SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 1-OXACEPHEM DERIVATIVES

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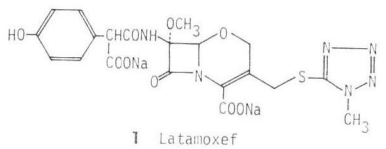
A number of new optically active 1-oxacephem compounds were synthesized and tested for antibacterial activity. Various 7α-unsubstituted 1-oxacephem nuclei **2a**~**e** and a 7α-methoxy-1-oxacephem nucleus **3**, reported previously, were converted into the corresponding phenylacetylamino-, 2-thienylacetylamino-, D-mandelylamino-, D-phenylglycylamino-, and arylmalonylamino-1-oxacephem carboxylic acids. All the compounds except for the phenylglycylamino derivatives exhibited four- to sixteen-fold enhanced antibacterial activity compared with that of the corresponding cephalosporins. A combination of the 7α-methoxy-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-oxacephem nucleus and a 7β-arylmalonylamino side chain, as represented by compound **1** (disodium salt of **33**), produced the highest efficacy among them: high antibacterial activity with a widely expanded spectrum against Gram-negative bacteria including resistant strains and *Pseudomonas aeruginosa* was observed.

Recently, increasing efforts to obtain better β-lactam antibiotics have been focused on the synthesis of cephalosporin nuclear analogues in which the sulfur atom is replaced by either another atom or a group of atoms. CHRISTENSEN and co-workers first reported preparation of racemic 1-oxacephalothin[1] and 1-oxacefamandole[2] as well as some 1-carbacephems[2,3] exhibiting significant antibacterial activity. WOLFE *et al.* reported[4] the synthesis of an optically active 3-methyl 1-oxacephem ester but did not comment on the antibacterial activity of the compound. The synthesis of optically active 3-methyl 1-oxacephems exhibiting antibacterial activity was first carried out by BRANCH and PEARSON.[5,6]

In previous papers, we have reported the synthesis of optically active 3-methyl 1-oxacephems,[7] which exhibit four- to eight-fold higher antibacterial activity than that of the corresponding cephalosporins, as well as the synthesis[8~10] and structure-activity relationships[8~11] of some 3-substituted-methyl 1-oxacephems including 7α-methoxy derivatives. Since then, several improved synthetic routes to 1-oxacephem nuclei have been reported from our laboratories,[12~18] while other research groups have also reported on syntheses[19~23] and the antibacterial activity[21] of 1-oxacephem derivatives.

In the present paper, we report in detail on chemical modifications at the C-7β position in 1-oxacephems as well as a novel method for introducing an arylmalonyl group into a 7α-methoxy 1-oxacephem nucleus. Investigation of the effect of C-3, C-7α, and C-7β groups upon the *in vitro* antibacterial activity of the resulting 1-oxacephems including latamoxef (**1**, moxalactam, 6059-S, LY127935), is also discussed.

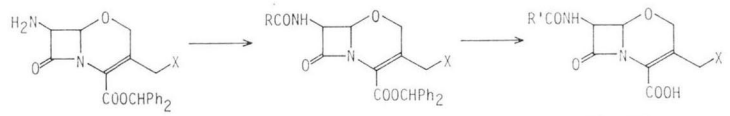


1 Latamoxef

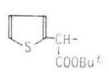
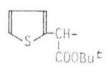
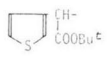
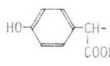
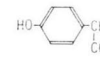
Chemistry

Several series of 7β-acylamino-1-oxacephems were prepared from the previously reported 7α-unsubstituted 1-oxacephem nuclei **2a**,[7] **2b**~**e**[8] (Table 1) and the 7α-methoxy-1-oxacephem nucleus **3**[8]

Table 1. Synthesis of 7β-acylamino-1-oxacephems.

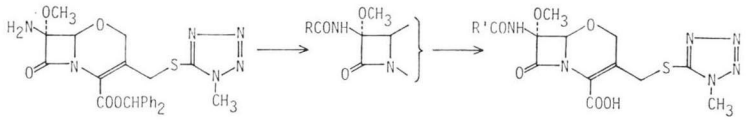


2a ~ e 4a ~ 10e 11a ~ 17e

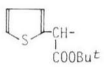
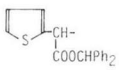
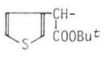
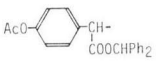
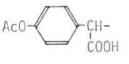
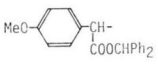
Amine	X	Amide ester acylation[a] Method (Yield)	R	Amide acid deprotection[a] Method (Yield)	R′
2a	H	A (98%) **4a**		I (94%) **11a**	R′=R
2b	OAc	A (56%) **4b**		I (87%) **11b**	R′=R
2a	H	B (82%) **5a**	[D]-PhCH(OH)-	I (98%) **12a**	R′=R
2b	OAc	B (77%) **5b**	[D]-PhCH(OH)-	I (74%) **12b**	R′=R
2c	OMe	B (84%) **5c**	[D]-PhCH(OH)-	I (97%) **12c**	R′=R
2d	S-Tdz[b]	B (85%) **5d**	[D]-PhCH(OH)-	I (62%) **12d**	R′=R
2e	S-Tz[c]	B (94%) **5e**	[D]-PhCH(OH)-	I (55%) **12e**	R′=R
2a	H	C (99%) **6a**	[D]-PhCH(NHCO$_2$Bu^t)-	J$_1$ (100%) **13a**	[D]-PhCH(NH$_2$·CF$_3$CO$_2$H)-
2c	OMe	C (72%) **6c**	[D]-PhCH(NHCO$_2$Bu^t)-	J$_1$ (86%) **13c**	[D]-PhCH(NH$_2$·CF$_3$CO$_2$H)-
2a	H	D (63%) **7a**	PhCH(CO$_2$CHPh$_2$)-	I (89%) **14a**	PhCH(CO$_2$H)-
2b	OAc	D (56%) **7b**	PhCH(CO$_2$CHPh$_2$)-	I (44%) **14b**	PhCH(CO$_2$H)-
2c	OMe	E (58%) **7c**	PhCH(CO$_2$CHPh$_2$)-	I (43%) **14c**	PhCH(CO$_2$H)-
2d	S-Tdz[b]	D (48%) **7d**	PhCH(CO$_2$CHPh$_2$)-	I (45%) **14d**	PhCH(CO$_2$H)-
2e	S-Tz[c]	D (40%) **7e**	PhCH(CO$_2$CHPh$_2$)-	I (84%) **14e**	PhCH(CO$_2$H)-
2e	S-Tz[c]	D (35%) **8e**		J$_1$ (33%) **15e**	
2e	S-Tz[c]	F (96%) **8e**		— —	
2e	S-Tz[c]	D (40%) **9e**		J$_2$ (97%) **16e**	
2e	S-Tz[c]	E (46%) **10e**		J$_2$ (59%) **17e**	

[a] For the Method A~K, see Experimental.
[b] S-Tdz: [2-methyl(1.3.4)thiadiazol-5-yl]thio.
[c] S-Tz: (1-methyl-1*H*-tetrazol-5-yl)thio.

Table 2. Synthesis of 7β-acylamino-7α-methoxy-1-oxacephems.



3 18~27 28~35

Amide ester acylation[a] Method	(Yield)	Product	R	Amide acid deprotection[a] Method	(Yield)	Product	R′
A	(95%)	**18**		I	(95%)	**28**	R′=R
G	(70%)	**19**	[D]-PhCH(OCHO)-	I	(93%)	**29**	R′=R
H	(87%)	**20**	PhCH(CO_2CHPh_2)-	I	(60%)	**30**	PhCH(CO_2H)-
F	(26%)	**21**			—	—	
H	(85%)	**22**		I	(70%)	**31**	
H	(95%)	**23**		J_2	(61%)	**32**	
H	(90%)	**24**		I	(82%)	**32**	
H	(90%)	**25**		I K	(90%) (90%)	**33**	
H	(75%)	**26**		I	(92%)	**34**	
H	(95%)	**27**		I	(98%)	**35**	

[a] For reaction conditions, see Experimental.

(Table 2).

2-Thienylacetylation with thienylacetyl chloride (Method A), D-mandelylation with mandelic acid *O*-carboxy anhydride[24] (Method B), and D-phenylglycylation using a combination of the *tert*-butoxycarbonyl derivative of D-phenylglycine and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (Method C) of the 7α-unsubstituted 1-oxacephem nuclei produced **4a**, **b**, **5a~e**, **6a**, **c**, respectively, while in general the 7α-methoxy-1-oxacephem nucleus **3** was acylated to a sufficient extent only when powerful acylating agents such as 3-thienylacetyl chloride were used, and thus, transformation of **3** into **19** was carried out using D-mandelyl chloride *O*-formate (Method G)

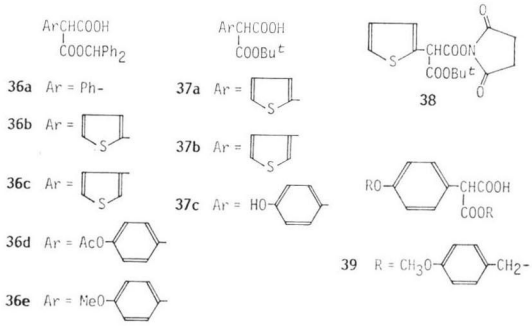


Table 3. IR and NMR spectra of 7β-acylamino-1-oxacephems.

