 (1H, d of d, 7-CH), 6.40 (1H, s, thiazole 5-H), 6.76 (1H, s, ϕ_2CH).

Diphenylmethyl 7β-[2-[5-chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanate (**VI**)

(a) Acylimine method applied to **IV**: A solution of **IV** (754 mg) in a mixture of THF (3 ml) and MeOH (5 ml) was cooled to −70°C and stirred under an atmosphere of nitrogen. To this was added a methanol solution of lithium methoxide [prepared from lithium (21 mg) and MeOH (15 ml)] in one portion. After stirring for 5 minutes at −70°C, *t*-butylhypochlorite (168 mg) was added and stirring continued for another 20 minutes. Acetic acid (200 mg) was added and the reaction mixture was poured into water and extracted with AcOEt. The reaction product obtained from the washed and dried extract was chromatographed on silica gel using $CHCl_3$ as eluent to give **VI** as yellowish powder (146 mg). NMR ($CDCl_3$): δ 1.99 (3H, s, $OCOCH_3$), 3.42 (2H, b.s, CH_2CO), 3.59 (2H, q, 2-CH_2), 4.86 (4H, b.s, CCl_3CH_2 and 3-CH_2), 5.02 (1H, d, 6-CH), 5.95 (1H, d of d, 7-CH), 6.95 (1H, s, CH), 7.31 (10H, b.s, $C_6H_5\times2$), 8.28 (1H, d, NH).

Unreacted **IV** (160 mg) was recovered from the column after elution of **VI**.

(b) To a solution of 7-ACA (2.20 g) in a mixture of DMA (10 ml) and CH_2Cl_2 (5 ml) was added 2-[5-chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetyl chloride hydrochloride (**XI**) (3.38 g). After stirring for 1 hour at room temperature, the reaction mixture was poured into water and extracted with AcOEt. From the washed and dried extract was obtained crude 7β-[2-[5-chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanic acid (4.64 g). This was treated similarly as described in section **(a)** with diphenyldiazomethane followed by purification to afford **VI** as yellowish powder (3.30 g). Comparison of NMR spectrum confirmed the identity of the product with the material in section **(a)**.

For further confirmation of the structure, **VI** was converted into the deprotected compound. Thus conventional removal of trichloroethoxycarbonyl group with zinc dust in 90% formic acid and the diphenylmethyl group with CF_3COOH-anisole from **VI** (500 mg) followed by purification by chromatography on Amberlite XAD-2 (Rohm & Haas Co.) column afforded sodium 7β-[2-(2-amino-5-chlorothiazol-4-yl)acetamido]cephalosporanate as colorless powder (95 mg).

Anal. Calcd. for $C_{15}H_{14}ClN_4O_6S_2Na\cdot2H_2O$: C, 34.45; H, 3.85; N, 10.71.
Found: C, 34.70; H, 3.64; N, 9.71.

NMR (D_2O): δ 2.19 (3H, s, $COCH_3$), 3.56 (2H, q, 2-CH_2), 3.69 (2H, s, CH_2CO), 3.70 (3H, s, OCH_3), 4.81 (2H, q, 3-CH_2), 5.20 (1H, d, 6-CH), 5.74 (1H, d, 7-CH).

Diphenylmethyl 7α-methoxy-7β-[2-[2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]cephalosporanate (**V**)

(a) Diphenylmethyl 7β-di(2,2,2-trichloroethyl)phosphoramido-7α-methoxycephalosporanate (**VII**)[5] (388 mg) was dissolved in THF (5 ml) and cooled to −78°C under an atmosphere of nitrogen. To this solution were added Et_3N (100 mg) and *n*-BuLi (9% hexane solution, 0.5 ml). After stirring for 15 minutes **III** (352 mg) was added to the solution and stirring continued for 30 minutes. Then AcOH (0.5 ml) was added and after stirring for 5 minutes, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The residue obtained from the washed and dried ex-

tract was chromatographed on a silica gel column to give **V** as yellowish powder (60 mg). Comparison of IR and NMR spectra confirmed the identity of the product with the sample obtained in the following section (**b**).

