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Synthesis of Cephalosporins with Substituted Thiadiazoles directly attached to the C_3-Position. I. Synthesis of 3-(5-Substituted-1,3,4-thiadiazol-2-yl)ceph-3-em Derivatives⁽¹⁾

TOHRU SUGAWARA, HIROTOMO MASUYA, TAISUKE MATSUO, and TAKUICHI MIKI

Central Research Division, Takeda Chemical Industries, Ltd.⁽²⁾

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3-(5-Substituted-1,3,4-thiadiazol-2-yl)ceph-3-em derivatives were prepared by oxidative ring closure with 2,3-dichloro-5,6-dicyanobenzoquinone directly or after acetylation of 3-thiocarbonylhydrazones, which were obtained from the reaction of 3-formylceph-3-ems and thiocarbonylhydrazines. The antibacterial activity of 7-thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em derivatives (**4**) against gram-positive organisms was similar to that of cephalothin (CET), while the activity against gram-negative organisms was superior to that of CET. A similar oxidative ring closure reaction with other thiocarbonylhydrazones is also discussed.

Keywords——thiocarbonylhydrazines; thiocarbonylhydrazones; 1,3,4-thiadiazole ring; DDQ; oxidative ring closure; 3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-ems; antibacterial activity

During the past decade, considerable improvements have been made in the usefulness of cephalosporins by synthetic variation of the acyl side chain attached to the amino group at the C_7-position and by replacement of the acetoxyl group at the $C_{3'}$-position with different nucleophiles.⁽³⁾ Recently, potent new cephalosporins with a substituent such as a methoxyl or halogeno group directly attached to the C_3-position have been reported.⁽⁴⁾ However, there are few reports concerning the introduction of a heterocyclic ring directly into the C_3-position: the total synthesis of 3-phenyl- and 3-(4-thiazolyl)ceph-3-em derivatives was reported by Firestone *et al.*,⁽⁵⁾ and cycloadditions of cephalosporin 3-N-methylnitrones and 3-diazomethyl derivatives with acetylenic compounds to give C_3-heterocyclic substituted cephalosporins were reported by Spry⁽⁶⁾ and Christensen,⁽⁷⁾ respectively.

We have previously reported a new and efficient synthesis of cephalosporin derivatives bearing a thiadiazole ring at the C_3-position by application of the oxidative ring closure reaction of thiocarbonylhydrazones prepared from 3-formylceph-3-em derivatives (Chart 1).⁽¹⁾ This report describes these reactions in detail.

Reaction of 3-formylceph-3-em benzhydryl ester (**1**)⁽⁸⁾ with thiocarbonylhydrazines (1.2

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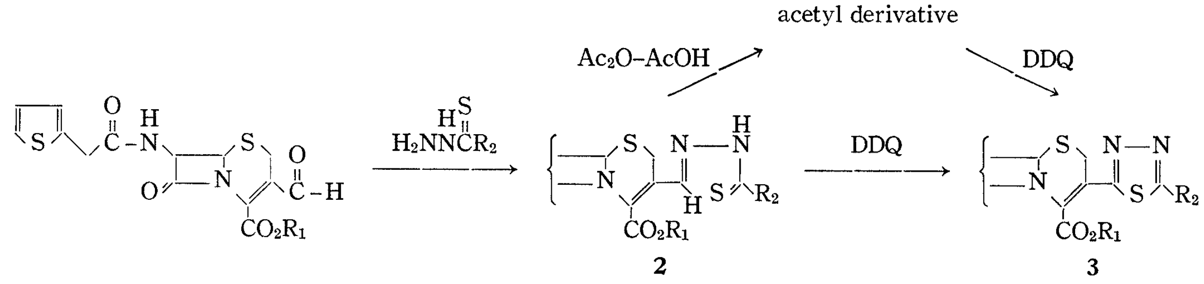
1) T. Sugawara, H. Masuya, T. Matsuo, and T. Miki, *Chem. Pharm. Bull.*, **27**, 2544 (1979).
2) Location: *17-85, Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) E.H. Flynn (ed.), "Cephalosporins and Penicillins," Academic Press, New York and London, Chapters 3 and 4, 1972.
4) J. Elks (ed.), "Recent Advances in the Chemistry of β-Lactam Antibiotics," The Chemical Society, London, Chapter 19, 1977.
5) R.A. Firestone, N.S. Maciejewicz, and B.G. Christensen, *J. Org. Chem.*, **39**, 3384 (1974).
6) D.O. Spry, *J. Org. Chem.*, **40**, 2411 (1975).
7) J.L. Fahey, R.A. Firestone, and B.G. Christensen, *J. Med. Chem.*, **19**, 562 (1976).
8) 3-Formylceph-3-em benzhydryl ester (**1**) was prepared by treatment of the corresponding cephalosporin 3'-bromolactone derivative with DMSO, followed by esterification with diphenyldiazomethane. *Cf.* T. Sugawara, H. Masuya, T. Matsuo, Y. Kawano, and Y. Kuwada, *Chem. Pharm. Bull.*, **28**, 1339 (1980). Compound **1** was also prepared by oxidation of the corresponding 3-hydroxymethyl cephalosporin derivative with chromium trioxide-sulfuric acid followed by treatment with diphenyldiazomethane. Cf. Takeda Chem. Ind., Ltd., Japan. Patent Provisional Publication 49-80097 (1974).