	IR ($CHCl_3$) cm^{-1}	NMR ($CDCl_3$) δ									
		3-substituent					7-side chain			$CHPh_2$	aromatic/NH
		2-H	6-H	7-H	3′-H	CH_3	α-H	others			
4a	3420, 1722, 1792, 1680, 1505	4.13 s 2H	4.97 d 1H 4 Hz	5.67 dd 1H 4, 9 Hz	1.93 s 3H	—	3.83 s 2H			6.98 s 1H	6.94 m 2H 7.2~7.7 m 11H / 6.62 d 1H 9 Hz
4b	3545, 1740, 1800, 1690, 1507	4.40 s 2H	5.02 d 1H 4 Hz	5.76 dd 1H 4, 9 Hz	5.00 5.22 ABq 2H 16 Hz	2.00 s 3H	3.87 s 2H			7.08 s 1H	7.00 d 2H 2 Hz 7.2~7.7 m 11H / 6.64 d 1H 9 Hz
5a	3425, 1727, 1797, 1695, 1510	4.20 s 2H	5.00 d 1H 4 Hz	5.63 dd 1H 4, 9 Hz	1.97 s 3H	—	5.13 s 1H	3.92 s 1H OH		6.98 s 1H	*ca.* 7.4 m 16H / —[b]
5b	3420, 1740, 1800, 1690, 1510	4.50 s 2H	5.05 d 1H 4 Hz	5.70 dd 1H 4, 9 Hz	5.00 5.30 ABq 2H 15 Hz	2.00 s 3H	5.20 s 1H			7.00 s 1H	7.3~7.6 m 16H / —[b]
5c	3420, 1730, 1800, 1690, 1512	4.45[e] s 2H	4.97 d 1H 4 Hz	5.62 dd 1H 4, 9 Hz	4.45[e] s 2H	3.25 s 3H	5.10 br s 1H			6.97 s 1H	*ca.* 7.4 m 16H / —[b]
5d	3420, 1722, 1799, 1690, 1512	4.50 s 2H	4.93 d 1H 4 Hz	5.55 dd 1H 4, 9 Hz	4.25 br s 2H	2.53 s 3H	5.08 br s 1H			6.97 s 1H	*ca.* 7.4 m 16H / —[b]
5e	3405, 1724, 3330, 1688, 1796, 1507	4.63 4.68 ABq 2H[d]	5.07 d 1H 4 Hz	5.69 dd 1H 4, 10 Hz	4.32 s 2H	3.84 s 3H	5.17 br s 1H	1.83 br s 1H OH		6.98 s 1H	*ca.* 7.4 m 16H / —[b]
6a	3430, 1720, 1800, 1695, 1510	4.18 s 2H	5.00 d 1H 4 Hz	5.65 dd 1H 4, 8 Hz	1.98 s 3H	—	5.27 d 1H 7 Hz	1.43 s 9H *t*-Bu	5.67 d 1H 7 Hz NH	—[a]	*ca.* 7.4 m 16H ($CHPh_2$) / 6.77 d 1H 8 Hz
6c	3430, 1718, 1799, 1692, 1510	4.40[e] s 2H	4.90 d 1H 4 Hz	5.68 dd 1H 4, 9 Hz	4.40[e] s 2H	3.23 s 3H	5.30 d 1H 7 Hz	1.40 s 9H *t*-Bu	5.80 d 1H 7 Hz NH	6.93 s 1H	*ca.* 7.4 m 15H / 7.00 d 1H 9 Hz

7a	3420, 1725, 3350, 1680, 1795, 1516	4.10 s 2H	4.90 d 1H 4 Hz	5.60 dd 1H 4, 10 Hz	1.93 s 3H	—	4.68 s 1H		6.85 s 2H	*ca.* 7.25 m 26H	—[b]
7b	3350, 1720, 1800, 1690, 1510	4.47 s 2H	5.03 d 1H 4 Hz	5.74 dd 1H 4, 9 Hz	4.95 5.27 ABq 2H 15 Hz	2.05 s 3H	4.75 s 1H		7.00 s 2H	7.3~7.6 m 26H	—[b]
7c	3435, 1726, 1798, 1680, 1513	4.48[c] s 2H	5.00 d 1H 4 Hz	5.73 dd 1H 4, 9 Hz	4.48[c] s 2H	3.27 s 3H	4.77 s 1H		6.97 s 2H	*ca.* 7.4 m 26H	—[b]
7d	3350, 1715, 1799, 1690, 1512	4.57 s 2H	5.00 d 1H 4 Hz	5.73 dd 1H 4, 9 Hz	4.22 4.53 ABq 2H 14 Hz	2.67 s 3H	4.75 s 1H		6.92 6.97 2s 2H	7.1~7.7 m 25H	7.93 br d 1H 9 Hz
7e	3340, 1720, 1800, 1680, 1517	4.58 br s 2H	5.02 d 1H 4 Hz	5.76 dd 1H 4, 9 Hz	4.30 br s 2H	3.84 s 3H	4.69 4.71 2s 1H[c]		6.86 6.90 2s 2H	7.0~7.5 m 25H	7.76 d 1H 9 Hz
8e	3400, 1720, 1800, 1690, 1511	4.69 br s 2H	5.09 d 1H 4 Hz	5.75 dd 1H 4, 10 Hz	4.32 s 2H	3.93 s 3H	4.80 br s 1H	1.47 s 9H *t*-Bu	6.97 s 1H	6.9~7.7 m 14H	—[b]
9e	3380, 1720, 3310, 1685, 1798, 1515	4.67[c] m 2H	5.06 d 1H 4 Hz	5.78 dd 1H 4, 10 Hz	4.32 s 2H	3.85 s 3H	4.67[c] m 1H	1.45 s 9H *t*-Bu	7.00 s 1H	7.1~7.7 m 14H	—[b]
10e	3410, 1717, 3320, 1679, 1800, 1510	4.62 br s 2H	5.04 d 1H 4 Hz	5.70 dd 1H 4, 10 Hz	4.27 br s 2H	3.80 s 3H	4.38 4.42 2s 1H[e]	1.40 s 9H *t*-Bu	6.93 s 1H	6.5~8.3 m 16H (OH)	—[b]

[a] Unclear.
[b] Overlapped by aromatic proton signals.
[c] Mutually overlapped.
[d] Coupling constant unclear.
[e] Two signals corresponding diastereomers at the α-carbon.

Table 4. IR and NMR spectra of 7β-acylamino-7α-methoxy-1-oxacephems.

	IR ($CHCl_3$) cm^{-1}	NMR ($CDCl_3$) δ										
		3-substituent					7-side chain				$CHPh_2$	aromatic/NH
		2-H	6-H	7-OCH_3	3′-H	CH_3	α-H	others				
18	3410, 1720 sh, 1793, 1708, 1494	4.66 s 2H	5.10 s 1H	3.52 s 3H	4.30 s 2H	3.83 s 3H	3.71 s 2H				7.01 s 1H	7.0~7.8 m 13H 6.60 s 1H
19	3400, 1730 sh, 1780, 1712, 1487	4.55 s 2H	5.08 s 1H	3.53 s 3H	4.23 s 2H	3.77 s 3H	6.27 s 1H	8.20 s 1H OC*H*O			6.98 s 1H	*ca.* 7.4 m 16H —[b]
20	3320, 1725, 1792, 1700 sh, 1492	4.45 s 2H	5.00 s 1H	3.40 3.42 2s 3H[e]	4.22 s 2H	3.72 s 3H	4.75 s 1H				6.92 s 2H	7.1~7.9 m 25H 7.85 s 1H
21	— —	4.65 s 2H	5.12 s 1H	3.56 3.58 2s 3H[e]	4.34 s 2H	3.88 s 3H	4.84 s 1H	1.49 s 9H *t*-Bu			7.03 s 1H	7.1~7.8 m 14H —[b]
22	3310, 1720, 1785, 1700 sh, 1486	4.50 s 2H	5.00[e] s 1H	3.40 br s 3H	4.15 br s 2H	3.80 s 3H	5.00[e] s 1H				6.93 s 2H	7.0~7.7 m 24H —[b]
23	3420, 1720, 3320, 1700 sh, 1795, 1502,	4.60[e] br s 2H	5.05 5.07 2s 1H[e]	3.50 3.53 2s 3H[e]	4.30 br s 2H	3.83 s 2H	4.60 br s 1H	1.41 s 9H *t*-Bu			6.96 s 1H	7.1~7.8 m 14H —[b]
24	3415, 1728, 3320, 1710 sh, 1790, 1495	4.53 s 2H	5.04 5.06 2s 1H[e]	3.43 3.45 2s 3H[e]	4.28 s 2H	3.81 s 3H	4.90 s 1H				6.99 s 2H	7.0~7.8 m 24H —[b]
25	3340, 1720, 3310, 1700 sh, 1790, 1505	4.57[e] br s 2H	5.03 s 1H	3.45 3.48 2s 3H[e]	4.27 br s 2H	3.82 s 3H	4.57[e] br s 1H	3.78 s 6H CH_3O	4.98 s 2H CH_2O	5.13 s 2H CH_2O	6.91 6.98 2s 2H	6.7~7.0 m 6H 7.1~8.7 m 17H —[b]
26	3325, 1730, 1792, 1700 sh, 1505	4.42 s 2H	4.98 s 1H	3.40 s 3H	4.17 s 2H	3.67 s 3H	4.77 s 1H	2.23 s 3H CH_3CO			6.88 br s 2H	6.9~7.8 m 24H 7.93 br s 1H
27	3400, 1723, 3310, 1700 sh, 1786, 1505	4.48 s 2H	5.02 s 1H	3.42 s 3H	4.23 s 2H	3.77 s 3H	4.60 s 1H	3.65 s 3H CH_3O			6.91 6.95 2s 2H	6.7~7.8 m 24H 7.81 br s 1H

[b~e] See Table 3.

instead of Method B given above.

