STUDIES ON β-LACTAM ANTIBIOTICS

XIII.† SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 7β-[(Z)-2-ARYL-2-CARBOXYMETHOXYIMINOACETAMIDO]-3-VINYLCEPHALOSPORINS

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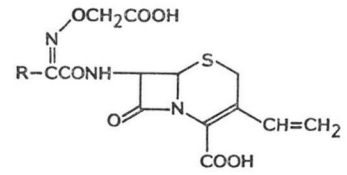
The synthesis, antibacterial activity and oral absorption of the 7β-[(Z)-2-aryl-2-carboxymethoxyiminoacetamido]-3-vinylcephalosporins (**1**) are described. Of these cephalosporin derivatives (**1**), 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]-3-vinylcephalosporin (**1a**; FK027) exhibited the highest activity against Gram-negative bacteria and showed also good excretion after oral administration to rats. In addition, the effects on the antibacterial activity and oral absorption of the amino function on the thiazole ring are discussed.

In our preceding papers[1~3] we have reported the influence on the antibacterial activity and oral absorption of various substituents at the 3-position of the 7β-[(Z)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]cephalosporin derivatives. Among these cephalosporins, FK027 (**1a**; cefixime)[4,5] showed the highest activity against most of Gram-negative bacteria and even good recovery after oral administration to rats. We directed our next efforts towards studies on the structure-activity relationships and oral absorption concerning the aryl moieties of the 7β-[(Z)-2-aryl-2-carboxymethoxyiminoacetamido]-3-vinylcephalosporins in order to search for a suitable heterocycle (R) showing both higher activity and better oral absorption than the aminothiazole cephalosporin (**1a**).

This paper describes the preparation of (Z)-2-aryl-2-*tert*-butoxycarbonylmethoxyiminoacetic acids (**4**) and 7β-[(Z)-2-aryl-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acids (**1**) prepared from **4**. We also report the effect of replacing the heterocyclic ring (R) in

Fig. 1. 7β-[(Z)-2-Aryl-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid.



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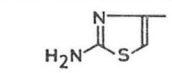
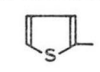
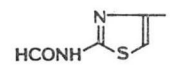
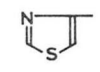
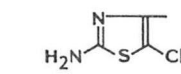
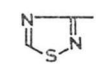
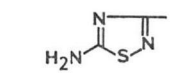
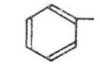
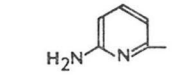
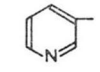
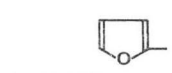
	R		R
a		g	
b		h	
c		i	
d		j	
e		k	
f			

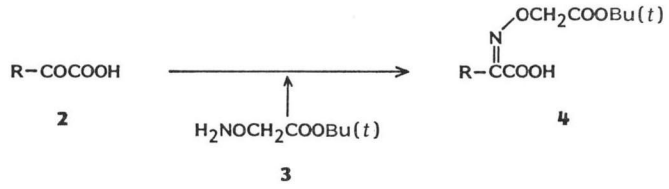
† Paper XII. See ref 3).

the 7-acyl side chain of the 3-vinylcephalosporin represented by structure (**1**) on the antibacterial activity and oral absorption (Fig. 1).

