SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A NEW SERIES OF CEPHALOSPORINS, BMY-28142 AND RELATED COMPOUNDS

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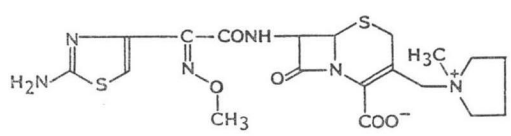
The synthesis of a series of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-oxyiminoacetamido]-3-ammoniomethyl-3-cephems is described. Variations of an oxyimino moiety in the 7-side chain and a quaternary ammonium moiety in the 3-side chain were examined and structure-activity relationships studied. BMY-28142, the 3-(*N*-methylpyrrolidinio)methyl derivative of the 7-α-methoxyimino series of cephalosporins, exhibited broad antimicrobial activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*.

Many of the recently introduced cephalosporins have a common structural feature in that they have a 2-aminothiazolylacetamido group in the 7-side chain with an α-oxyimino substitution. These include cefotaxime[1~3], ceftizoxime[4,5], cefmenoxime[6], ceftriaxone[7,8] and ceftazidime[9~11] which are characterized by their excellent activity against Enterobacteriaceae. They are, however, relatively weak in anti-staphylococcal activity as compared to older cephalosporins such as cephalothin and cefazolin. Among the new family of cephalosporins, only ceftazidime exhibits a potent anti-pseudomonal activity, but unfortunately it is less active than other members of this group of cephalosporins against Staphylococci.

Our primary target in the present work was to obtain ceftazidime analogs with improved anti-staphylococcal activity while retaining high anti-pseudomonal activity. Modifications by replacing the pyridinium group of ceftazidime with an aliphatic ammonium group gave compounds with excellent Gram-negative activity though they were only weakly active against Staphylococci. Substantial improvement in anti-staphylococcal activity was achieved by replacing the 2-carboxy-2-propoxyimino group in the 7-side chain with an alkoxyimino substitution. Thus, a series of the 7-α-alkoxyimino derivatives having a quaternized ammonium group in the 3-side chain were prepared. Among them, 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolidinio)-methyl-3-cephem-4-carboxylate, designated BMY-28142, was found to be most promising in view of its antimicrobial spectrum and other biological properties[12~21].

Fig. 1.



BMY-28142

This paper describes the synthesis and the structure-activity relationships of BMY-28142 and analogs†. Detailed microbiological evalua-

† A part of this paper has been presented at the 23rd Interscience Conference on Antimicrobial Agents & Chemotherapy (Las Vegas, 1983)[23].

tion of BMY-28142 will be reported in a separate paper[22].

Synthesis

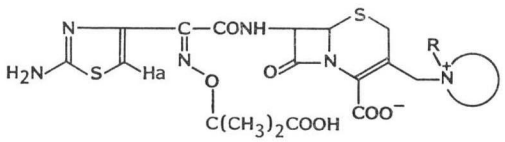
Preparation of the 7-α-oxyimino derivatives having a quaternary ammonium group in the 3-side chain was performed according to the procedure illustrated in Scheme 1. The starting material, diphenylmethyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (**II**)[24], was acylated with (*Z*)-2-(substituted-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid, **Ia**[25] or **Ib**~**f**[26], by the acid chloride method using PCl_5 to afford the 3-chloromethyl derivative (**IIIa**~**f**), which was converted to the corresponding iodide (**IVa**~**f**).

The 2-carboxy-2-propoxyimino derivatives (ceftazidime analogs) having a quaternary alicyclic ammonium group at the 3-side chain were prepared from the key intermediate **IVa** by Method A of Scheme 1 by quaternization with a tertiary amine, followed by deblocking and purification by HPLC. These derivatives are shown in Table 1.

On the other hand, three methods (Methods A, B and C of Scheme 1) were employed for the preparation of 7-α-methoxyimino derivatives listed in Table 2. In Method A, the key intermediate **IVb** was treated with tertiary aliphatic or alicyclic amines of Group A-1, A-2 or A-3 in Table 3 to give the quaternized ammonium derivatives (**Vb**), which was deblocked and purified by HPLC to afford the desired Δ^3 isomer of the final products (**VIb**) in 4~42% overall yield from **IVb**. Formation of a considerable amount of the Δ^2 isomer was observed during the quaternization step. The isomer was removed by HPLC at the final stage.

When tertiary amines of Groups A-2 and A-3 in Table 3 were used for introduction of the quaternary side chain, an additional asymmetric center was generated on the quaternary nitrogen and the final products were obtained as mixtures of diastereomers. The isomers having Group A-2 amines

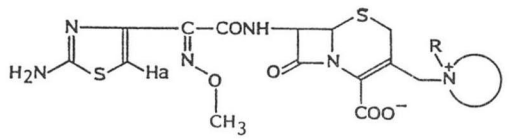
Table 1. Yield, mp, IR and ^{1}H NMR data of 2-carboxy-2-propoxyimino derivatives (**1**~**6**).



Compound	R	Yield from **IV** (%)	MP (°C, dec)	IR (KBr) β-lactam (cm^{-1})	^{1}H NMR (80 MHz, δ in D_2O, ppm)				
					CCH_3 (s)	$\overset{+}{N}CH_3$ (s)	6-H, 7-H (d, J=4~5 Hz)		Ha (s)
1[a]	$-\overset{+}{N}(CH_3)_3$	30	160	1770	1.63	3.24	5.48	5.97	7.07
2	$H_3C-\overset{+}{N}$	7	160	1775	1.65	3.09	5.44	5.94	7.15
3	$-\overset{+}{N}$	10	155	1775	1.65	—	5.43	5.93	7.14
4	$H_3C-\overset{+}{N}$ N–CH_3	7	165	1765	1.62	3.43	5.4	5.9	7.06
5	$-\overset{+}{N}$ N	18	175	1765	1.62	—	5.5	5.93	7.12
6	$H_3C-\overset{+}{N}$ O	5	175	1770	1.64	3.26	5.46	5.95	7.14

[a] Glaxo, Jpn Kokai 59196 (May 2, 1980); Brit. 2,943,437 (May 8, 1980).

Table 2. Yield, mp, IR and ^{1}H NMR data of methoxyimino derivatives (**7**~**33**).