Arylmalonylation of the 7α-unsubstituted 1-oxacephem nuclei was effected by using a combination of a malonyl half ester (**36a**, **37a**~**c**) and either EEDQ (Method D) or isobutyl chloroformate (Method E) to give the corresponding arylmalonylamino derivative **7a**~**e**, **8e**, **9e**, and **10e** in moderate yield. While succimino hydrogen malonate **38**, described in a patent,[25] was found extraordinarily effective for acylation of **2e** into **8e** (Method F), acylation of **3** possessing the 7α-methoxy group with this reagent proceeded very sluggishly to give **21** in low yield. Arylmalonylation of **3** with **36a**~**e**, **37a**, **b**, or **39** proceeded satisfactorily when the corresponding chloride prepared by treatment with oxalyl chloride and triethylamine was used (Method H). Thus, **20**, **22**~**27** were obtained in high yield.

The structure of the resulting acylamino derivatives was confirmed on the grounds of IR and NMR spectral data shown in Tables 3 and 4. In the case of arylmalonylamino derivatives, pairs of signals present in the NMR spectra were assigned to the two possible epimers at the α-carbon atom of the side chain.

Removal of diphenylmethyl and *p*-methoxybenzyl ester groups in the resulting acylamino derivatives as well as the *p*-methoxybenzyl group of the ether in **25** was performed under mild conditions (Method I) (Tables 1 and 2). Deprotection of the *tert*-butyl ester group in **8e**, **9e**, **10e**, and **23** and *tert*-butyl carbamate in **6a** and **6c** necessitated more drastic conditions (Method J_1 and J_2: for details, see Experimental) and gave slightly deteriorated products. Procedures using aluminum trichloride and anisole (Method K), developed in our laboratories for deprotection of cephalosporin benzyl esters,[26] worked quite nicely for the deprotection of both the ester groups and the ether group in **25** to afford **33** in a purer state than that of the product obtained by Method I. As a result, the 7α-unsubstituted 1-oxacephems, **11a**~**17e** (Table 1), and the 7α-methoxy-1-oxacephems, **28**~**35** (Table 2), were prepared in satisfactory yield. Conversion of **33** into its disodium salt **1** was carried out by treatment of **33** with 2-ethylhexanoate in the method described[27] for penicillin.

In addition, phenylacetylamino derivatives **40a**~**e** were also prepared by deprotection of the previously reported corresponding benzhydryl esters[7,8] in the Method I.

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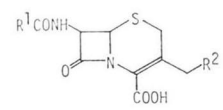
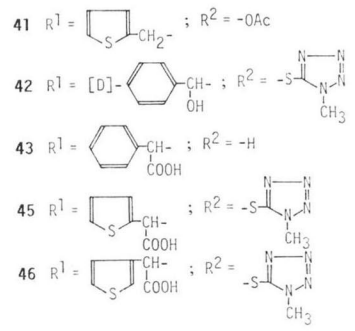
The minimum inhibitory concentrations (MIC) of thus prepared 1-oxacephems against several Gram-positive and Gram-negative bacteria are shown in Tables 5 and 6.

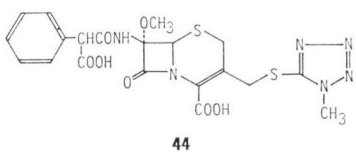
All the 1-oxacephems except for the phenylglycylamino derivatives were found to exhibit four- to sixteen-fold higher antibacterial activity than the corresponding 1-thia-congeners. For comparison, the MIC values of the representative 1-thia congener such as cephalothin (**41**), cefamandole (**42**), **43**[28,29], **44**[30], **45**[25] and **46**[25] are shown in the Tables below those of the corresponding 1-oxacephems.

The effects of the substituents at C-3 on the antibacterial activity were found to be similar in the series of phenylacetylamino- (**40a**~**e**), 2-thienylacetylamino- (**11a**, **b**, **28**), D-mandelylamino- (**12a**~**e**, **29**), or phenylmalonylamino-(**14a**~**e**, **30**) derivatives. Thus, the MIC values decreased in each series in the order of methyl>methoxymethyl>acetoxymethyl > [2-methyl(1.3.4)thiadiazol-5-yl]thiomethyl > (1-methyl-1*H*-tetrazol-5-yl)thiomethyl. The increment of antibacterial activity generated by the introduction of (1-methyl-1*H*-tetrazol-5-yl)thio moiety into the 3-methyl group approaches to twenty-fold for Gram-positive strains and seventy-fold for Gram-negative strains.

The characteristics of the antibacterial spectra were greatly influenced by the variation of the 7β-acylamino side chain and the 7α-methoxy group. Phenylmalonyl derivatives (**14a**~**e**, **30**) exhibited







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extraordinarily expanded Gram-negative antibacterial spectra even including *Pseudomonas aeruginosa*,*1 although the Gram-positive activity of these compounds was greatly diminished. Some of the arylmalonyl compounds manifested good Gram-positive activity, but it was found to be artificial values resulted from contamination of the decarboxylated phenylacetylamino derivatives which were quite active against Gram-positive bacteria. D-Mandelylamino derivatives (**12a**~**e**, **29**) showed moderately expanded Gram-negative antibacterial spectra. Phenylacetylamino- (**40a**~**e**) and 2-thienylacetylamino- (**11a**, **b**, **28**) derivatives exhibited poor Gram-negative spectra. D-Phenylglycylamino derivatives (**13a**, **c**) were devoid of Gram-negative antibacterial activity. This was ascribed to probable decomposition of the compounds during the assay since the hydrolysis rate of **13a** measured at 35°C and pH 7.3 ($\tau_{1/2}$=2.0 hours) was much higher than the corresponding value*2 ($\tau_{1/2}$=81 hours) of cephalexin. The decomposition might take place in an intramolecular aminolysis of the activated β-lactam ring with the side chain amino group. The introduction of the 7α-methoxy group conferred antibacterial activity against a resistant strain (*E. coli* 73), as indicated by the comparison of **28**, **29**, **30**, **31**, **32**, and **33** with **11b**, **12e**, **14e**, **15e**, **16e**, and **17e**, respectively.

Effects of the arylmalonylamino group on antibacterial activity against Gram-negative bacteria were investigated in the two series of **14e**~**17e**, and of **30**~**35**. High activity of 2-thienyl- (**15e**, **31**) and 3-thienyl-malonylamino (**16e**, **32**) derivatives against Gram-negative bacteria and also moderate anti-pseudomonal activity of *p*-hydroxyphenylmalonylamino derivatives (**17e**, **33**) are noteworthy.

From these findings, it was concluded that the combination of the 7α-methoxy-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-oxacephem nucleus and a 7β-arylmalonylamino side chain produced the highest Gram-negative activity*3 amongst the examined combinations. Compound **1**, which is the disodium salt of **33**, is of this combination and was chosen[11] as the best compound for clinical evaluations based on its further assessment on pharmacological properties.[34] Laboratory evaluation[35] of compound **1**, interpretation[36] of the enhancement of antibacterial activity by replacement of the sulfur atom in cephalosporin with an oxygen atom, and the role[37] of the 7α-methoxy group and the side chain carboxyl group with respect to the stability against β-lactamases have been reported from these laboratories.

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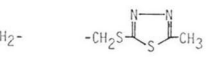
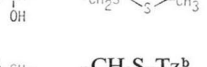
*1 Interesting activity of phenylmalonyl amino derivative of 3-ethoxycarbonylvinylcephalosporin against Gram-negative and *Pseudomonas* had been reported.[31]

*2 $\tau_{1/2}$ 35°C was calculated for pH 7.3 using the equation and the rate constants reported by YAMANA and TSUJI.[32]

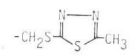
*3 Interesting activity of phenylmalonyl 7α-methoxycephalosporins against *Pseudomonas aeruginosa* was commented in a review.[33]

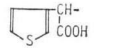
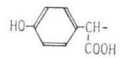
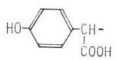
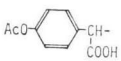
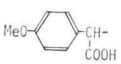
Table 5. MIC values of 1-oxacephems (I).