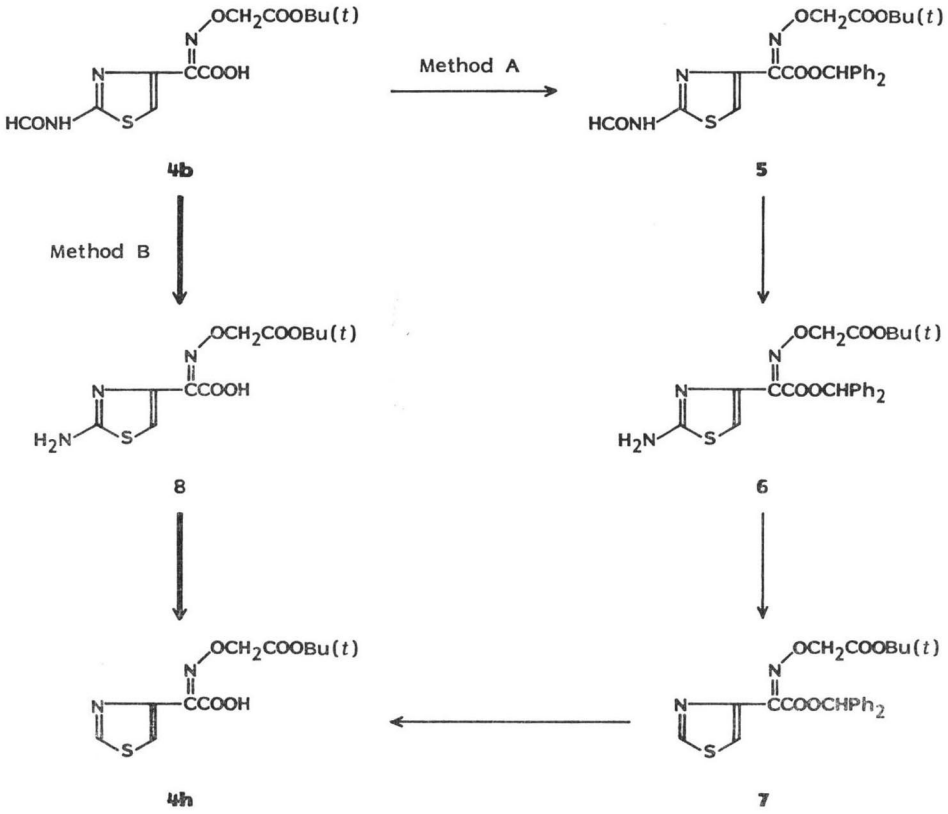
Chemistry

A general synthetic method for the preparation of (*Z*)-2-aryl-2-*tert*-butoxycarbonylmethoxyiminoacetic acids (**4**) is outlined in Scheme 1. Arylglyoxalic acids (**2h, k, m**)[6~8] were treated with *tert*-butoxycarbonylmethoxyamine (**3**) to afford the corresponding (*Z*)-2-aryl-2-*tert*-butoxycarbonylmethoxyiminoacetic acids (**4h, k, m**). The acids (**4d, f, g, j, l**) were obtained in a similar manner as reported in the

Scheme 1.



Scheme 2.



references[9~11].

We also investigated a convenient deamination of the aminothiazole ring into the corresponding thiazole ring (**4h**) having the *tert*-butoxycarbonylmethoxyimino group (Scheme 2).

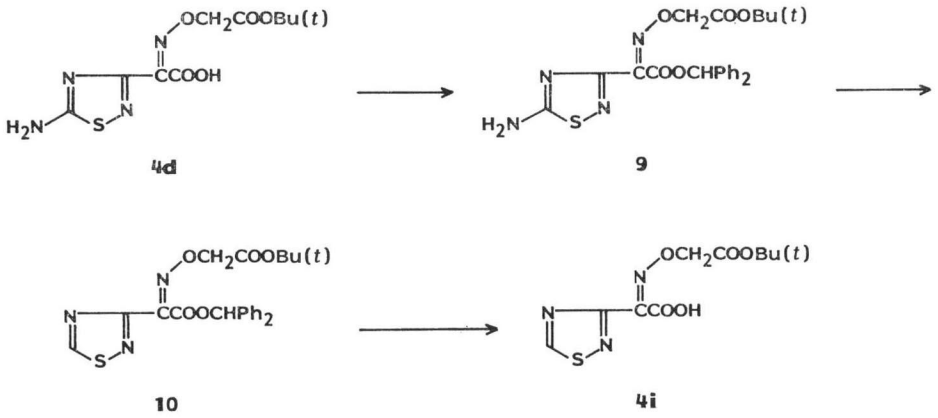
According to the Method A, (*Z*)-2-*tert*-butoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)-acetic acid (**4b**)[12] was treated with diphenyldiazomethane to give the corresponding diphenylmethyl ester (**5**), which was converted to diphenylmethyl (*Z*)-2-(2-amino-4-thiazolyl)-2-*tert*-butoxycarbonylmethoxyiminoacetate (**6**) by deformylation with concentrated hydrochloric acid in methanol. Deamination of **6** with *tert*-butyl nitrite[13] successfully afforded diphenylmethyl (*Z*)-2-*tert*-butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetate (**7**). The diphenylmethyl group of **7** was selectively deprotected with trifluoroacetic aicd (TFA) and anisole to yield (*Z*)-2-*tert*-butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetic acid (**4h**).