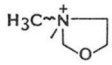
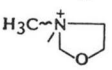
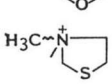
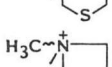
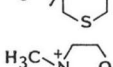
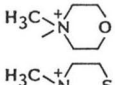
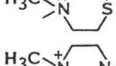
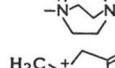
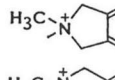
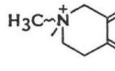
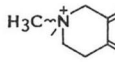
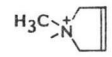
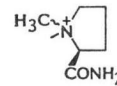
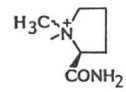
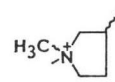
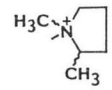
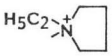
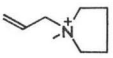
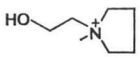
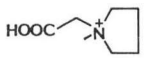
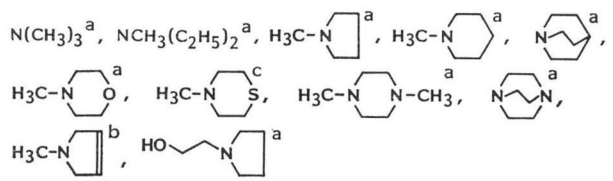
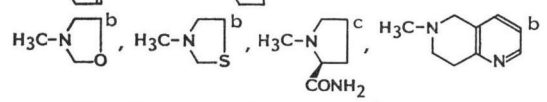
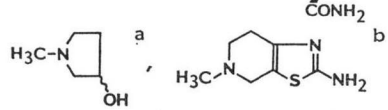
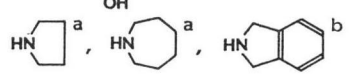
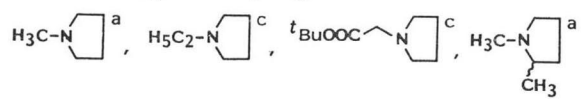
Compound	Method	R	Yield from IV (%)	MP (°C, dec)	IR (KBr) β-lactam (cm^{-1})	^{1}H NMR (80 MHz, δ in D_2O, ppm)				
						$^+NCH_3$ (s)	OCH_3 (s)	6-H, 7-H (d, J=4~5 Hz)		Ha (s)
7 (BMY-28142)	A, B, C		22, 17, 30	150	1770	3.08	4.09	5.43	5.93	7.08
8	A		14	145	1775	3.11	4.10	5.46	5.95	7.09
9	B		20	150	1770	3.12	4.10	5.5	5.95	7.08
10	A		32	150	1770	—	4.12	5.44	5.96	7.10
11	A	$-\overset{+}{N}(CH_3)_3$	42	160	1775	3.22	4.10	5.44	5.94	7.08
12	A	$-\overset{+}{N}CH_3(C_2H_5)_2$	10	150	1770	3.05	4.10	5.44	5.95	7.10
13	A		5	160	1770	3.26	4.08	5.43	5.93	7.07
14	A		6	160	1770	3.24	4.09	5.43	5.93	7.07
15	A		8	175	1770	3.40	4.10	5.5	5.95	7.10
16	A		6	175	1770	3.28	4.07	5.5	5.92	7.05
17	A		12	125	1775	3.28	4.12	5.47	5.97	7.10
18	A		10	140	1765	2.95	4.07	5.42	5.92	7.05
19	A		4	150	1780	3.22	4.13	5.4	5.95	7.12
20	A		22	150	1775	—	4.12	5.47	5.98	7.10
21	B		25	165	1770	3.32	4.08	5.26	5.89	7.05
22	A		7	160	1770	3.21	4.07	5.45	5.93	7.05
23	A		12	>163	1770	3.15	4.06	5.43	5.90	7.02
24	A		23	153	1760	3.21 3.15	4.07	5.42	5.91	7.04

Table 2. (Continued)

Compound	Method	R	Yield from IV (%)	MP (°C, dec)	IR (KBr) β-lactam (cm^{-1})	^{1}H NMR (80 MHz, δ in D_2O, ppm) $\overset{+}{N}CH_3$ (s)	OCH_3 (s)	6-H, 7-H (d, J=4~5 Hz)		Ha (s)
25	A		12	140	1770	3.25	4.08	5.41	5.92	7.05
26	A		6	155	1775	3.26	4.10	5.43	5.93	7.08
27	A		5	155	1775	3.11	4.10	5.45	5.95	7.08
28	A		17	160	1770	3.08 3.13 3.26	4.08	5.42	5.92	7.06
29	C		10	150	1770	2.94	4.05	5.45	5.90	7.05
30	C		6	150	1770	—	4.07	5.39	5.92	7.05
31	B		7	160	1770	—	4.08	5.5*	5.9*	7.06
32	A		4	160	1765	—	4.10	5.42	5.94	7.08
33	C		4	150	1765	—	4.12	5.45	5.97	7.11

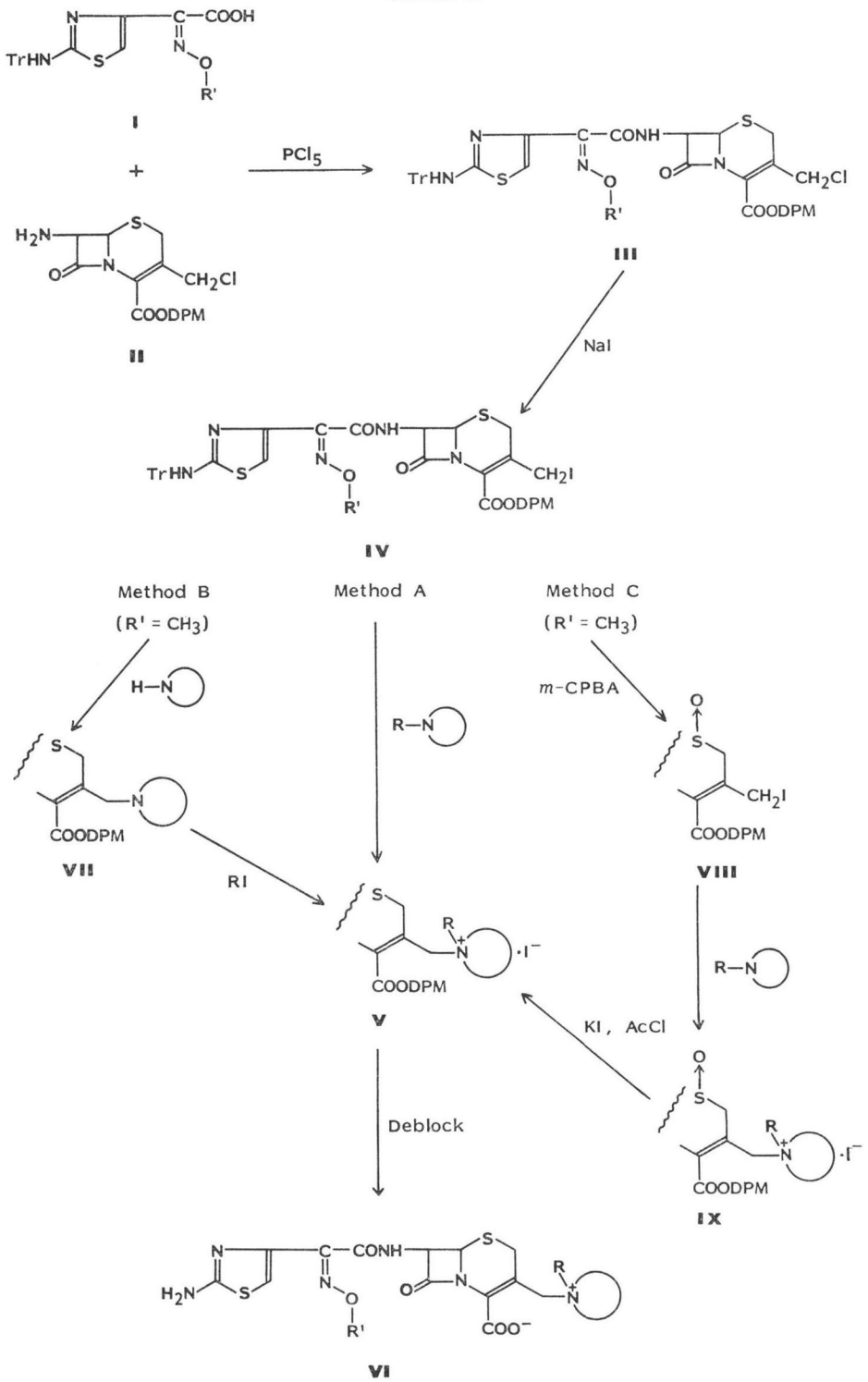
* Overlapping with vinyl protons.