Compound	*Staph. aureus* 209P JC-1	*Staph. pyogenes* C-203	*E. coli* NIHJ JC-2	*E. coli* 73 (R)	*Proteus vulgaris* CN-329	*Enterob. cloacae* 233	*Serratia marcescens* ATCC 13880	7	3
40a	0.4	0.2	12.5	50	>100	>100	>100		–Me
40b	0.02	0.02	1.6	>100	50	>100	>100		$-CH_2OAc$
40c	0.05	0.02	12.5	>100	>100	>100	>100		$-CH_2OMe$
40d	≦0.01	≦0.01	0.8	>100	3.1	>100	>100		
40e	0.02	≦0.01	0.1	>100	0.8	100	>100		$-CH_2S-Tz^b$
11a	0.4	0.2	6.3	50	100	>100	>100		–Me
11b	≦0.01	0.02	0.8	>100	50	100	>100		$-CH_2OAc$
(41)[a]	0.1	0.1	6.3	100	100	>100	>100		
28	0.1	0.05	0.1	0.8	0.4	12.5	3.1		$-CH_2OAc$ (7α-MeO)
12a	0.8	0.2	1.6	25	>100	12.5	>100		–Me
12b	0.05	0.02	0.4	>100	12.5	12.5	>100		$-CH_2OAc$
12c	0.2	≦0.01	1.6	>100	50	>100	>100		$-CH_2OMe$
12d	0.02	≦0.01	0.1	>100	0.4	3.1	25		
12e	0.05	≦0.01	0.05	>100	0.1	0.8	12.5		$-CH_2S-Tz^b$
(42)[a]	0.1	0.05	0.4	25	0.8	3.1	50		
29	0.2	0.1	0.1	0.8	0.4	6.3	3.1		$-CH_2S-Tz^b$ (7α-MeO)
13a	50	6.3	>100	>100	>100	>100	>100		–Me
13c	50	>3.1	>100	>100	>100	>100	>100		$-CH_2OMe$

[a] 1-Thia congener corresponding to the compound listed above.
[b] Tz: 1-methyl-1*H*-tetrazol-5-yl.

Table 6. MIC values of 1-oxacephems (II) — arylmalonyl derivatives.

Compound	*Staph. aureus* 209P JC-1	*Staph. pyogenes* C-203	*E. coli* NIHJ JC-2	*E. coli* 73 (R)	*Proteus vulgaris* CN-329	*Enterob. cloacae* 233	*Serratia marcescens* ATCC 13880	*Pseudomonas aeruginosa* ATCC 25619	*Pseudomonas aeruginosa* PS-24	7	3
14a	50	>3.1	6.3	12.5	25	6.3	25	6.3	>100		–Me
(43)[a]	100	>3.1	100	>100	100	100	>100	100	>100		
14b	1.6	3.1	0.8	>100	1.6	0.8	1.6	3.1	>100		–CH_2OAc
14c	3.1	3.1	1.6	>100	3.1	1.6	3.1	6.3	>100		–CH_2OMe
14d	0.8	0.8	0.2	100	0.1	0.2	0.4	3.1	>100		
14[c]	0.8	0.4	0.05	12.5	0.1	0.1	0.2	1.6	>100		–CH_2S–Tz[b]
30	3.1	3.1	0.05	0.2	0.05	0.05	0.1	3.1	25		–CH_2S–Tz[b] (7α-MeO)
(44)[a]	6.3	12.5	0.4	1.6	0.1	0.4	1.6	1.6	50		
15e	0.4	0.2	0.05	6.3	0.1	0.1	0.2	1.6	>100		–CH_2S–Tz[b]
(45)[a]	1.6	0.8	0.8	12.5	0.8	1.6	3.1	6.3	>100		

16e	1.6	1.6	0.1	12.5	0.1	0.1	0.2	3.1	>100		$-CH_2S-Tz^b$
(46)[a]	6.3	3.1	0.8	12.5	0.4	0.8	3.1	6.3	>100		
17e	3.1	0.8	0.2	50	0.4	0.4	0.8	3.1	>100		$-CH_2S-Tz^b$
31	0.4	0.8	0.02	0.05	0.05	0.02	0.1	3.1	25		$-CH_2S-Tz^b$ (7α-MeO)
32	1.6	1.6	0.05	0.1	0.1	0.05	0.1	3.1	25		$-CH_2S-Tz^b$ (7α-MeO)
33	6.3	1.6	0.2	0.4	0.2	0.1	0.4	6.3	25		$-CH_2S-Tz^b$ (7α-MeO)
34	6.3	1.6	0.2	0.8	0.2	0.4	0.8	3.1	50		$-CH_2S-Tz^b$ (7α-MeO)
35	6.3	12.5	0.8	6.3	0.2	1.6	6.3	3.1	50		$-CH_2S-Tz^b$ (7α-MeO)

[a, b] See, footnote *a*, *b* Table 5.

Experimental

All reactions under anhydrous conditions were carried out in a nitrogen atmosphere using anhydrous solvents dried in advance over Molecular Sieves type 4A. Melting points were determined on a Yanagimoto apparatus and were not corrected. Infrared (IR) spectra were recorded on a Hitachi 215 or JASCO DS-403G spectrometer. ^{1}H Magnetic resonance (NMR) spectra were obtained on a Varian A-60 or Varian T-60A spectrometer with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-1-sulfonate (in D_2O) as an internal reference. Ultraviolet (UV) spectra were recorded on a Hitachi 323 spectrometer. Rotations were determined on a Perkin Elmer 141 spectrometer. For column chromatography, silica gel (Merck silica gel 60) deactivated by addition of 10% water was used. Qualitative thin-layer chromatography was performed using precoated silica gel plates (Merck 60 F-254) and EtOAc - HOAc - H_2O (8: 1: 1) as the solvent system unless otherwise noted.

General Procedures for Removal of Protecting Groups

Deprotection was carried out using one of the following procedures. Method I: An ice-cold solution of ester (0.10 mmole) in anhydrous dichloromethane (1.6 ml) mixed with anisole (0.15 ml) and trifluoroacetic acid (0.17 ml) was stirred at 0°C for 1.3±0.7 hours. The reaction solution was concentrated *in vacuo* to dryness and the residue was purified by: (1) partition between an ice-cold 5% solution of $NaHCO_3$ and ether followed by extraction of the acidified aqueous layer and subsequent concentration of the dried (Na_2SO_4) organic layer *in vacuo*; (2) silica gel chromatography using EtOAc - HOAc (9: 1) as the eluant; or (3) trituration with a suitable solvent. Method J: An ice-cold mixture of ester (0.10 mmole) in either a mixture of anhydrous dichloromethane (1.4 ml), anisole (0.7 ml), and trifluoroacetic acid (1.4 ml) (Method J_1) or a mixture of anisole (0.50 ml) and trifluoroacetic acid (0.05 ml) (Method J_2) was stirred at 0°C for 2.2±1.1 hours. The reaction solution was worked up similarly and the residue was purified in a manner similar to one of the three ways described above. Method K: See preparation of **33**.

Phenylacetylamino Derivatives **40a**~**e**

Deprotection of the corresponding benzhydryl esters[7,8] by Method I yielded **40a**~**e** in yields of 69, 84, 98, 83, and 76%, respectively. **40a**, mp 180~182°C (dec.) (recrystallized from dichloromethane - ether): IR (KBr) 3404 (NH), 1778 (β-lactam), 1725 (sh, CO_2H), 1650 (amide I), 1536 cm^{-1} (amide II); TLC Rf 0.51. **40b**, mp 191~193°C (dec.) (recrystallized from EtOAc): IR (Nujol) 3280 (NH), 1790 (β-lactam), 1760 (OAc), 1715 (CO_2H), 1665 (amide I), 1545 cm^{-1} (amide II); TLC Rf 0.49. **40c** (amorphous powder): IR (KBr) 3400 (NH), 1778 (β-lactam), 1675 (CO_2H, amide I), 1601 (sh), 1535 cm^{-1} (amide II); TLC Rf 0.36. **40d** (amorphous powder): IR ($CHCl_3$) 3430 (NH), 1799 (β-lactam), 1720 (CO_2H), 1685 (amide I), 1510 cm^{-1} (amide II); TLC Rf 0.25. **40e**, mp 147~151°C (crystallized from EtOAc - ether): $[\alpha]_D^{22.5}$ −69.0±3.0° (*c* 0.358, 1% $NaHCO_3$); IR (KBr) 3400 (NH), 1772 (β-lactam), 1665 (CO_2H, amide I), 1600, 1530 cm^{-1} (amide II); NMR (D_2O-$NaHCO_3$) δ 3.66 (s, 2 H, PhCH_2CO), 3.98 (s, 3 H, NCH_3), 4.08, 4.24 (ABq, 2 H, J=13.5 Hz, CH_2S), 4.52 (br s, 2 H, C_2-H), 5.12 (d, 1 H, J=4.0 Hz, C_6-H), 5.44 (d, 1 H, J=4.0 Hz, C_7-H), 7.30 (s, 5 H, aromatic H); UV (1% $NaHCO_3$) 265 nm (ε 9980); TLC Rf 0.42.