According to the Method B, **4b** was deformylated by treatment with concentrated hydrochloric acid to give (*Z*)-2-(2-amino-4-thiazolyl)-2-*tert*-butoxycarbonylmethoxyiminoacetic acid (**8**), which was smoothly converted to (*Z*)-2-*tert*-butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetic acid (**4h**) by deamination with *tert*-butyl nitrite.

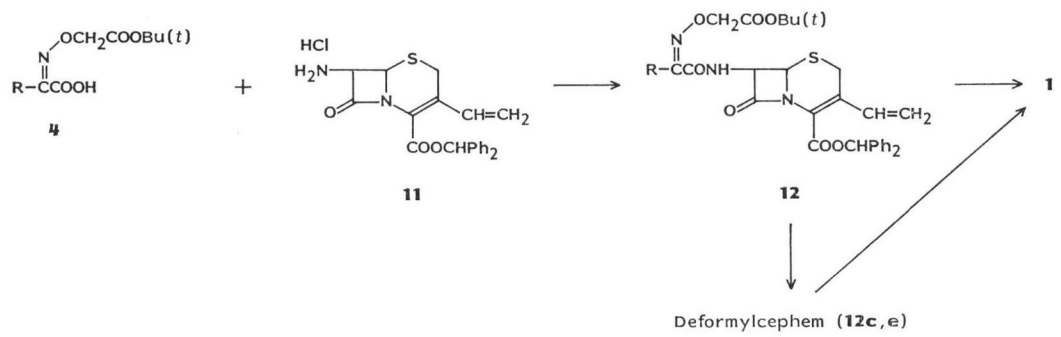
The 1,2,4-thiadiazole acid (**4i**) was also obtained from the 5-amino-1,2,4-thiadiazole acid (**4d**)[9] by a similar manner to that of the Method A as described for the preparation of **4h** (Scheme 3).

Acylated cephalosporins (**12d, f~m**) were prepared by coupling the 7-amino-3-vinylcephalosporin

Scheme 3.

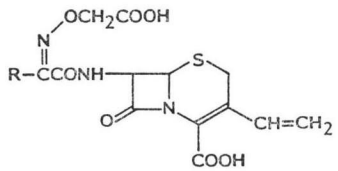


Scheme 4.

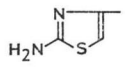
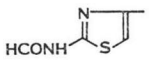
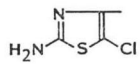
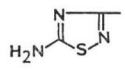
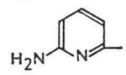


(**11**) with the acids (**4d, f~m**) containing the *tert*-butoxycarbonylmethoxyimino group. The 5-amino-1,2,4-thiadiazole acid (**4d**) was converted to the corresponding acid chloride with phosphorus pentachloride (PCl_5) and the other acids (**4f~m**) were activated with Vilsmeier reagent which was prepared from phosphoryl chloride and *N*,*N*-dimethylformamide for the above coupling reaction. Deformylation of the *N*-formyl compounds (**12l, m**) was carried out by treatment with concentrated hydrochloric acid to give the corresponding amino compounds (**12c, e**). Both the *tert*-butyl and diphenylmethyl groups of (**12c~k**) were simultaneously deprotected with TFA and anisole to afford the desired cephalosporins (**1c~k**). **1b** was similarly obtained from **12b**[3] by deprotection of the ester groups (Scheme 4).

Table 1. Antibacterial activity and 24-hour urinary and biliary excretion after oral administration (100 mg/kg) to rats of cephalosporins (**1**).