Table 3. Amines used for the preparation of the 3-side chain of the cephalosporins in this study.

Group	Amine
A-1	
A-2	
A-3	
B	
C	

[a] Commercially available.
[b] Prepared according to the reported procedure.
[c] Prepared by conventional procedures from known secondary amines.

Scheme 1.



a R′: $C(CH_3)_2COO^tBu$ for **I**~**V**, $C(CH_3)_2COOH$ for **VI**, **b** R′: CH_3, **c** R′: C_2H_5, **d** R′: $CH(CH_3)_2$, **e** R′: $CH_2CH{=}CH_2$, **f** R′: $CH_2C{\equiv}CH$
DPM: $CH(C_6H_5)_2$, Tr: $C(C_6H_5)_3$

were separated by HPLC (such as **13** and **14**; **15** and **16**; **22** and **23**; **26** and **27** in Table 2), although the stereochemistry of the quaternary nitrogen of the isomers was not determined. The products from Group A-3 amines (**24** and **28**) were characterized as mixtures of the diastereomers.

In Method B (Scheme 1) the iodide **IVb** was first treated with secondary amines (Group B of Table 3) to give the tertiary amino derivatives (**VIIb**), which were then quaternized with an appropriate alkyl iodide to afford **Vb**. This method was applied for the preparation of **7**, **9**, **21** and **31** in Table 2 with no advantages in terms of yield and Δ^3/Δ^2 ratio.

Method C in Scheme 1 was used in an attempt to minimize the formation of the Δ^2 isomer. The key intermediate **IVb** was oxidized with *m*-chloroperbenzoic acid and then treated with tertiary amines of Group C in Table 3 to afford the quaternized sulfoxide (**IXb**) in a good yield. Reduction of the sulfoxide **IXb** was carried out by addition of potassium iodide and acetyl chloride, followed by quenching with sodium metabisulfite to afford **Vb** as a single isomer. Although no Δ^2 isomer was detected in this method, the reaction was rather sluggish requiring a tedious purification procedure at the final stage. Employment of other reducing agents (*e.g.* PBr_3 *etc.*) or work-up by other procedures resulted in a complex mixture or contamination of Δ^2 isomer in the product.

Another method shown in Scheme 2 was explored for the bulk preparation of BMY-28142, the representative compound of this series. In contrast to the above-described methods, this procedure comprised initial introduction of the 3-side chain and subsequent formation of the 7-side chain by 7-*N*-acylation. The amino group of **II** was masked to afford the crystalline Schiff base (**X**), which was converted to the 3-iodomethyl derivative (**XI**) and subsequently treated with *N*-methylpyrrolidine in carbon tetrachloride at 0°C. The precipitated quaternary product (**XII**) was deblocked to afford the crystalline intermediate **XIII**, which was not contaminated with its Δ^2 isomer. Acylation of **XIII** with the benzotriazole active ester of the 7-side chain acid (**XIV**)[27] smoothly proceeded to afford

Scheme 2.

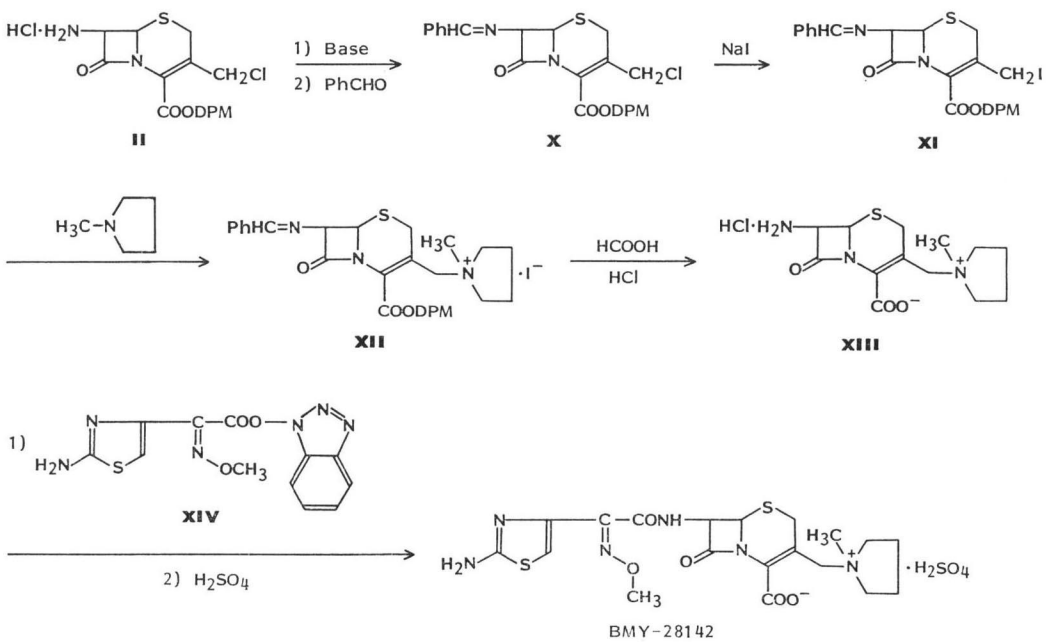
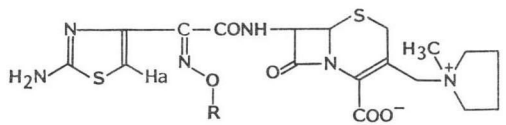


Table 4. Yield, mp, IR and ^{1}H NMR data of alkoxyimino analogs (**34**~**37**) of BMY-28142.