(**b**) To an ice-cooled solution of **VIII**[6] (1.63 g) in CH_2Cl_2 (10 ml) were added pyridine (1.5 ml) and **III** (2.70 g) and the mixture was stirred for 15 minutes. After stirring for another 20 minutes at room temperature, the reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with 0.5 N HCl, water, 5% aqueous $NaHCO_3$ and then with saturated aqueous NaCl, and dried over $MgSO_4$. An oily product obtained from the extract was chromatographed on silica gel to afford **V** as yellowish powder (1.09 g). IR: 1770 cm^{-1} (β-lactam). NMR ($CDCl_3$): δ 1.98 (3H, s, $OCOCH_3$), 3.33 (2H, s, 2-CH_2), 3.34 (3H, s, OCH_3), 3.74 (2H, s, CH_2CO), 4.84 (3H, s, CCl_3CH_2), 4.90 (2H, q, 3-CH_2), 5.05 (1H, s, 6-CH), 6.57 (1H, s, thiazole 5-H), 6.85 (1H, s, CH), 7.30 (10H, s, $C_6H_5\times2$).

Sodium 7β-[2-(2-aminothiazol-4-yl)acetamido]-7α-methoxycephalosporanate (**IXa**)

To an ice-cooled solution of **V** (990 mg) in 90% formic acid (25 ml) was added zinc dust (860 mg) gradually with stirring. After stirring for 1 hour, the mixture was poured into saturated aqueous NaCl and extracted with AcOEt. From the washed and dried extract was obtained diphenylmethyl 7β-[2-(2-aminothiazol-4-yl)acetamido]-7α-methoxycephalosporanate as colorless powder (472 mg). IR: 1770 cm^{-1} (β-lactam). NMR ($CDCl_3$): δ 2.00 (3H, s, $OCOCH_3$), 3.36 (2H, q, 2-CH_2), 3.45 (3H, s, OCH_3), 3.56 (2H, s, CH_2CO), 4.90 (2H, q, 3-CH_2), 5.08 (1H, s, 6-CH), 6.28 (1H, s, thiazole 5-H), 6.93 (1H, s, CH), 7.30 (10H, s, $C_6H_5\times2$).

The crude ester (335 mg) was dissolved in a mixture of CF_3COOH (1.5 ml) and anisole (1.5 ml) and the mixture was stirred for 30 minutes under ice-cooling. The reaction mixture was poured into Et_2O (50 ml) and the separated solid was collected by suction and washed with Et_2O to give the CF_3COOH salt of 7β-[2-(2-aminothiazol-4-yl)acetamido]-7α-methoxycephalosporanic acid (180 mg). The solid was dissolved in a small amount of 5% aqueous $NaHCO_3$ and chromatographed on Amberlite XAD-2 column using water as eluent to afford **IXa** as colorless powder (131 mg). IR: 1750 cm^{-1} (β-lactam).

Anal. Calcd. for $C_{16}H_{17}N_4O_7S_2Na\cdot3H_2O$: C, 37.06; H, 4.47; N, 10.80.
Found: C, 37.36; H, 4.14; N, 10.50.

NMR (D_2O): δ 2.26 (3H, s, $OCOCH_3$), 3.52 (2H, q, 2-CH_2), 3.70 (3H, s, OCH_3), 3.80 (2H, s, CH_2CO), 4.95 (2H, q, 3-CH_2), 5.32 (1H, s, 6-CH), 6.70 (1H, s, thiazole 5-H).

Sodium 7β-[2-(2-aminothiazol-4-yl)acetamido]-7α-methoxy-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylate (**IXb**)

7β-[2-(2-Aminothiazol-4-yl)acetamido]-7α-methoxycephalosporanic acid CF_3COOH salt (431 mg), 1-methyl-1H-tetrazole-5-thiol (108 mg) and triethylbenzylammonium bromide (24.6 mg) were dissolved in water (4 ml) containing $NaHCO_3$ (208 mg) and the mixture was stirred for 6 hours at 60°C under an atmosphere of nitrogen. After cooling the reaction mixture was chromatographed on Amberlite XAD-2 column using water as eluent to give **IXb** as colorless powder (37 mg). IR: 1750 cm^{-1} (β-lactam).