Inoculum size 10^6 cfu/ml

Compound	R	MIC (μg/ml)						Recovery (%)	
		*Sa**	*Ec*N	*Ec***	*Kp*	*Pm*	*Pv*	Urine	Bile
1a		25	0.2	0.39	0.1	≦0.025	≦0.025	34.0	18.2
1b		25	0.39	12.5	3.13	0.39	0.39	3.4	1.1
1c		50	0.78	0.78	1.56	0.1	0.05	33.6	10.6
1d		50	0.78	0.39	0.2	0.1	0.2	28.8	2.7
1e		100	12.5	3.13	6.25	0.39	0.39	8.2	4.6
1f		50	6.25	25	50	1.56	1.56	43.8	26.9
1g		25	25	25	50	3.13	3.13	66.7	30.2
1h		25	3.13	3.13	3.13	0.39	0.39	43.1	22.1
1i		100	3.13	6.25	1.56	1.56	3.13	41.3	9.9
1j		12.5	12.5	12.5	100	3.13	3.13	29.6	16.0
1k		100	100	100	>100	6.25	3.13	55.4	45.9

* *Sa*; *Staphylococcus aureus* 209P JC-1, *Ec*N; *Escherichia coli* NIHJ JC-2, *Ec*; *E. coli* 28, *Kp*; *Klebsiella pneumoniae* 12, *Pm*; *Proteus mirabilis* 1, *Pv*; *P. vulgaris* 1.

** Cephalosporinase producer.

Biological Results and Discussion

The *in vitro* antibacterial activity of the 3-vinylcephalosporins (**1**) having various 7-acyl side chains and their 24-hour urinary and biliary excretion after oral administration (100 mg/kg) to rats are summarized in Table 1. For comparison, the MIC values and excretion of FK027 (**1a**) are listed at the top of Table 1. The data showed the following effect of different heterocyclic rings on the antimicrobial activity and excretion.

Antibacterial Activity

1) Among the aryl derivatives (**1f**~**k**) without an amino function, the cephalosporins (**1f, g, j, k**) exhibited poor activity against Gram-negative bacteria, which showed that the phenyl ring and the heterocycles containing one hetero-atom in the ring are unfavorable. On the other hand, the thiazole cephalosporin (**1h**) where one nitrogen atom is introduced into the thienyl ring of **1g** showed much improved activity against Gram-negative bacteria. Also, comparison between **1h** and **1i** showed that the introduction of two nitrogen atoms into the ring is not beneficial.

2) The order of the activity of the aminoaryl analogs was 2-aminothiazole cephalosporin (**1a**)>5-amino-1,2,4-thiadiazole cephalosporin (**1d**)>2-aminopyridine cephalosporin (**1e**). This relation was the same as observed in the heterocycles without the amino group. The *N*-formyl aminothiazole cephalosporin (**1b**) reduced the activity against Gram-negative bacteria in comparison with **1a**, especially against *Escherichia coli* 28 that is a cephalosporin-resistant strain. **1a** against **1c** also showed that the introduction of a chlorine atom is slightly disadvantageous. Among the tested cephalosporins (**1**), the aminothiazole cephalosporin (**1a**) was found to be the most active antibiotics.

3) With regard to the effect of the amino function on the hetero-aromatic ring, the cephalosporins (**1a, d, e**) containing the amino group displayed much higher activity than the corresponding cephalosporins (**1h, i, k**) without the amino group. Thus, we found that the amino function on the heterocycles seems to be associated with a potent antimicrobial activity against Gram-negative bacteria. An acylated amino such as **1b** is only slightly better than no amino at all as **1h**.

Urinary and Biliary Excretion

1) Of the cephalosporins (**1f**~**k**) without the amino group on the heterocycles, the antibiotics (**1f, g, h, k**) containing one or two hetero-atoms in the hetero-aromatic ring were found to show the high excretion in the urine and bile, whereas **1i** with three hetero-atoms was mainly excreted in the urine.

2) The aminoaryl derivatives (**1a, c, d**) except **1e** were moderately excreted in the urine and bile, although the excretion of the cephalosporins without the amino group was better than that of the cephalosporins having the amino function. In addition, when the *N*-formyl aminothiazole cephalosporin (**1b**) was orally dosed to rats, **1b** was scarcely excreted and the *N*-deformylated aminothiazole cephalosporin (**1a**) was not observed in both urine and bile. Thus, while the amino does not add to oral absorption, it does increase antibacterial activity very dramatically making it an essential feature.

The cephalosporins (**1**) with the carboxymethoxyimino group, which are entirely distinct from the marketed oral cephalosporins having the phenylglycyl or its analogous side chains such as *p*-hydroxyphenylglycyl and cyclohexadienylglycyl, turned out to show good oral absorption. From this series of cephalosporins having various aryl rings, the aminothiazole cephalosporin (**1a**; FK027) was selected as a candidate for human trial, because **1a** displayed the highest activity against Gram-negative bacteria and good recovery in the urine and bile. Moreover, the amino function on the thiazole ring was found to be essential for the excellent antibacterial activity.