Anal. Calcd. for $C_{18}H_{18}N_6O_5S\cdot 2H_2O$: C 46.34, H 4.75, N 18.02, S 6.87.
Found: C 46.50, H 4.11, N 17.36, S 6.42.

Thienylacetylamino Derivatives **11a**, **b**, **28** (Method A)

A solution of **2a** (85.5 mg, 0.235 mmole), thien-2-ylacetyl chloride (56.5 mg, 1.5×0.235 mmole), and pyridine (19 μl, 1.5×0.235 mmole) in dichloromethane (3.0 ml) was stirred with ice-water cooling for 1.5 hours. The reaction solution diluted with EtOAc was washed with H_2O and dried (Na_2SO_4), and then the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (20 g) using benzene - EtOAc (2: 1) as the eluant and gave **4a** (111.9 mg). In a similar way, **4b** and **18** (3-thienylacetylamino derivative) were prepared from **2b** and **3**, respectively. Spectral data of these compounds are shown in Tables 3 and 4.

Deprotection of **4a**, **b**, and **18** in Method I yielded **11a**, **b**, and **28**, respectively. **11a** (foam): IR (Nujol) 3320 (NH), 1775 (β-lactam), 1720 (CO_2H), 1655 (amide I), 1500 cm^{-1} (amide II); TLC Rf

0.54. **11b**, mp 181~183°C (crystallized from EtOAc): IR (Nujol) 3380 (NH), 1790 (β-lactam), 1760 (OAc), 1715 (CO_2H), 1665 (amide I), 1545 cm^{-1} (amide II); TLC Rf 0.75. **28** (amorphous powder): IR (KBr) 3430 (NH), 1783 (β-lactam), 1690 (CO_2H, amide I), 1633, 1517 cm^{-1} (amide II); UV (MeOH) 273 nm (ε 8030); TLC Rf 0.64 (EtOAc - HOAc - H_2O, 5: 1: 1).

D-Mandelylamino Derivatives **12a~e**, **29**

Method B used in the preparation of **12a~e** is described in the following example. To a vigorously stirred solution of **2a** (71.6 mg, 0.196 mmole) in EtOAc (8.0 ml) was successively added a solution of $NaHSO_3$ (100 mg, 4.8×0.196 mmole) in H_2O (4.0 ml) and D-mandelic acid *O*-carboxyanhydride (52.5 mg, 1.5×0.196 mmole) and the resulting mixture was stirred at room temperature for one hour. After dilution with EtOAc, the reaction mixture was washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (10 g). Elution with benzene - EtOAc (1: 1) yielded **5a** (80.4 mg). In a similar way, **5b~e** were prepared from **2b~e**. Spectral data for **5a~e** are shown in Table 3.

Deprotection of **5a~e** using Method I yielded **12a~e**, respectively. **12a** (amorphous powder): IR (KBr) 3400 (OH, NH), 1781 (β-lactam), 1712 (CO_2H), 1673 (amide I), 1524 cm^{-1} (amide II); TLC Rf 0.44. **12b** (amorphous powder): IR (Nujol) 3370 (OH, NH), 1785 (β-lactam), 1740 (OAc), 1720 (CO_2H), 1675 (amide I), 1515 cm^{-1} (amide II); TLC Rf 0.40. **12c** (amorphous powder): IR (KBr) 3400 (OH, NH), 1776 (β-lactam), 1676 (CO_2H, amide I), 1601 (sh), 1522 cm^{-1} (amide II); TLC Rf 0.36. **12d** (amorphous powder): IR (Nujol) 3200~3400 (OH, NH), 1778 (β-lactam), 1710 (CO_2H), 1675 (amide I), 1600, 1515 cm^{-1} (amide II); TLC Rf 0.23. **12e** (amorphous powder): IR (Nujol) 3490 (OH, NH), 1776 (β-lactam), 1672 (CO_2H, amide 1), 1595, 1515 cm^{-1} (amide II); TLC Rf 0.20.

Method G was used in the preparation of **29**. A mixture of D-mandelic acid *O*-formate (72 mg, 0.40 mmole), thionyl chloride (0.20 ml, 6.9×0.40 mmole) and benzene (1.0 ml) was heated at 70°C for one hour. The mixture was concentrated *in vacuo* to dryness. The resulting acid chloride dissolved in dichloromethane (2.0 ml) was added to an ice-cold solution of **3** (101.7 mg, 0.20 mmole) and pyridine (24 μl, 1.5×0.20 mmole) in dichloromethane (4.0 ml). After the resulting mixture had been stirred at 0°C for one hour, it was diluted with EtOAc, washed successively with H_2O, a diluted solution of $NaHCO_3$, and H_2O, and then dried (Na_2SO_4). The solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (20 g) by using benzene - EtOAc (3: 1) as the eluant to give **19** (94.5 mg) as a foam; its spectral data are given in Table 4.

Deprotection of **19** by Method I afforded **29** (amorphous powder): IR (KBr) 3400 (NH), 3265, 1786 (β-lactam), 1769 (OCHO), 1730, 1714 (CO_2H), 1682 (amide I), 1623, 1534 cm^{-1} (amide II); UV (MeOH) 275 nm (ε 10,300); TLC Rf 0.59.

D-Phenylglycylamino Derivatives **13a, c** (Method C)

A mixture of **2a** (150 mg, 0.412 mmole), *N*-(1-*tert*-butoxycarbonyl)-D-α-phenylglycine (155 mg, 1.5×0.412 mmole), and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (152 mg, 1.5×0.412 mmole) in anhydrous tetrahydrofuran (8.0 ml) and acetone (4.0 ml) was stirred at room temperature for 14 hours. The reaction mixture was diluted with EtOAc, washed successively with H_2O, diluted HCl, a solution of $NaHCO_3$, and H_2O, and dried (Na_2SO_4). Next, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel (30 g) using benzene - EtOAc (9: 1) as the eluant, yielding **6a** (248 mg). The spectral data of **6a** and **6c**, prepared in a manner similar to that described above, are shown in Table 3.

Deprotection of **6a, c** in Method J_1 followed by trituration with ether - *n*-pentane afforded **13a** and **13c** respectively as CF_3CO_2H salts, **13a** (amorphous powder): IR (KBr) 3410 (NH), 1775 (β-lactam), 1695 (sh, CO_2H), 1675 (amide I), 1572 cm^{-1} (amide II); NMR (D_2O-DCl) δ 1.97 (s, 3 H, CH_3), 4.23 (s, 2 H, C_2-H), 5.10 (d, 1 H, J=3.8 Hz, C_6-H), 5.32 (s, 1 H, PhC*H*), 7.53 (s, 5 H, phenyl H), C_7-H is covered with the HDO signal; UV (H_2O) 255 nm (ε 7080). **13c** (amorphous powder): IR (KBr) 3410, 3060 (NH), 1781 (β-lactam), 1695 (sh, CO_2H), 1673 (amide I), 1630 (sh), 1535 (amide II).

Phenylmalonylamino Derivatives **14a~e**, **30**

Synthesis of **36a**: To a stirred solution of phenylmalonic acid (7.40 g, 41 mmole) in ether (150 ml) cooled at 0°C was added dropwise a solution of diphenyldiazomethane (7.96 g, 41 mmoles) in ether

(30 ml) over a period of 15 minutes. After the solution had been stirred at 0°C for 30 minutes and then at room temperature for 2.0 hours, it was extracted several times with a 5% solution of $NaHCO_3$. The aqueous solution was washed with ether, acidified with 2 N HCl to pH 1.0 and then extracted with dichloromethane. The organic solution was washed three times with H_2O and dried (Na_2SO_4). When the solvent was removed, a crystalline residue was obtained. Recrystallization of the residue from dichloromethane - petroleum ether yielded **36a** (6.35 g, 44.5%), mp 120~120.5°C: NMR ($CDCl_3$) δ 4.77 [s, 1 H, PhC*H*(CO_2H)CO_2R], 6.93 (s, 1 H, C*H*Ph_2), *ca.* 7.3 (br s, 15 H, phenyl H), 10.53 (s, 1 H, CO_2*H*).

Phenylmalonylation in Method D: A mixture of a solution of **2a** (85.6 mg, 0.235 mmole) dissolved in anhydrous tetrahydrofuran (6.0 ml) and acetone (3.0 ml), **36a** (245 mg, 3.0×0.235 mmole), and EEDQ (174 mg, 3.0×0.235 mmole) was stirred at room temperature for 4.0 hours. Extraction of the product with EtOAc, followed by silica gel chromatography (30 g) using benzene - EtOAc (4: 1) as the eluant, yielded **7a** (102.6 mg) as a foam after trituration with ether - *n*-pentane. In as imilar way, **2b, d, e** were acylated to obtain **7b, d, e**, respectively. Spectral data of the resulting compounds are shown in Table 3.