Compound	R	Yield from **IV** (%)	MP (°C, dec)	IR (KBr) β-lactam (cm^{-1})	^{1}H NMR (80 MHz, δ in D_2O, ppm)				
					$\overset{+}{N}CH_3$ (s)	OR	6-H, 7-H (d, J=4~5 Hz)		Ha (s)
34	CH_2CH_3	5	>175	1770	3.10	1.43 (3H, t, J=6.5 Hz), 4.36 (2H, q)	5.44	5.95	7.08
35	$CH(CH_3)_2$	3	170	1760	3.10	1.42 (6H, d, J=6.0 Hz)	5.45	5.95	7.05
36	$CH_2CH=CH_2$	5	155	1770	3.10	5.4 (2H, m), 6.1 (1H, m)	5.50	5.95	7.10
37	$CH_2C\equiv CH$	4	150	1765	3.10	3.05 (1H, t, J=2.0 Hz), 4.94 (2H, d)	5.44	5.84	7.15

BMY-28142 as a crystalline sulfate in 25% overall yield from **II**.

Modification in the methoxyimino moiety of BMY-28142 was also accomplished by Method A using an appropriate 3-iodomethyl derivative (**IVc~f**). Table 4 shows the derivatives of this group prepared in this study.

Antimicrobial Activity

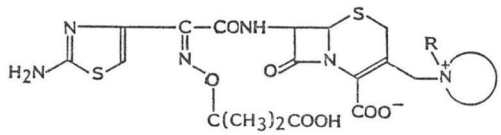
The minimum inhibitory concentrations (MICs) of the cephalosporins of this series were determined by two-fold serial agar dilution method in Mueller-Hinton agar against 32 test organisms which are classified into 6 groups as shown in Table 5. The *in vitro* activity of cephalosporins in the primary evaluation was assessed by the geometric mean of MICs of a compound for each group of the test organisms. Results are shown in Tables 6, 7 and 8.

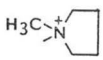
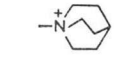
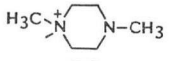
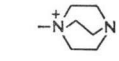
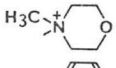
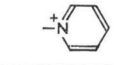
Table 6 shows *in vitro* activity of 2-carboxy-2-propoxyimino derivatives (ceftazidime analogs).

Table 5. Test organisms for the primary evaluation of cephalosporins in this study.

Group	Organisms	Number of strains
Gp-Ia	Penicillinase(Pen-ase) - negative *Staphylococcus aureus*	5
Gp-Ib	Pen-ase - positive *S. aureus*	5
Gn-Ia	Cephalothin(CET) - sensitive *Escherichia coli* (2 strains), *Klebsiella pneumoniae* (1) and *Proteus mirabilis* (2)	5
Gn-Ib	CET-resistant *E. coli* (3) and *K. pneumoniae* (2)	5
Gn-II	*Morganella morganii* (1), *Enterobacter cloacae* (2) and *Serratia marcescens* (2)	5
Gn-III	*Pseudomonas aeruginosa*	7

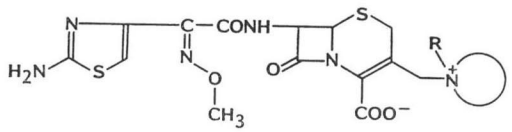
Table 6. *In vitro* antibacterial activity of 2-carboxy-2-propoxyimino derivatives (**1~6**).



Compound	R	Geometric mean of MIC (μg/ml)					
		Gp-Ia[a]	Gp-Ib	Gn-Ia	Gn-Ib	Gn-II	Gn-III
1	$-\overset{+}{N}(CH_3)_3$	11	43	0.038	0.60	0.35	1.8
2		12	28	0.056	0.67	0.34	3.4
3		12	48	0.085	0.67	0.68	3.8
4		65	>100	0.15	1.2	0.71	11
5		>100	>100	0.12	0.70	0.56	5.0
6		37	>100	0.14	1.1	0.96	5.4
Ceftazidime		4.2	11	0.066	1.9	0.53	1.7

[a] See Table 5.

Table 7. *In vitro* antibacterial activity of methoxyimino derivatives (**7**~**33**).



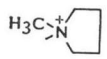
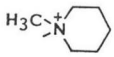
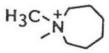
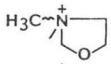
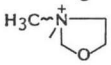
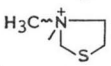
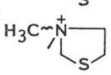
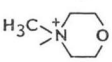
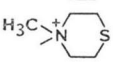
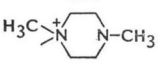
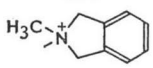
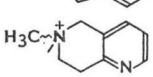
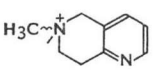
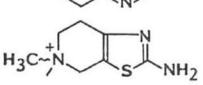
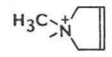
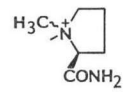
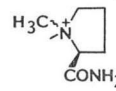
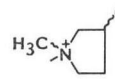
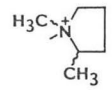
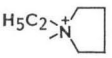
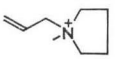
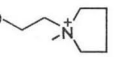
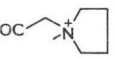
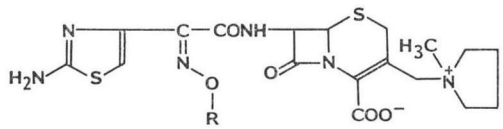
Compound	R	Geometric mean of MIC (μg/ml)					
		Gp-Ia[a]	Gp-Ib	Gn-Ia	Gn-Ib	Gn-II	Gn-III
7 (BMY-28142)		1.1	1.6	0.012	0.076	0.10	1.8
8		1.3	2.9	0.03	0.14	0.19	3.2
9		0.9	3.2	0.05	0.13	0.17	3.1
10		0.77	2.5	0.04	0.14	0.28	2.8
11	$-\overset{+}{N}(CH_3)_3$	1.3	2.9	0.02	0.16	0.19	3.2
12	$-\overset{+}{N}CH_3(C_2H_5)_2$	1.2	3.6	0.037	0.18	0.22	3.7
13		1.1	4.4	0.046	0.25	0.21	5.4
14		1.3	4.4	0.040	0.21	0.18	4.0
15		0.84	3.1	0.046	0.28	0.28	5.9
16		0.72	1.6	0.029	0.13	0.13	2.5
17		1.7	5.0	0.061	0.22	0.32	4.6
18		1.2	4.1	0.064	0.25	0.25	3.7
19		2.3	4.7	0.057	0.12	0.26	3.6
20		2.9	5.8	0.070	0.16	0.27	3.6
21		0.51	1.7	0.042	0.13	0.13	7.7
22		1.2	4.2	0.044	0.20	0.15	5.0
23		1.6	4.1	0.049	0.17	0.17	7.2
24		1.1	2.8	0.034	0.16	0.18	4.6