Experimental

MP were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a Jeol-MH 100 NMR spectrometer using Me_4Si as an internal standard. IR spectra were taken on a Hitachi 260-10 spectrophotometer or a Shimadzu IR-420 spectrophotometer.

Antibiotic Susceptibility

All the *in vitro* antibacterial activity data are given as the minimum inhibitory concentration (MIC) in μg/ml required to prevent growth of the bacterial culture. MICs were determined by the agar dilution method using heart infusion agar (Difco) after incubation at 37°C for 20 hours with inoculum size of about 10^6 cfu/ml. *E. coli* 28 is a cephalosporin-resistant strain.

Urinary and Biliary Excretion

Sprague Dawley rats were fasted overnight and orally dosed with 100 mg/kg of the test drugs. Urine samples were collected for 24 hours after dosing. For bile collection another group of rats was cannulated with a polystyrene tube into the bile duct and the test drugs were given orally at doses of 100 mg/kg. The samples were assayed by a disc-agar diffusion method using *E. coli* NIHJ JC-2 or *E. coli* ATCC 33546 as test organism and nutrient agar (Difco) as the test medium.

General Preparation of (*Z*)-2-Aryl-2-*tert*-butoxycarbonylmethoxyiminoacetic Acid (**4**)

To a soln of arylglyoxalic acid (**2**) (10 mmol) in MeOH (20 ml) was added *tert*-butoxycarbonylmethoxyamine (12 mmol) at room temp under stirring, and the mixture was stirred at the same temp for 1~5 hours. After removing MeOH, the residue was dissolved in EtOAc. The soln was washed with H_2O and brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give **4**.

Preparation of (*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetic Acid (**4h**)

Method A:

Diphenylmethyl (*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)acetate (**5**): To a soln of 2-*tert*-butoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)acetic acid (**4b**) (65.9 g, 0.2 mol) in EtOAc (300 ml) and THF (200 ml) was added a soln of diphenyldiazomethane (0.22 mol) in EtOAc (220 ml) at room temp, and the mixture was stirred for 1 hour. The resultant mixture was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* to give 99.0 g (100.0%) of **5**.

Diphenylmethyl (*Z*)-2-(2-Amino-4-thiazolyl)-2-*tert*-butoxycarbonylmethoxyiminoacetate (**6**): To a soln of **5** (99.0 g, 0.2 mol) in MeOH (500 ml) was added concd HCl (41.6 g, 0.4 mol) at room temp, and the mixture was stirred at the same temp for 2 hours. The reaction mixture was poured into a soln of sodium bicarbonate (33.6 g, 0.4 mol) in H_2O (2.5 liters) and extracted with EtOAc. The extract was washed with brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* to give 72.3 g (77.4%) of **6**: IR (Nujol) 1740, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.60~7.07 (10H, m), 6.98 (1H, s), 6.73 (1H, s), 4.18 (2H, s), 1.43 (9H, s).

Diphenylmethyl (*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetate (**7**): A soln of *tert*-butyl nitrite (1.7 g, 16.5 mmol) in THF (10 ml) was dropwise added to a soln of **6** (5 g, 10.7 mmol) in THF (50 ml) at 50~53°C under stirring and the mixture was stirred at the same temp for 25 minutes. The reaction mixture was poured into a mixture of EtOAc and H_2O, and the separated organic layer was washed with brine and dried ($MgSO_4$). The soln was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with benzene - EtOAc (19: 1) to afford 2.2 g (45.4%) of **7**: IR (film) 1740, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.15 (1H, d, J=2 Hz), 8.03 (1H, d, J=2 Hz), 7.60~7.15 (10H, m), 7.08 (1H, s), 4.68 (2H, s), 1.43 (9H, s).