Phenylmalonation in Method E: To a stirred solution of **36a** (151 mg, 1.5×0.290 mmole) in anhydrous dichloromethane (4.0 ml) cooled at −25°C was added successively triethylamine (60 μl, 1.5×0.29 mmole) and isobutyl chloroformate (57 μl, 1.5×0.29 mmole). The resulting mixture was stirred at −25°C for 30 minutes and then at 0°C for 10 minutes. To the resulting solution containing mixed anhydride cooled in a cold bath of −25°C was added a solution of **2c** (114.5 mg, 0.29 mmole) in dichloromethane (2.0 ml) and the mixture was stirred for 30 minutes. After further stirring of the mixture at 0°C for 1.5 hours, the product was extracted with EtOAc. The extract was purified by preparative layer chromatography (silica gel) using benzene - EtOAc (10: 1) as the eluant to yield **7c** as a foam (for spectral data, see Table 3).

Phenylmalonylation in Method H: To a stirred solution of **36a** (103.9 mg, 1.5×0.20 mmole) in dichloromethane (2.0 ml) cooled in an ice-water bath was added successively triethylamine (41.6 μl, 1.5×0.20 mmole) and oxalyl chloride (25.6 μl, 1.5×0.20 mmole). The resulting mixture, stirred for 10 minutes, gave a solution containing the corresponding acid chloride, which was transferred to an ice-cold solution of **3** (101.7 mg, 0.20 mmole) in dichloromethane (5.0 ml) mixed with pyridine (59.4 μl, 3.0×0.20 mmole). After the resulting mixture had been stirred at 0°C for one hour, it was extracted with EtOAc. Chromatography of the extract on silica gel (20 g) using benzene - EtOAc (4: 1) as the eluant yielded **20** (121.2 mg) as a foam (for spectral data, see Table 4).

Deprotection of **7a~e, 20** in Method I yielded **14a~e, 30**, respectively. **14a** (amorphous powder): IR (Nujol) 3400~2300 (NH, CO_2H), 1770 (β-lactam), 1720 (CO_2H), 1630 (amide I), 1525 cm^{-1} (amide II); TLC Rf 0.30. **14b** (amorphous powder): IR (Nujol) 3300 (NH), 1780 (β-lactam), 1720 (OAc, CO_2H), 1680 (amide I), 1600, 1530 cm^{-1} (amide II); TLC Rf 0.35. **14c** (amorphous powder): IR (KBr) 3410 (NH), 1767 (β-lactam), 1682 (CO_2H, amide I), 1605, 1529 cm^{-1} (amide II); TLC Rf 0.17. **14d** (amorphous powder): $[\alpha]_D^{23.5}$ −138.7±6.7° (*c* 0.266, 1.0% $NaHCO_3$); IR (KBr) 3410 (NH), 1772 (β-lactam), 1660 (sh, amide I), 1600, 1530 cm^{-1} (amide II); TLC Rf 0.11. **14e** (amorphous powder): $[\alpha]_D^{23.0}$ −90.3±4.2° (*c* 0.310, 1.0% $NaHCO_3$); IR (KBr) 3420 (NH), 2520 (br, CO_2H), 1775 (β-lactam), 1674 (CO_2H, amide I), 1606, 1529 cm^{-1} (amide II); NMR (D_2O-$NaHCO_3$) δ 4.02 (s, 3 H, NCH_3), 4.05, 4.32 (ABq, 2 H, *J*=13.5 Hz, C*H*$_2$S), 4.55 (br s, 2 H, C_2-H), 5.08 (br s 1 H, PhC*H*(CO_2H)CONH, gradually deuterated), 5.16, 5.21 (2 d, 1 H, *J*=4.0 Hz, C_6-H), 5.48 (d, 1 H, *J*=4.0 Hz, C_7-H), 7.37 (s, 5 H, phenyl H); UV (1.0% $NaHCO_3$) 265.5 nm (ε 9440). **30** (amorphous powder): $[\alpha]_D^{25.0}$ −19.4±2.8° (*c* 0.211, MeOH); IR (KBr) 3450 (sh), 3280 (NH, H_2O), 1780 (β-lactam), 1717 (CO_2H, amide I), 1631, 1513 cm^{-1} (amide II); NMR (D_2O+$NaHCO_3$) δ 3.46, 3.53 (2 s, 3 H, OCH_3), 3.99, 4.02 (2 s, 3 H, NCH_3), 4.1~4.2 (m, 2 H, C*H*$_2$S), 4.48 (s, 2 H, C_2-H), 4.53 (s, 1 H, PhC*H*(CO_2H)CONH, gradually deuterated), 5.13 (s, 1 H, C_6-H), 7.38 (s, 5 H, phenyl H); UV (MeOH) 275.5 nm (ε 9400); TLC Rf 0.12.

Anal. Calcd. for $C_{20}H_{20}N_6O_5S$: C 47.61, H 4.00, N 16.66, S 6.35.
Found: C 47.64, H 4.09, N 16.42, S 6.10.

2-Thienylmalonylamino Derivatives **15e, 31**

Synthesis of **37a** and **38** has been reported in a patent.[25] Carboxylation of diphenylmethyl 2-thienylacetate in a similar way to the patent[25] produced **36b**: NMR ($CDCl_3$) δ 5.03 [s, 1 H, ArC*H*

(CO_2H)CO_2R], 6.87 (s, 1 H, C*H*Ph_2), 6.79~7.33 (m, 3 H, thienyl H), 7.19 (s, 10 H, phenyl H), 9.85 (s, 1 H, CO_2H).

2-Thienylmalonylation of **2e** with **37a** using Method D described in the section on phenylmalonylamino derivatives gave **8e** (for spectral data, see Table 3).

2-Thienylmalonylation in Method F: To a stirred suspension of **2e** (383 mg, 0.80 mmole) in acetonitrile (10 ml) was added successively **38** (407 mg, 1.5×0.80 mmole) and *N*-methylmorpholine (88 μl, 1.0×0.80 mmole). The resulting mixture was stirred at room temperature for 1.6 hours. After the excess of the reagent had been quenched by stirring the mixture with a 5% solution of $NaHCO_3$ at room temperature for 30 minutes, the mixture was extracted with EtOAc. Chromatography of the extract on silica gel (30 g) using benzene - EtOAc (4: 1) as the eluant gave **8e** (518 mg) as a foam. Spectral data of the compound is shown in Table 3.

Unlike in this case, 2-thienylmalonylation of **3** in Method F proceeded very sluggishly. To a stirred solution of **3** (101 mg, 0.20 mmole) in dichloromethane (3.0 ml) and acetonitrile (1.0 ml) was added **38** (135 mg, 2.0×0.20 mmole) then *N*-methylmorpholine (22 μl, 1.0×0.20 mmole). The resulting solution was stirred at room temperature for 78 hours. Next, after the reaction mixture had been stirred with a 5% $NaHCO_3$ solution at room temperature for 10 minutes, the product was extracted with dichloromethane. Column chromatography of the oily extract using silica gel (20 g) and benzene - EtOAc (9: 1) as the eluant afforded **21** (38 mg, foam) (for spectral data, see Table 4).

2-Thienylmalonylation of **3** with **36b** using Method H as described in the section on phenylmalonylamino derivatives yielded **22** (for spectral data, see Table 4).

Deprotection of **8e** by Method J_1 and **22** by Method I yielded **15e** and **31**, respectively. **15e** (foam): $[\alpha]_D^{23.0}$ −62.0±3.7° (*c* 0.279, 1.0% $NaHCO_3$); IR (KBr) 3390 (NH), 1765 (β-lactam), 1670 (CO_2H, amide I), 1608, 1520 cm^{-1} (amide II); TLC Rf 0.20. **31** (amorphous powder): $[\alpha]_D^{24.0}$ −15.0±1.5° (*c* 0.374, MeOH); IR (KBr) 3340 (NH, H_2O), 3150~2560 (br, CO_2H), 1785 (β-lactam), 1715 (CO_2H), 1700 (amide I), 1634, 1517 cm^{-1} (amide II); NMR (D_2O-$NaHCO_3$) δ 3.48, 3.54 (2 s, 3 H, OCH_3), 4.04 (s, 3 H, NCH_3), 5.15 (s, 1 H, C_6-H), 7.00~7.50 (m, 3 H, thienyl H), other signals were unclear; UV (MeOH) 275 nm (ε 8800); TLC Rf 0.29 (EtOAc - HOAc - H_2O, 3: 1: 1).

3-Thienylmalonylamino Derivatives **16e**, **32**

The synthesis of **37b** has been reported in a patent.[25] Carboxylation of diphenylmethyl 3-thienylacetate in a similar way to the patent[25] gave **36c**: NMR ($CDCl_3$) δ 4.96 (s, 1 H, ArC*H*(CO_2H)CO_2R), 7.00 (s, 1 H, C*H*Ph_2), 7.13~7.46 (m, 3 H, thienyl H), 7.35 (2 s, 10 H, phenyl H), signal for CO_2H was unclear.