Anal. Calcd. for $C_{16}H_{17}N_8O_5S_3Na\cdot H_2O$: C, 35.68; H, 3.55; N, 20.86.
Found: C, 35.56; H, 3.36; N, 18.83.

NMR (D_2O): δ 3.60 (2H, q, 2-CH_2), 3.65 (3H, s, OCH_3), 3.77 (2H, s, CH_2CO), 4.17 (3H, s, N-CH_3), 4.30 (2H, q, 3-CH_2), 5.24 (1H, s, 6-CH), 6.67 (1H, s, thiazole 5-H).

Sodium 7β-[2-(2-aminothiazol-4-yl)acetamido]-7α-methoxy-3-[(6-methyl-1-oxopyridazin-3-yl)thiomethyl]ceph-3-em-4-carboxylate (**IXc**)

Similar reaction as described above, using 6-methyl-1-oxopyridazine-3-thiol[9] (59 mg), afforded **IXc** as colorless powder (62 mg). IR: 1760 cm^{-1} (β-lactam).

Anal. Calcd. for $C_{19}H_{19}N_6O_6S_3Na\cdot4.5H_2O$: C, 36.36; H, 4.58; N, 13.39.
Found: C, 36.12; H, 3.96; N, 12.64.

NMR (D_2O): δ 2.61 (3H, s, CH_3), 3.60 (2H, q, 2-CH_2), 3.65 (3H, s, OCH_3), 3.77 (2H, s, CH_2CO), 5.24 (1H, s, 6-CH), 6.67 (1H, s, thiazole 5-H), 7.51 and 7.88 (2H, two d, pyridazine H).

Diphenylmethyl 7β-[2-[5-chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetamido]-7α-methoxycephalosporanate (XII)

VI (777 mg) was dissolved in a mixture of THF (20 ml) and MeOH (4 ml) and cooled to −75°C with stirring under an atmosphere of nitrogen. To this was added a methanol solution of lithium methoxide [prepared from lithium (25 mg) and MeOH (4 ml)] in one portion and the mixture was stirred for 5 minutes at −75°C. *t*-Butylhypochlorite (129 mg) was added to the reaction mixture and it was stirred for 1 hour. The reaction mixture, after addition of AcOH (1 ml), was poured into water and extracted with AcOEt. The residue obtained from the washed and dried extract was chromatographed on a silica gel column using $CHCl_3$ as eluent to afford **XII** as yellowish powder (293 mg). NMR ($CDCl_3$): δ 2.00 (3H, s, $OCOCH_3$), 3.23 (2H, b.s, 2-CH_2), 3.42 (3H, s, OCH_3), 3.74 (2H, b.s, CH_2CO), 4.86 (2H, b.s, CCl_3CH_2), 4.87 (2H, q, 3-CH_2), 5.05 (1H, s, 6-CH), 6.90 (1H, s, CH), 7.30 (10H, s, $C_6H_5\times2$).

Sodium 7β-[2-(2-amino-5-chlorothiazol-4-yl)acetamido]-7α-methoxycephalosporanate (XIII)

To an ice-cooled solution of **XII** (292 mg) in 90% formic acid (5 ml) was added zinc dust (233 mg) gradually with stirring . The mixture was stirred for 1 hour, filtered, and the filtrate was poured into ice-water followed by extraction with AcOEt. An oily product obtained from the extract was chromatographed on silica gel column using $CHCl_3$ - AcOEt (4: 1) as eluent to give diphenylmethyl 7β-[2-(2-amino-5-chlorothiazol-4-yl)acetamido]-7α-methoxycephalosporanate as yellowish powder (50 mg). This was dissolved in a mixture of CF_3COOH (0.2 ml) and anisole (0.2 ml) and the mixture was stirred for 40 minutes under ice-cooling. After addition of Et_2O (10 ml) the separated solid was collected by suction, and dissolved in 5% aqueous $NaHCO_3$ and chromatographed on Amberlite XAD-2 column using water as eluent to afford **XIII** as yellowish powder (7 mg). Because only small amount of **XIII** was available, **XIII** was characterized without elemental analysis, by NMR spectroscopy which gave a reasonable spectrum. NMR (D_2O): δ 2.25 (3H, s, $OCOCH_3$), 3.70 (5H, s, CH_2CO and 7-OCH_3), 3.75 (2H, q, 2-CH_2), 5.29 (1H, s, 6-CH),