Table 7. (Continued)

Compound	R	Geometric mean of MIC (μg/ml)					
		Gp-Ia[a]	Gp-Ib	Gn-Ia	Gn-Ib	Gn-II	Gn-III
25		0.78	2.1	0.019	0.17	0.15	2.5
26		2.1	4.7	0.098	0.39	0.35	11
27		1.6	4.1	0.057	0.20	0.23	7.2
28		1.3	3.3	0.027	0.14	0.14	2.9
29		1.4	3.8	0.078	0.27	0.27	6.0
30		1.0	2.0	0.037	0.13	0.13	3.1
31		1.1	2.9	0.045	0.15	0.18	6.5
32		1.6	4.1	0.057	0.15	0.20	4.1
33		6.5	17	0.020	0.23	0.14	5.1
Cefotaxime		0.92	2.2	0.018	0.39	0.72	21
Ceftazidime		4.2	11	0.066	1.9	0.53	1.7

[a] See Table 5.

Table 8. *In vitro* antibacterial activity of alkoxyimino analogs (**34**~**37**) of BMY-28142.



Compound	R	Geometric mean of MIC (μg/ml)					
		Gp-Ia[a]	Gp-Ib	Gn-Ia	Gn-Ib	Gn-II	Gn-III
34	CH_2CH_3	0.69	1.4	0.033	0.12	0.45	3.4
35	$CH(CH_3)_2$	0.84	2.2	0.21	0.78	1.3	6.6
36	$CH_2CH=CH_2$	0.81	1.6	0.23	0.50	0.60	5.9
37	$CH_2C\equiv CH$	0.77	2.2	0.061	0.32	0.36	4.0
7 (BMY-28142)	CH_3	1.1	1.6	0.012	0.076	0.10	1.8
Ceftazidime		4.2	11	0.066	1.9	0.53	1.7

[a] See Table 5.

Replacement of the 3-pyridinium group of ceftazidime by alicyclic ammonium groups caused a decrease of the activity against both groups of Staphylococci, Gp-Ia and Gp-Ib. As compared to ceftazidime, compounds **1** and **2** showed somewhat better activity against Gram-negative organisms (Gn-Ia, Gn-

Ib and Gn-II) except *Pseudomonas aeruginosa* (Gn-III), which was more susceptible to ceftazidime. Compounds **3** through **6** derived from 6-membered amines were less active than ceftazidime against most groups of the test organisms.

Table 7 shows the *in vitro* activity of 27 derivatives of the α-methoxyimino series (compounds **7** through **33**). Most of them are similar to each other in the spectrum with a markedly improved anti-staphylococcal activity over ceftazidime. Furthermore, they showed high Gram-negative activity especially against cephalothin-resistant Enterobacteriaceae (Gn-Ib and Gn-II), as compared to ceftazidime. They were somewhat less active than ceftazidime against *P. aeruginosa*. Compound **7**, designated BMY-28142, was selected as a lead compound in this series in view of its well-balanced activity profile.

Table 8 shows the geometric mean of MICs of four analogs of BMY-28142 (**7**) (compounds **34** through **37**), in which the methoxyimino moiety of **7** was modified. The ethoxyimino analog (**34**) was somewhat more active ($\times 1 \sim 2$) than **7** against *Staphylococcus aureus* species, but less active ($\times 1/2 \sim 1/4$) against Gram-negative organisms. Other derivatives (**35**$\sim$**37**) were also more active than **7** against Gp-Ia, but none of them exceeded the activity of **7** against Gram-negative strains including *P. aeruginosa*.

Experimental

Melting points were determined with a Yanagimoto micro hot-stage apparatus and are uncorrected. IR spectra were recorded on Jasco IRA-1 and UV spectra on Shimadzu UV-200 spectrophotometer. NMR spectra were recorded on a Jeol CL-60HL or on a Varian FT-80A spectrometer.

3-Chloromethyl Derivatives, **III**. General Procedure Illustrated with the Preparation of Diphenylmethyl 3-Chloromethyl-7-[(*Z*)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (**IIIb**)

Diphenylmethyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (**II**)[24] (2.29 g, 5.07 mmol) in acetonitrile (57 ml) was treated with *N,O*-bis(trimethylsilyl)acetamide (4.09 ml, 16.6 mmol) at room temp for 50 minutes to give a clear solution. To the solution was added an acid chloride solution, which was prepared from (*Z*)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (**Ib**)[26] (2.04 g, 4.60 mmol) and phosphorous pentachloride (1.15 g, 5.52 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at room temp for 30 minutes, poured into cold H_2O (200 ml) and extracted with EtOAc (3×100 ml). The combined extracts were washed with aq NaCl, dried and evaporated. The residual syrup (4 g) was chromatographed on a silica gel (150 g) column by eluting with 10:1 and 3:1 mixtures of toluene and EtOAc, successively. The fractions containing the desired compound were combined and evaporated to afford 2.61 g (74%) of **IIIb** as an amorphous powder: MP 130°C; IR ν_{max}^{KBr} cm^{-1} 1780, 1720, 1670; ^1H NMR (60 MHz, $CDCl_3$) δ 3.50 (2H, s, 2-H), 4.02 (3H, s, OCH_3), 4.33 (2H, s, 3-CH_2), 4.98 (1H, d, $J_{6,7}$=4.5 Hz, 6-H), 5.87 (1H, dd, $J_{7,NH}$=8 Hz, 7-H), 6.65 (1H, s, thiazole-H), 6.90 (1H, s, C*H*Ph_2), 7.3 (25H, m, Ph).