3-Thienylmalonylation of **2e** with **37b** by Method D described in the section on phenylmalonylamino derivatives produced **9e** (for spectral data, see Table 3).

3-Thienylmalonylation of **3** with either **37b** or **36c** by Method H described in phenylmalonylamino derivatives yielded **23** or **24**, respectively (for spectral data, see Table 4).

Deprotection of **9e** in Method J_2 and either deprotection of **23** in Method J_2 or of **24** in Method I gave **16e** and **32**, respectively. **16e** (amorphous powder): IR (Nujol) 3400 (NH), 3100~2500 (br, CO_2H), 1770 (β-lactam), 1692 (CO_2H, amide I), 1610, 1535 cm^{-1} (amide II); TLC Rf 0.22. **32** (amorphous powder): $[\alpha]_D^{25.0}$ −12.8±2.5° (*c* 0.211, MeOH); IR (KBr) 3300, 3210 (NH), 3100~2550 (CO_2H), 1780 (β-lactam), 1705 (CO_2H, amide I), 1633, 1515 cm^{-1} (amide II); NMR (D_2O+$NaHCO_3$) δ 3.46, 3.54 (2 s, 3 H, OCH_3), 4.03 (s, 3 H, NCH_3), 4.11, 4.21 (2 m, 2 H, SCH_2), 4.51, 4.53 (2 s, 2 H, C_2-H), 5.15 (s, 1 H, C_6-H), 7.05~7.52 (m, 3 H, thienyl H); UV (MeOH) 273 nm (ε 8400); TLC Rf 0.35 (EtOAc - HOAc - H_2O, 3: 1: 1).

p-Hydroxyphenylmalonylamino Derivatives **17e**, **33**, and Its Disodium Salt **1**

Synthesis of **37c**: A mixture of *p*-hydroxyphenylacetic acid (15.2 g, 0.10 mole), KOH (86% pure, 14.36 g, 2.2×0.10 mole), H_2O (14.4 ml), EtOH (70 ml), and benzyl chloride (13.90 ml, 2.4×0.10 mole) was refluxed for 12 hours. After removal of neutral material, the reaction mixture was acidified and extracted with EtOAc. The EtOAc solution was washed with H_2O and then dried (Na_2SO_4). Next, the solvent was evaporated *in vacuo* and the residue was crystallized from petroleum ether - *n*-pentane, giving *p*-benzyloxyphenylacetic acid (19.20 g), mp 110~116°C: NMR ($CDCl_3$) δ 3.55 (s, 2 H, $C_6H_4CH_2$-

CO), 5.02 (s, 2 H, PhCH_2OC$_6$H$_4$), 6.73~7.33 (m, 4 H, phenylene H), 7.37 (s, 5 H, phenyl H), 10.04 (br s, 1 H, CO_2H).

A mixture of acid chloride (4.269 g, 16.5 mmole), which was prepared by treatment of the above-described acid with PCl_3 at 65~70°C for 3.0 hours, plus *tert*-butanol (1.34 g, 1.1×16.5 mmole) and *N*, *N*-dimethylaniline (2.19 ml, 1.05×16.5 mmole) in ether (10 ml) was refluxed for 5.0 hours. After decomposition of the generated acid anhydride with aqueous pyridine, the reaction product was extracted with EtOAc. The organic solution was washed successively with 2 N HCl, H_2O, a diluted solution of $NaHCO_3$, and H_2O, and then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled in the presence of a trace of K_2CO_3 under reduced pressure and gave *tert*-butyl *p*-benzyloxyphenylacetate (2.606 g) as a semisolid, bp 155~157°C (0.7 mmHg): IR ($CHCl_3$) 1728 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 3.47 (s, 2 H, C$_6$H$_4$ CH_2CO$_2$R), 5.07 (s, 2 H, PhCH_2OC$_6$H$_4$), 6.8~7.4 (m, 4 H, phenylene H), 7.42 (s, 5 H, phenyl H).

To a solution of lithium diisopropylamide in tetrahydrofuran (11.0 ml), which was prepared from diisopropylamine (1.37 ml, 1.12×8.73 mmole) and *n*-BuLi (1.90 M, 5.08 ml, 1.11×8.73 mmole) at −5°C, was added a solution of the above-described ester (2.60 g, 8.73 mmole) in tetrahydrofuran (3.0 ml) at −10°C. The mixture was stirred for 15 minutes at −10°C and then carboxylated by addition of small pieces of dry ice. The tetrahydrofuran was evaporated *in vacuo* and the concentrate was partitioned between H_2O and ether. The aqueous layer was acidified with ice-cold 2 N HCl to pH 2.5 and extracted with ether. The ethereal solution was washed twice with saturated solution of NaCl, dried (Na_2SO_4), and concentrated *in vacuo*. The residue, crystallized from *n*-pentane, gave *tert*-butyl α-carboxy-*p*-benzyloxyphenylacetate (2.60 g), mp unclear: IR ($CHCl_3$) 3500~3000 (br, CO_2H), 1728 cm^{-1} (br, CO_2-H); NMR ($CDCl_3$) δ 1.42 (s, 9 H, *t*-Bu), 4.53 (s, 1 H, ArCH(CO_2H)CO_2R), 5.10 (s, 2 H, PhCH_2OC$_6$H$_4$), 6.90~7.37 (m, 4 H, phenylene H), 7.43 (s, 5 H, phenyl H), 10.22 (br s, 1 H, CO_2H).

A mixture of a solution of the benzyl ether in HOAc (50 ml) and 5% palladium on charcoal (1.0 g) was shaken under hydrogen. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue dissolved in dichloromethane was washed twice with H_2O and dried (Na_2SO_4), and then the solvent was removed *in vacuo*. Crystallization of the residue from *n*-pentane gave **37c** (473 mg), mp 109~110°C: IR ($CHCl_3$) 3570 (OH), 3500~3000 (br, CO_2H), 1728 cm^{-1} (CO_2H, ester); NMR ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu), 4.47 (s, 1 H, ArCH(CO_2H)CO_2R), 6.67~7.37 (m, 6 H, phenylene H, OH, CO_2H).

Synthesis of **39**: A stirred mixture of *p*-hydroxyphenylacetic acid (22.25 g, 146 mmole), acetone (400 ml), anhydrous K_2CO_3 (60.7 g, 3.0×146 mmole), NaI (52.64 g, 2.4×146 mmole), and *p*-methoxybenzyl chloride (55 g, 2.4×146 mmole) was heated at 55°C for 24 hours. The precipitate was filtered off and washed with acetone. The combined solution was concentrated to *ca.* 200 ml and partitioned between H_2O and EtOAc. The organic layer was washed twice with H_2O and dried (Na_2SO_4). The solution was concentrated *in vacuo*, giving a crystalline residue. Recrystallization of the residue from MeOH afforded *p*-methoxybenzyl *p*-(*p*-methoxybenzyloxy)phenylacetate (40.79 g, 71%), mp 88~90°C: NMR ($CDCl_3$) δ 3.53 (s, 2 H, C$_6$H$_4$CH_2CO$_2$R), 3.75 (s, 6 H, CH$_3$O), 4.88 (s, 2 H, C$_6$H$_4$CH_2OC$_6$H$_4$), 5.00 (s, 2 H, CO_2-CH_2C$_6$H$_4$), 6.8~7.4 (m, 12 H, phenylene H).

Carboxylation of the above-described ester (42.0 g) in a manner similar to that described for the preparation of **37c** yielded **39** (34.12 g), mp 124~126°C (crystallized from ether): IR (KBr) 3260 (br, CO_2H), 1740 (CO_2H), 1612 cm^{-1}; NMR (acetone-d_6) δ 3.78 (s, 6 H, OCH$_3$), 4.75 (s, 1 H, ArCH(CO_2H)CO_2R), 5.05 (s, 2 H, C$_6$H$_4$CH_2OC$_6$H$_4$), 5.15 (s, 2 H, CO_2CH_2C$_6$H$_4$), 6.8~7.5 (m, 12 H, phenylene H).

p-Hydroxyphenylmalonylation of **2e** with **37c** in Method D described in the section on phenylmalonylamino derivatives afforded **10e** (for spectral data, see Table 3).

p-Hydroxyphenylmalonylation of **3**: To a stirred suspension of **39** (1.37 g, 2.0×1.57 mmole) in dichloromethane (8.0 ml) was added triethylamine (330 μl, 1.5×1.57 mmole) and then oxalyl chloride (200 μl, 1.5×1.57 mmole) at −15°C. The resulting solution was stirred at that temperature for 45 minutes and gave a solution containing the corresponding acid chloride, which was transferred into a stirred solution of **3** (800 mg, 1.57 mmole) in dichloromethane (34.0 ml) cooled at −10°C. The resulting solution was stirred at −10 to −5°C for 30 minutes and then diluted with EtOAc. The solution was washed successively with 2 N HCl, H_2O, a 5% solution of $NaHCO_3$, and H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with benzene -

EtOAc (4: 1 ~ 1: 1) gave **25** as a foam (1.45 g, 99%). Spectral data of this compound are shown in Table 4.