(*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetic Acid (**4h**): To a soln of **7** (2.2 g, 4.88 mmol) and anisole (2.2 ml) in dichloromethane (22 ml) was added TFA (4 ml) at room temp, and the mixture was stirred at the same temp for 30 minutes. The reaction mixture was poured into a mixture of EtOAc and H_2O. To the separated organic layer was added H_2O, and the resultant mixture was adjusted to pH 7.5 with 20% sodium carbonate soln. The separated aq layer was acidified to pH 2.0

with 10% HCl, and extracted with EtOAc. The EtOAc layer was washed with brine and dried ($MgSO_4$). The soln was evaporated *in vacuo* to give 1.07 g (77.0%) of **4h**. This compound was identified with the authentic sample obtained from 2-(4-thiazolyl)glyoxalic acid and *tert*-butoxycarbonylmethoxyamine by the general preparation.

Method B:

(*Z*)-2-(2-Amino-4-thiazolyl)-2-*tert*-butoxycarbonylmethoxyiminoacetic Acid (**8**): To a soln of **4b** (15 g, 45.6 mmol) in MeOH (75 ml) was added concd HCl (9.5 g, 91.2 mmol) at room temp and the resultant mixture was stirred at the same temp for 2.5 hours. The reaction mixture was diluted with H_2O (100 ml) and adjusted to pH 3 with 10% sodium hydroxide soln. The precipitate was collected by filtration to afford 12.7 g (92.5%) of **8**: IR (Nujol) 3350, 1740, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.80 (1H, s), 4.53 (2H, s), 1.40 (9H, s).

(*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(4-thiazolyl)acetic Acid (**4h**): To a soln of **8** (11.5 g, 38.2 mmol) in THF (80.5 ml) was added a soln of *tert*-butyl nitrite (6.5 g, 63.0 mmol) in THF (32.5 ml) at 50~55°C under stirring and the mixture was stirred at the same temp for 20 minutes. The reaction mixture was poured into a mixture of EtOAc and H_2O, and the resulting mixture was acidified to pH 1.0 with 10% HCl. The separated organic layer was washed with brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* to give 6.11 g (55.9%) of **4h**. This compound was identified with the authentic sample obtained from 2-(4-thiazolyl)glyoxalic acid and *tert*-butoxycarbonylmethoxyamine by the general preparation.

Preparation of Diphenylmethy (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-*tert*-butoxycarbonylmethoxyiminoacetate (**9**)

9 was obtained (47.2%) from **4d** by a similar manner as described for the prepn of **5**: IR (Nujol) 1740, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.25 (2H, br s), 7.58~7.20 (10H, m), 7.08 (1H, s), 4.72 (2H, s), 1.46 (9H, s).

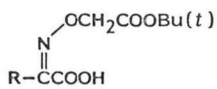
Preparation of Diphenylmethyl (*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(1,2,4-thiadiazol-3-yl)-acetate (**10**)

10 was obtained (73.3%) from **9** by a similar procedure as described for the prepn of **7**: IR (Nujol) 1740, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.32 (1H, s), 7.58~7.18 (10H, m), 7.11 (1H, s), 4.80 (2H, s), 1.43 (9H, s).

Preparation of (*Z*)-2-*tert*-Butoxycarbonylmethoxyimino-2-(1,2,4-thiadiazol-3-yl)acetic Acid (**4i**)

4i was obtained (57.7%) from **10** by a similar manner to that of the Method A as used for the prepn

Table 2. Physical data of (*Z*)-2-aryl-2-*tert*-butoxycarbonylmethoxyiminoacetic acids (**4**).



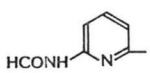
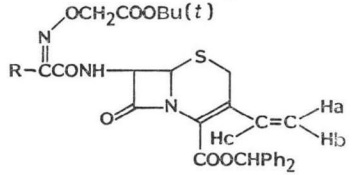
Compound	R	MP (°C, dec)	^1H NMR (DMSO-d_6, δ)			IR (Nujol, cm^{-1})
			R	CH_2 (2H, s)	Bu(*t*) (9H, s)	
4h		136~139	9.21 (1H, d, *J*=2 Hz), 8.08 (1H, d, *J*=2 Hz)	4.69	1.46	1730
4i		137~138	10.32 (1H, s)	4.77	1.45	1740
4k		105~112	9.30~7.30 (4H, m)	4.70	1.46	1730
4m		162~168	9.17 (1H, br s), 8.30~7.30 (3H, m)	4.73	1.47	1741

Table 3. ^{1}H NMR and IR spectral data of **12**.