Anal Calcd for $C_{40}H_{38}N_5O_5S_2Cl \cdot \frac{1}{2}C_7H_8$: C 67.07, H 4.78, N 7.90, S 7.23, Cl 4.00.
Found: C 66.86, H 4.78, N 7.80, S 7.29, Cl 3.95.

3-Iodomethyl Derivatives, **IV**. General Procedure Illustrated with the Preparation of Diphenylmethyl 3-Iodomethyl-7-[(*Z*)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (**IVb**)

A mixture of the 3-chloromethyl derivative (**IIIb**) (1.50 g, 1.79 mmol) and NaI (1.34 g, 8.93 mmol) in methyl ethyl ketone (30 ml) was stirred at room temp for 1 hour. After evaporation of the solvent, the residue was dissolved in EtOAc (100 ml) and washed with H_2O, aq $Na_2S_2O_3$ and aq NaCl, dried and evaporated to give the title compound **IVb** (1.47 g, 89%), as an amorphous powder: MP 120°C

(dec); IR ν_{max}^{KBr} cm^{-1} 1780, 1720, 1670; ^1H NMR (60 MHz, $CDCl_3$) δ 3.55 (2H, ABq, 2-H), 4.00 (3H, s, OCH_3), 4.25 (2H, s, 3-CH_2), 4.97 (1H, d, $J_{6,7}$=4.5 Hz, 6-H), 5.80 (1H, dd, $J_{7,NH}$=8 Hz, 7-H), 6.65 (1H, s, thiazole-H), 6.90 (1H, s, C*H*Ph_2), 7.3 (25H, m, Ph).

3-Quaternary Cephalosporins (VI in Scheme 1)

Introduction of the quaternary side chain to the 3'-position was accomplished by quaternization of the iodide (**IV**) with tertiary amines (Method A), by reaction of **IV** and secondary amines followed by quaternization with alkyl iodides (Method B) or by oxidation to the 1-oxide (**VIII**), quaternization with tertiary amines and subsequent reduction of the 3-quaternized 1-oxides (**IX**) (Method C). Amines used in these three methods are shown in Table 3.

The preparation procedures of BMY-28142 by Methods A, B and C (Scheme 1) are described as representative examples for 3-quaternized cephalosporins prepared in this study. The physical data of the 2-carboxy-2-propoxyimino (**1**~**6**), methoxyimino (**7**~**33**) and alkoxyimino (**34**~**37**) derivatives are listed in Tables 1, 2 and 4, respectively.

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolidinio)methyl-3-cephem-4-carboxylate (**7**, BMY-28142)

Method A: To a suspension of the 3-iodomethyl derivative (**IVb**, 5.0 g, 5.37 mmol) in ether (500 ml) was added *N*-methylpyrrolidine (915 mg, 11.5 mmol) and the mixture was stirred for 1 hour at room temp. The resulting precipitate was collected by filtration, washed with ether (2×100 ml) and dried *in vacuo* to give the quaternized product **Vb** (3.38 g). From the filtrate, the second crop of **Vb** (610 mg) was obtained after standing for 1 hour at room temp (total yield of **Vb** was 73%): IR ν_{max}^{KBr} cm^{-1} 1780, 1715, 1665; ^1H NMR (60 MHz, DMSO-d_6) δ 1.9 (4H, m, pyrrolidine-H), 2.23 (3H, s, N^+CH_3), 3.4 (4H, m, pyrrolidine-H), 3.85 (3H, s, OCH_3), 5.34 (1H, d, J=4.8 Hz, 6-H), 5.85 (1H, dd, 7-H), 6.74 (1H, s, thiazole-H), 7.02 (1H, s, C*H*Ph_2), 7.3 (25H, m, Ph).

A 3.99-g sample of **Vb** obtained above was treated with 90% trifluoroacetic acid (TFA, 20 ml) for 1 hour at room temp, and then evaporated *in vacuo*. The residue was triturated with ether (200 ml) to give 3.03 g of the TFA salt of **7**, which was found to be a 2.6:1 mixture of the Δ^3 and Δ^2 isomer [determined by HPLC: Lichrosorb RP-18, MeOH - 0.01 M phosphate buffer (pH 7), 15:85]. A solution of the TFA salt of **7** in MeOH (5 ml) was treated with sodium 2-ethylhexanoate (SEH, 1.0 M solution in EtOAc, 10 ml) and the mixture was diluted with EtOAc (150 ml) to precipitate the crude product of **7** (2.27 g), which was purified by preparative HPLC [System 500, Waters PrepPAK-500/C_{18}; eluted with MeOH - 0.01 M phosphate buffer (pH 7), 15:85] to afford two fractions.

The fraction containing the desired product (the second fraction) was evaporated to a small volume and charged on an Diaion HP-20 column (150 ml), which was washed with H_2O (1,000 ml) and then eluted with 50% aq MeOH. The UV-positive fractions were collected and evaporated to a small volume and lyophilized to afford BMY-28142 (**7**, 573 mg, 22% from **IVb**) as a colorless powder: MP 150°C (dec); IR ν_{max}^{KBr} cm^{-1} 1770, 1615; UV λ_{max} (pH 7 phosphate buffer) nm (ε) 235 (16,700), 257 (16,100); ^1H NMR (80 MHz, D_2O) δ 2.31 (4H, m, pyrrolidine-H), 3.08 (3H, s, N^+CH_3), 3.63 (4H, m, pyrrolidine-H), 4.09 (3H, s, OCH_3), 5.43 (1H, d, J=4.8 Hz, 6-H), 5.93 (1H, d, 7-H), 7.08 (1H, s, thiazole-H).

From the first fraction, the Δ^2 isomer was isolated after a similar work-up procedure to that described above. Yield, 250 mg (10% from **IVb**): MP 140°C (dec); IR ν_{max}^{KBr} cm^{-1} 1755, 1610; UV λ_{max} (pH 7 phosphate buffer) nm (ε) 234 (16,400), 252 (16,000), 293 (6,100); ^1H NMR (80 MHz, D_2O) δ 2.33 (4H, m, pyrrolidine-H), 3.13 (3H, s, N^+CH_3), 3.65 (4H, m, pyrrolidine-H), 4.10 (3H, s, OCH_3), 4.30 (2H, ABq, 3-CH_2), 5.08 (1H, s, 4-H), 5.52 (2H, m, 6, 7-H), 6.88 (1H, s, 2-H), 7.18 (1H, s, thiazole-H).