2-[5-Chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetic acid (X)

To an ice-cooled solution of **IIb** (5 g) in $CHCl_3$ (75 ml) was added a solution of Cl_2 in CH_2Cl_2 (10% w/v, 14.9 ml) dropwise with stirring. After stirring for 15 minutes **IIb** went into solution which was then extracted with 5% aqueous $NaHCO_3$. The extract was acidified with 5% aqueous *HCl* (pH 2.0) and the separated solid was collected by suction and recrystallized from $CHCl_3$ - AcOEt to give **X** as colorless crystals (3.5 g) ,mp 112°C.

Anal. Calcd. for $C_8H_6Cl_4O_4N_2S$: C, 26.10; H, 1.64; N, 7.61.
Found: C, 25.71; H, 1.62; N, 7.46.

NMR (d_6-DMSO): δ 3.55 (2H, s, CH_2CO), 4.98 (2H, s, CCl_3CH_2).

2-[5-Chloro-2-(2,2,2-trichloroethoxycarbonylamino)thiazol-4-yl]acetyl chloride hydrochloride (XI)

To a strried suspension of **X** (4.2 g) in CH_2Cl_2 (20 ml) was added PCl_5 (2.38 g) under ice-cooling. Solution resulted followed by precipitation of another solid material. After stirring for 30 minutes at room temperature the separated solid was collected by suction and washed with petroleum ether to give **XI** as colorless needles (3.38 g), mp 99.8°C.

Anal. Calcd. for $C_8H_5Cl_5N_2O_3S\cdot HCl$: C, 22.72; H, 1.43; N, 6.62.
Found: C, 23.44; H, 1.63; N, 6.77.

Acknowledgement

The authors thank Dr. E. OHMURA and Dr. K. MORITA of this Division for their advice and encouragement.

References

1) OCHIAI, M.; A. MORIMOTO, Y. MATSUSHITA, T. KANEKO & M. KIDA: Synthesis and structure-activity relationships of 7β-[2-(2-aminothiazol-4-yl)acetamido]cephalosporin derivatives. I. Synthesis and antibacterial activity of 7β-[2-alkyl- and 2-hydroxy-2-(2-aminothiazol-4-yl)acetamido]cephalosporins. J. Antibiotics 33: 1005~1013, 1980

2) WEBER, J. A. & J. L. OTT: Structure-activity relationships among the semisynthetic antibiotics. (*Ed.* D. PERLMAN) pp. 182~183, Academic Press, New York, 1977
3) BALDWIN, J. E.; F. J. URBAN, R. D. G. COOPER & F. L. JOSE: Direct 6-methoxylation of penicillin derivatives. A convenient pathway to substituted β-lactam antibiotics. J. Am. Chem. Soc. 95: 2401~2403, 1973
4) STEUDE, M.: Üeber Thiazolderivate aus Brombrenztraubensäuren und Bromacetessigester. Ann. 261: 22~47, 1891
5) MORIMOTO, A.; Y. MATSUSHITA & M. OCHIAI: A method for the preparation of 7α-methoxycephalosporins. J. Chem. Soc. Perkin I 1980: 1109~1113, 1980
6) LUNN, W. H. W. & E. V. MASON: The synthesis of 7α-methoxy-7β-aminocephalosporanic acids by methoxylation of 7β-(*p*-nitrobenzyloxycarboxamide)cephalosporanic acid. Tetrahed. Lett. 1974: 1311~1313, 1974
7) CHICK, F. & N. T. M. WILSMORE: The polymerization of keten. Cyclobutan-1: 3-dione ("Acetylketen"). J. Chem. Soc. 97: 1978~2000, 1910
8) MILLER, J. B.: Preparation of crystalline diphenyldiazomethane. J. Org. Chem. 24: 560~561, 1959
9) OCHIAI, M.; O. AKI, A. MORIMOTO & T. OKADA: Cephalosporins. U. S. Patent 3,892,737, July 1, 1975