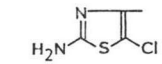
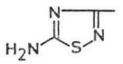
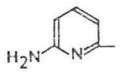
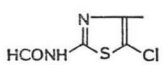
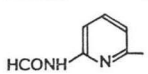
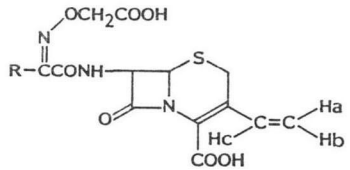
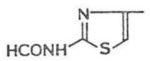
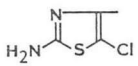
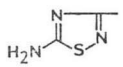
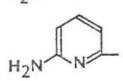
Compound	R	^{1}H NMR (DMSO-d_6, δ)											IR (Nujol, cm^{-1})
		CONH (1H, d, J= 8 Hz)	Hc (1H, dd, J=11, 16 Hz)	C(7)-H (1H, dd, J=5, 8 Hz)	Ha (1H, d, J= 16 Hz)	Hb (1H, d, J= 11 Hz)	C(6)-H (1H, d, J= 5 Hz)	CH_2 (2H, s)	C(2)-H_2 (2H, br s)	Bu(t) (9H, s)	CH (1H, s)	R+Ph_2	β-Lactam
12c		9.60	6.85	6.00	5.68	5.32	5.30	4.63	3.77	1.43	7.03	7.90~7.22 (10H, m)	1780
12d		9.63	6.80	5.96	5.66	5.33	5.30	4.67	3.77	1.46	6.99	8.23 (2H, br s), 7.43 (10H, m)	1770
12e		9.47	6.90	5.98	5.95	5.29	5.29	4.65	3.76	1.45	6.97	7.70~6.80 (13H, m)	1778
12f		9.70	6.81	5.87	5.60	5.26	5.25	4.58	3.73	1.43	6.90	7.78~6.60 (13H, m)	1785
12g		9.75	6.72	5.85	5.57	5.26	5.23	4.54	3.70	1.39	6.90	7.60~7.00 (13H, m)	1780
12h		9.62	6.77	5.93	5.60	5.40	5.28	4.65	3.75	1.43	6.93	9.12 (1H, d, J=2 Hz), 7.90 (1H, d, J=2 Hz), 7.55~7.20 (10H, m)	1775
12i		9.70	6.70	5.97	5.60	5.33	5.27	4.70	3.73	1.47	6.92	9.23 (1H, s), 7.51~7.20 (10H, m)	1775
12j		9.75	6.79	5.93	5.62	5.31	5.26	4.64	3.76	1.46	6.94	7.78~7.16 (15H, m)	1770
12k		9.75	6.90	5.81	5.56	5.27	5.20	4.76	3.68	1.41	6.85	9.30~7.30 (14H, m)	1760
12l		9.73	6.83	6.03	5.65	5.32	5.30	4.62	3.77	1.43	7.02	8.60 (1H, s), 7.80~7.23 (10H, m)	1780
12m		9.53	6.90	5.95	5.56	5.25	5.20	4.60	3.72	1.40	6.90	8.40 (1H, s), 8.30~7.30 (13H, m)	1777

Table 4. ^{1}H NMR and IR spectral data of **1b**~**k**.



Compound	R	^{1}H NMR (DMSO-d_6, δ)									IR (Nujol, cm^{-1})	
		CONH (1H, d, J=8 Hz)	Hc (1H, dd, J=11, 16 Hz)	C(7)-H (1H, dd, J=5, 8 Hz)	Ha (1H, d, J=16 Hz)	Hb (1H, d, J=11 Hz)	C(6)-H (1H, d, J=5 Hz)	CH_2 (2H, s)	C(2)-H_2 (2H, br s)	R	β-Lactam	CONH
1b		9.59	6.93	5.84	5.58	5.28	5.22	4.66	3.71	8.50 (1H, s), 7.44 (1H, s)	1770	1670
1c		9.45	6.95	5.83	5.56	5.33	5.18	4.63	3.70	—	1770	1685
1d		9.56	6.98	5.86	5.60	5.33	5.21	4.69	3.73	8.16 (2H, br s)	1760	1670
1e		9.70	6.85	5.83	5.87	5.30	5.25	4.77	3.68	8.00~6.90 (3H, m)	1763	1660
1f		9.70	7.08	5.84	5.55	5.28	5.20	4.63	3.73	7.80~6.50 (3H, m)	1770	1680
1g		9.69	6.92	5.79	5.53	5.29	5.21	4.61	3.71	7.63~6.93 (3H, m)	1770	1670
1h		9.65	6.98	5.90	5.60	5.37	5.27	4.72	3.70	9.20 (1H, d, J=2 Hz), 8.00 (1H, d, J=2 Hz)	1760	1665
1i		9.67	6.92	5.83	5.55	5.30	5.22	4.75	3.72	10.27 (1H, s)	1770	1680
1j		*	7.11	5.65 (1H, d, J=5 Hz)	5.16	4.95	5.10	4.37	3.48	7.75~7.28 (5H, m)	1755	1660
1k		9.80	6.91	5.83	5.55	5.27	5.24	4.74	3.74	9.30~7.30 (4H, m)	1774	1670