Method B: To an ice-cooled solution of pyrrolidine (0.12 ml, 1.44 mmol) in H_2O (30 ml) was added a solution of the 3-iodomethyl compound **IVb** (610 mg, 0.65 mmol) in acetone (6 ml) and the mixture was stirred at 0°C for 2 hours and then at room temp for 3 hours. After addition of 1 N HCl (5 ml), the mixture was extracted with EtOAc (3×30 ml). The combined extracts were washed with satd aq $NaHCO_3$ and NaCl solutions, successively, dried and evaporated. The residual syrup, (crude **VIIb**, 573 mg) was dissolved in a mixture of THF (6 ml) and diisopropylether (IPE, 6 ml) and

then treated with methyl iodide (6 ml) at room temp overnight. To the mixture was added IPE (50 ml) to give a precipitate, which was collected by filtration to afford the quaternized product **Vb** (484 mg, 73% from **IVb**).

The crude compound **Vb** (484 mg) was deblocked with 90% TFA to give the TFA salt of **7** (336 mg) as a mixture of Δ^3 and Δ^2 isomer in the ratio of 2.5:1. This sample was purified by the similar procedure described before to afford the final product **7** (48 mg, 17% from **IVb**), which was identical with the sample prepared by Method A.

Method C: A mixture of the 3-iodomethyl compound (**IVb**) (1.10 g, 1.19 mmol) and *m*-chloroperbenzoic acid (322 mg, 1.30 mmol) in CH_2Cl_2 (22 ml) was stirred at 0°C for 15 minutes, poured into H_2O (50 ml), and then extracted with $CHCl_3$ (3×50 ml). The combined extracts were washed with satd aq $NaHCO_3$ (50 ml) and NaCl, successively, dried and evaporated to afford the sulfoxide **VIIIb** (1.12 g, quantitative) as an amorphous powder: MP 130°C (dec); IR ν_{max}^{KBr} cm^{-1} 1790, 1715, 1665; ^1H NMR (60 MHz, $CDCl_3$) δ 3.6 (2H, m, 2-H), 4.00 (3H, s, OCH_3), 6.03 (1H, dd, J=4.5 and 9.6 Hz, 7-H), 6.65 (1H, s, thiazole-H), 6.92 (1H, s, CHPh$_2$), 7.3 (25H, m, Ph).

A mixture of **VIIIb** (500 mg, 0.53 mmol) and *N*-methylpyrrolidine (0.11 ml, 1.06 mmol) in EtOAc (5 ml) was stirred at room temp for 20 minutes. To the mixture was added IPE (50 ml) and the precipitate formed was collected by filtration to give 3-(*N*-methylpyrrolidinio)methyl-**IXb** (527 mg, 97%): MP 155°C (dec); IR ν_{max}^{KBr} cm^{-1} 1795, 1720, 1670; ^1H NMR (60 MHz, DMSO-d_6) δ 1.9 (4H, m, pyrrolidine-H), 2.22 (3H, s, N^+CH_3), 3.83 (3H, s, OCH_3), 5.18 (1H, d, $J_{6,7}$=4.8 Hz, 6-H), 5.9 (1H, m, 7-H), 6.77 (1H, s, thiazole-H), 7.03 (1H, s, CHPh$_2$), 7.3 (25H, m, Ph).

To an ice-cooled solution of **IXb** (490 mg, 0.47 mmol) in dry acetone (9.8 ml) were added KI (315 mg, 1.90 mmol) and acetyl chloride (AcCl, 67.5 μl, 0.95 mmol) and the mixture was stirred at 0°C for 2 hours, meanwhile the same amount of KI and AcCl were added 3 times at 30 minutes intervals. The mixture was slowly added to a stirred 0.1 M aq solution of sodium metabisulfite ($Na_2S_2O_5$, 100 ml). The precipitate formed was collected by filtration and washed with H_2O, dried over P_2O_5 under reduced pressure to give **Vb** (483 mg, quantitative), which was treated with 90% TFA (5 ml) at room temp for 1 hour. The reaction mixture was evaporated under reduced pressure below 30°C. The residue was triturated with IPE to give the TFA salt of **7** (282 mg), which was dissolved in MeOH (5 ml). The insoluble material was filtered off and washed with MeOH. The combined filtrate and washings were evaporated to *ca.* 3 ml and then treated with SEH (1 M solution in EtOAc, 0.95 ml) at room temp for 15 minutes. After the addition of EtOAc (50 ml), the precipitate was collected by filtration to give the crude sample of **7** (233 mg). HPLC analysis showed that this sample was 42% pure, together with the corresponding 1-oxide compound (3.6%), but no Δ^2 isomer. Purification of the product by HPLC [Lichrosorb RP-18, 8×300 mm, eluted with 0.01 M ammonium phosphate buffer (pH 7.2) containing 10% MeOH], followed by removal of inorganic salt by HPLC (the same column as that described above, eluted with 10% aq MeOH) afforded BMY-28142 (69 mg, 30% from **IVb**) as a colorless powder, which was identical with the product obtained by Method A.

Alternative Preparation of BMY-28142 (**7**) (Scheme 2)

Diphenylmethyl 7-Benzylideneamino-3-chloromethyl-3-cephem-4-carboxylate (**X**)

To a stirred suspension of diphenylmethyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride[24] (**II**, 50 g, 0.11 mol) in EtOAc (400 ml) and H_2O (150 ml) was added 1 M NaOH (200 ml) under cooling on an ice-water bath. Stirring was continued for 30 minutes to give a clear two-phase solution. The EtOAc layer was separated, washed with H_2O (300 ml) and dried over anhydrous Na_2SO_4 (100 g). The EtOAc solution (without removing Na_2SO_4) was mixed with benzaldehyde (14.2 g, 0.13 mol) and the mixture was stirred for 2 hours at room temp. The insoluble material (Na_2SO_4) was filtered off. The filtrate was concentrated under reduced pressure. To the concentrate (200 ml) was added *n*-heptane (400 ml) to precipitate 47.6 g (86%) of the crystalline product **X**, which was collected by filtration. The filtrate was concentrated to about 100 ml and treated with *n*-heptane (300 ml) to give 4.6 g (8%) of the second crop. Total yield of **X**, 52.2 g (94%), pale yellow prisms: MP 110~111°C; IR ν_{max}^{KBr} cm^{-1} 1780, 1730, 1635; UV λ_{max}^{EtOH} nm (ε) 215 (27,600), 258 (25,500); ^1H NMR (60 MHz, $CDCl_3$) δ 3.40 and 3.70 (2H, ABq, J=18 Hz, 2-H), 4.28 and 4.47 (2H, ABq, J=12 Hz,

CH_2Cl), 5.18 (1H, d, J=4.5 Hz, 6-H), 5.43 (1H, dd, J=4.5 and 1.5 Hz, 7-H), 6.98 (1H, s, CHPh$_2$), 7.0~7.6 (15H, m, Ph), 8.59 (1H, d, J=1.5 Hz, PhCH=N).