Deprotection of **10e** by Method J_2 yielded **17e** (amorphous powder): IR (KBr) 3400 (NH, OH), 3040 ~ 2500 (br, CO_2H), 1787 (β-lactam), 1720 (CO_2H), 1670 (amide I), 1633, 1613, 1534 cm^{-1} (amide II); UV (MeOH) 273 nm (ε 7850); TLC Rf 0.42 (EtOAc - HOAc - H_2O, 5: 1: 1).

Deprotection of **25** by Method I produced **33**.

Deprotection of **25** by Method K described below, also produced **33**. To a stirred solution of **25** (1.20 g, 1.29 mmole) in dichloromethane (24 ml) was added anisole (2.4 ml, 6.0 × 1.29 mmole) and then a solution of aluminum trichloride (2.58 g, 5.0 × 1.29 mmole) in nitromethane (12 ml). The resulting mixture was stirred at 0°C for 15 minutes. The reaction mixture was poured into a stirred 5% solution of $NaHCO_3$ (100 ml) cooled in an ice-water bath. The resulting precipitates were filtered off and washed with ice-cold H_2O (2 × 50 ml). The combined filtrate and washings were shaken twice with dichloromethane. The aqueous layer was acidified with 2 N HCl to pH 1.2. The solution was charged on a column packed with high-porous styrene-divinylbenzene co-polymer (Mitsubishi-Diaion HP-20, 60 ml) and eluted with H_2O until aluminum ion could not be detected by the alizarin color test. Further elution with MeOH gave fractions of **33**. The combined fractions were concentrated *in vacuo* and extracted with EtOAc. The EtOAc solution was dried (Na_2SO_4) and concentrated *in vacuo*. Dilution of the concentrate with dichloromethane afforded **33** as an amorphous powder; $[\alpha]_D^{22.5}$ $-10.8 \pm 0.5°$ (*c* 1.015, MeOH); IR (Nujol) 3290 (OH, NH), 1780 (β-lactam), 1721 (CO_2H), *ca.* 1700 (sh, amide I), 1614, 1515 cm^{-1} (amide II); NMR (D_2O - $NaHCO_3$) δ 3.45, 3.52 (2 s, 3 H, OCH_3), 4.00, 4.02 (2 s, 3 H, NCH_3), 4.08 ~ 4.13 (m, 2 H, SCH_2), 4.45 (s, 1 H, $ArCH(CO_2H)CONH$–, gradually deuterated), 4.48 (s, 2 H, C_2-H), 5.12 (s, 1 H, C_6-H), 6.87, 7.28 (A_2B_2, 4 H, J=8 Hz, phenylene H); UV (MeOH) 276 nm (ε 10,200); TLC Rf 0.18 (EtOAc - HOAc - H_2O, 5: 1: 1).

Anal. Calcd. for $C_{20}H_{20}N_6O_9S$: C 46.15, H 3.87, N 16.15, S 6.16.
Found: C 45.99, H 3.89, N 16.07, S 6.21.

Preparation of **1**: To a solution of **33** (2.04 g, 4.0 mmole) in MeOH (20 ml) was added a methanolic solution of sodium 2-ethylhexanoate (2.0 M, 10 ml, 5.0 × 4.0 mmole). The resulting solution was stirred at 0°C for 10 minutes then diluted with EtOAc, giving precipitates. Their reprecipitation yielded **1** as an amorphous powder: IR (Nujol) 3370 (NH), 3230 (br, CO_2H), 1767 (β-lactam), 1675 (amide I), 1607 (carboxylate), 1513 cm^{-1} (amide II); NMR (acetone-d_6, external TMS) δ 3.91, 3.98 (2 s, 3 H, OCH_3), 4.44, 4.46 (2 s, 3 H, NCH_3), 4.55, 4.60, 4.63 (m, 2 H, SCH_2), 4.91, 4.95 (2 s, 2 H, C_2-H), 5.57, 5.58 (2 s, 1 H, C_6-H), 7.24, 7.39, 7.67, 7.82 (4 m, 4 H, phenylene H).

p-Acetoxyphenylmalonylamino Derivative **34**

Synthesis of **36d**: Diphenylmethyl *p*-hydroxyphenylacetate was carboxylated in a manner similar to that described for the synthesis of **37c** and gave diphenylmethyl α-carboxy-*p*-hydroxyphenylacetate, mp 153 ~ 154°C (crystallized from ether-petroleum ether): NMR ($CDCl_3$) δ 4.83 (s, 1 H, $ArCH(CO_2H)$-CO_2R), 6.88 (s, 1 H, $CHPh_2$), 6.82, 7.32 (A_2B_2, 4 H, J=8 Hz, phenylene H), 7.32 (s, 10 H, phenyl H), 9.42 (br s, 1 H, CO_2H).

To a stirred solution of the above-described half ester (500 mg, 1.37 mmole) and pyridine (377 μl, 3.4 × 1.38 mmole) in dichloromethane (10 ml), cooled at 0°C was added acetyl chloride (334 μl, 3.4 × 1.38 mmole). The resulting solution was stirred at 0°C for 30 minutes and at room temperature for 15 minutes and then diluted with EtOAc. The solution was washed with H_2O and dried (Na_2SO_4), and then the solvent was removed *in vacuo*. The residue dissolved in EtOAc was extracted with ice-cold 5% solution of $NaHCO_3$. The aqueous layer was acidified with 2 N HCl and extracted with EtOAc. The organic solution was washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*, giving **36d** as a foam (142 mg, 25.5%); NMR ($CDCl_3$) δ 2.25 (s, 3 H, AcO), 4.78 (s, 1 H, $ArCH(CO_2H)CO_2R$), 6.95 (s, 1 H, $CHPh_2$), 6.9 ~ 7.6 (m, 14 H, aromatic H), 10.33 (br s, 1 H, CO_2H).

p-Acetoxyphenylmalonylation of **3** with **36d** in Method H described in phenylmalonylamino derivatives yielded **26** (for spectral data, see Table 4).

Deprotection of **26** in Method I produced **34** (amorphous powder): $[\alpha]_D^{25.0}$ $-27.5 \pm 2.6°$ (*c* 0.258, MeOH); IR (KBr) 3430, 3300 sh (NH, H_2O), 1782 (β-lactam), 1728 (AcO, CO_2H), 1635, 1509 cm^{-1}

(amide II); NMR (D_2O-$NaHCO_3$) δ 2.33 (s, 3 H, OAc), 3.47, 3.53 (2 s, 3 H, OCH_3), 3.99, 4.02 (2 s, 3 H, NCH_3), *ca* 4.13 (br s, 2 H, SCH_2), 4.46 (br s, 2 H, C_2-H), 5.13 (s, 1 H, C_6-H), 7.12, 7.47 (A_2B_2, 4 H, J= 8 Hz, phenylene H); UV (MeOH) 275 nm (ε 9300); TLC Rf 0.30 (EtOAc - HOAc - H_2O, 3: 1: 1).

Anal. Calcd. for $C_{22}H_{22}N_6O_{10}S$: C 46.97, H 3.95, N 14.94, S 5.70.
Found: C 46.84, H 3.95, N 14.91, S 5.69.

p-Methoxyphenylmalonylamino Derivative **35**

Synthesis of **36e**: Carboxylation of diphenylmethyl *p*-methoxyphenylacetate in a manner similar to that described for preparation of **37c** gave **36e** (heavy syrup): NMR ($CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 4.75 (s, 1 H, $ArCH(CO_2H)CO_2R$), 6.97 (s, 1 H, $CHPh_2$), 6.88, 7.35 (A_2B_2, 4 H, J=8 Hz, phenylene H), 7.33 (br s, 10 H, phenyl H), 8.23 (s, 1 H, CO_2H).

p-Methoxyphenylmalonylation of **3** with **36e** in Method H afforded **27** (for spectral data, see Table 4).

Deprotection of **27** by Method I followed by treatment with sodium 2-ethylhexanoate gave the disodium salt of **35** (amorphous powder); $[\alpha]_D^{24.5}$ $-62.7\pm1.2°$ (c 0.828, MeOH); IR (KBr) 3420 (NH, H_2O), 1770 (β-lactam), 1675 (CO_2H, amide I), 1608, 1512 cm^{-1} (amide II); UV (MeOH) 273 nm (ε 10,800); TLC Rf 0.30 (EtOAc - HOAc - H_2O, 5: 1: 1).

In Vitro Antibacterial Activity

Antibacterial activity was determined by the agar dilution method using sensitivity test agar (Eiken, Japan). An overnight culture of bacteria in Tryptosoy broth (Eiken, Japan) was diluted to about 10^6 cells/ml with the same broth and inoculated with an inoculating device onto agar containing serial two-fold dilutions of an antibiotic. Organisms were incubated at 37°C for 18~20 hours. The minimum inhibitory concentration (MIC) of an antibiotic was defined as the lowest concentration that inhibited visible growth.

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