* Compound **1j** is a disodium salt and its NMR spectrum was recorded in D_2O.

of **4h**.

The properties of **4h, i, k** and **m** were listed in Table 2.

General Procedure for the Acylation of Diphenylmethyl 7β-Amino-3-vinyl-3-cephem-4-carboxylate Hydrochloride (**11**)

Vilsmeier Reagent Method: A soln of DMF (14.4 mmol) and phosphoryl chloride (14.4 mmol) in THF (15 ml) was stirred under ice-cooling for 30 minutes. To the above mixture was added **4f**~**m** (12 mmol) under ice-cooling, and the mixture was stirred at the same temp for 30 minutes to produce an activated acid soln of **4f**~**m**. To a soln of **11** (10 mmol) and *N*-(trimethylsilyl)acetamide (40 mmol) in EtOAc (50 ml) was added the above activated acid soln at −30°C, and the reaction mixture was stirred at −20~−10°C for 30 minutes. The reaction mixture was poured into a mixture of EtOAc and H_2O. The separated organic layer was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give the acylated cephalosporin (**12f**~**m**).

Acid Chloride Method: To a suspension of **4d** (10 mmol) in dichloromethane (20 ml) was added PCl_5 (10 mmol) under ice-cooling, and the reaction mixture was stirred at the same temp for 1 hour to produce the acid chloride solution of **4d**. To a soln of **11** (8 mmol) and *N*-(trimethylsilyl)-acetamide (32 mmol) in dichloromethane (40 ml) was added the above acid chloride soln at −20°C, and the reaction mixture was stirred at −20~−10°C for 30 minutes. The resulting soln was poured into a mixture of EtOAc and H_2O. The separated organic layer was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The solution was evaporated *in vacuo* to afford the acylated cephalosporin (**12d**).

General Procedure for Deformylation of the *N*-Formyl Compound (**12l, m**)

To a soln of the *N*-formyl compound (**12l, m**) (5 mmol) in MeOH (20 ml) was added concd HCl (1.56 g, 15 mmol) at room temp, and the mixture was stirred at the same temp for 2~4 hours. The reaction mixture was poured into a mixture of EtOAc and H_2O, and adjusted to pH 7.5 with satd sodium bicarbonate soln. The separated organic layer was washed with brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* to afford **12c** and **e**.

General Preparation of 7β-((*Z*)-2-Aryl-2-carboxymethoxyiminoacetamido)-3-vinyl-3-cephem-4-carboxylic Acid (**1b**~**k**)

To a mixture of **12b**~**k** (3 mmol) in anisole (2 ml) and dichloromethane (4 ml) was added TFA (6 ml) under ice-cooling. The resultant mixture was stirred at room temp for 1~4 hours. The reaction mixture was poured into diisopropyl ether, and the precipitate was collected by filtration. The precipitate was added to a mixture of EtOAc and H_2O, and the mixture was adjusted to pH 7.0 with satd sodium bicarbonate soln. The separated aq soln was evaporated *in vacuo* to remove the organic solvent, and then acidified to pH 2.5 with 10% HCl under ice-cooling. The resultant precipitate was collected by filtration, and dried (P_2O_5) to afford **1b**~**k**.

NMR and IR spectral data of compounds (**1** and **12**) were listed in Tables 3 and 4.

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