Anal Calcd for $C_{28}H_{23}N_2O_3SCl$: C 66.86, H 4.61, N 5.57, S 6.37, Cl 7.05.
Found: C 66.82, H 4.78, N 5.80, S 6.39, Cl 6.60.

Diphenylmethyl 7-Benzylideneamino-3-(1-methylpyrrolidinio)methyl-3-cephem-4-carboxylate Iodide (XII)

To a solution of **X** (52 g, 0.10 mol) in carbon tetrachloride (1 liter) was added dropwise a solution of NaI (18.6 g, 0.12 mol) in acetone (200 ml) under stirring. After the addition was completed, the mixture was stirred for 40 minutes at room temp and filtered through a Dicalite pad. The filtrate was washed consecutively with satd solution of $Na_2S_2O_3$ (750 ml) and NaCl (2×700 ml), dried over anhydrous Na_2SO_4 (100 g) and filtered. A part of the filtrate was evaporated to dryness to afford the 3-iodomethyl compound **XI**, which was unstable when kept at room temp for several days. 65% pure (HPLC): ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.37 and 3.81 (2H, ABq, J=18 Hz, 2-H), 4.17 and 4.40 (2H, ABq, J=10 Hz, CH_2I), 5.07 (1H, d, $J_{6,7}$=5.0 Hz, 6-H), 5.30 (1H, dd, $J_{7,CH=N-}$=1.5 Hz, 7-H), 6.97 (1H, s, CHPh$_2$), *ca.* 7.3 and 7.7 (15H, m, Ph), 8.52 (1H, d, PhCH=N).

A major part of the filtrate obtained above was used for the next step without isolation of **XI**. To the chilled (0°C) and stirred filtrate was added dropwise over a period of 30 minutes a solution of *N*-methylpyrrolidine (11.8 ml, 0.11 mol) in carbon tetrachloride (50 ml). The mixture was stirred for additional 1 hour at 0~5°C to afford a precipitate, which was collected by filtration, washed with carbon tetrachloride (300 ml) and dried over P_2O_5 *in vacuo* to give 70 g of compound **XII**: MP 120°C (dec); ^{1}H NMR (60 MHz, $CDCl_3$) δ *ca.* 2.0 (4H, m, pyrrolidine-H), 2.78 (3H, s, N^+CH_3), *ca.* 3.3 (2H, m, 2-H), *ca.* 3.6 (4H, m, pyrrolidine-H), 5.37 (1H, d, J=5.0 Hz, 6-H), 5.75 (1H, d, J=5.0 Hz, 7-H), 6.96 (1H, s, CHPh$_2$), 7.3~7.9 (15H, m, Ph), *ca.* 8.5 (1H, br s, PhCH=N).

7-Amino-3-(1-methylpyrrolidinio)methyl-3-cephem-4-carboxylate Hydrochloride (XIII)

A mixture of **XII** (68 g, 60% pure), 98% formic acid (68 ml) and concd HCl (42 ml) was stirred at room temp for 1 hour and then poured into acetone (2.5 liters) under vigorous stirring. The precipitate formed was collected by filtration and dried to give a hygroscopic solid (30 g), which was dissolved in H_2O (300 ml) and then crystallized by adding acetone (1.5 liters) to afford 13.7 g (yield, 37% from **X**) of compound **XIII** as colorless prisms: MP 165°C (dec); IR ν_{max}^{KBr} cm^{-1} 3400, 1800, 1595; UV λ_{max} (pH 7 phosphate buffer) nm (ε) 267 (9,000); ^{1}H NMR (60 MHz, D_2O) δ 2.30 (4H, m, pyrrolidine-H), 3.09 (3H, s, N^+CH_3), *ca.* 3.6 (4H, m, pyrrolidine-H), 3.62 and 4.07 (2H, ABq, J=18 Hz, 2-H), 4.08 and 4.80 (2H, ABq, J=14 Hz, CH_2N^+), 5.27 (1H, d, J=5 Hz, 6-H), 5.48 (1H, d, 7-H).

Anal Calcd for $C_{13}H_{19}N_3O_3S\cdot HCl\cdot 2H_2O$: C 42.22, H 6.54, N 11.36, S 8.67, Cl 9.59.
Found: C 42.24, H 6.24, N 11.35, S 8.91, Cl 10.22.

BMY-28142 Sulfate

To a stirred mixture of compound **XIII** (13.7 g, 37 mmol) in H_2O (140 ml) and DMF (280 ml) was added $NaHCO_3$ (6.2 g, 74 mmol) portionwise under ice cooling to give a clear solution within 5 minutes. To the mixture was added the active ester (**XIV**)[27] (17.7 g, 55.5 mmol) and the mixture was stirred at room temp for 1 hour and then acidified to pH 3 with 4 N H_2SO_4 (5 ml). The insolubles were filtered off and washed with H_2O (10 ml). The filtrate and the washings were combined and poured into acetone (3 liters) under vigorous stirring to give a precipitate, which was collected by filtration and dried to give crude BMY-28142 (**7**, 20.6 g, 85% pure by HPLC). To a solution of the crude product in H_2O (120 ml) was added 4 N H_2SO_4 (40 ml). The mixture was seeded with a few crystalline pieces of BMY-28142 sulfate and kept in a refrigerator for 2 hours to afford cyrstalline powder, which was collected by filtration, washed with 1 N H_2SO_4 (40 ml) and acetone (200 ml), successively, and dried to afford 15.0 g (70%) of BMY-28142 sulfate: MP 210°C (dec); IR ν_{max}^{KBr} cm^{-1} 1795, 1650; UV λ_{max} (pH 7 phosphate buffer) nm (ε) 236 (17,200), 258 (16,900); ^{1}H NMR (80 MHz, D_2O) δ 2.35 (4H, m, pyrrolidine-H), 3.12 (3H, s, N^+CH_3), *ca.* 3.7 (4H, m, pyrrolidine-H), 4.18 (3H, s, OCH_3), 5.47 (1H, d, J=5 Hz, 6-H), 5.94 (1H, d, J=5 Hz, 7-H), 7.23 (1H, s, thiazole-H).

Anal Calcd for $C_{19}H_{24}N_6O_5S_2\cdot H_2SO_4$: C 39.44, H 4.53, N 14.52, S 16.62.
Found: C 39.16, H 4.59, N 14.48, S 16.43.

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