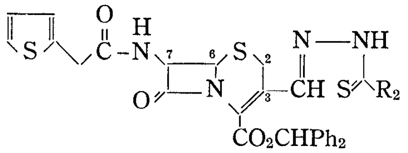
1: R_1=–CHPh$_2$

2a: R_2=–NMe$_2$
2b: R_2=–N O
2c: R_2=–Me
2d: R_2=–Ph
2e: R_2=–NH$_2$
2f: R_2=–NHMe

3a: R_2=–NMe$_2$
3b: R_2=–N O
3c: R_2=–Me
3d: R_2=–Ph
3e: R_2=–NHAc
3f: R_2=–N$<^{Me}_{Ac}$
3g: R_2=–NHMe

Chart 1

TABLE I. Yields and Spectral Data for Benzhydryl 7-Thienylacetamido-3-(4-substituted-thiocarbonylhydrazonomethyl)ceph-3-em-4-carboxylates (2)



R_2	Yield (%)	IR ν_{max}^{KBr} cm^{-1}	UV λ_{max}^{EtOH} nm (ε)	NMR (DMSO-d_6, ppm) C_2–H[a]	C_6–H[b]	C_7–H	C_3–CH=	CONH	R_2
–NMe$_2$	91	1782, 1720, 1672	343 (23700)	3.65, 4.17	5.23	5.70[c]	8.40 (s)	9.17[e]	3.21 (s)
–N O	84	1783, 1720, 1680	347 (25200)	—[g]	5.20	5.78[d]	8.33 (s)	9.19[f]	3.4—4.0 (m)
–Me	89	1780, 1718, 1655	363 (32800)	3.60, 4.15	5.22	5.82[c]	8.40 (s)	9.20[e]	2.54 (s)
–Ph	97	1790, 1720, 1670	370 (13800)	3.63, 3.87	5.14	5.83[c]	—[g]	9.23[e]	7.0—7.7 (m)
–NH$_2$	93	1780, 1720, 1663	350 (27800)	3.53, 4.52	5.19	5.79[d]	8.23 (s)	9.17[f]	3.3 (br. s)
–NHMe	81	1785, 1720, 1678	350 (31100)	3.57, 4.53	5.21	5.79[d]	8.24 (s)	9.17[f]	2.98(d)[h] 8.45(q)[h]

a) ABq, J=18 Hz. *b*) d, J=5 Hz. *c*) q, J=5 Hz and 9 Hz. *d*) q, J=5 Hz and 8 Hz. *e*) d, J=9 Hz. *f*) d, J=8 Hz. *g*) Overlapped with other protons. *h*) J=5 Hz.

mol eq) in dimethyl sulfoxide (DMSO) at room temperature gave the corresponding thiocarbonylhydrazone derivatives (**2**). Yields and spectral data for **2** are given in Table I.

Substituted-thiocarbonylhydrazines (R_2=–NMe$_2$, –N O, –Ph, –NHMe) were synthesized according to the procedure of McFlhinney.[9] Thioacetylhydrazine (R_2=–Me, mp

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[9] R.S. McFlhinney, *J. Chem. Soc.* (*C*), **1966**, 950.

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73—75°) was synthesized by the reaction of methyl dithioacetate[10] and hydrazine hydrate in ethanol at −78°. In this reaction, the different products were obtained by changing the reaction temperature as shown in Chart 2. The reaction of methyl dithioacetate and hydrazine hydrate in ethanol at 50° gave 4-amino-3,5-dimethyl-1,2,4-triazole,[11] which was reacted with cinnamaldehyde to yield 4-cinnamylideneamino-3,5-dimethyl-1,2,4-triazole.[12] On the other hand, the same reaction at 0° gave N-thioacetylaminoacetamidrazone, which was transformed into cinnamaldehyde azine.[13]

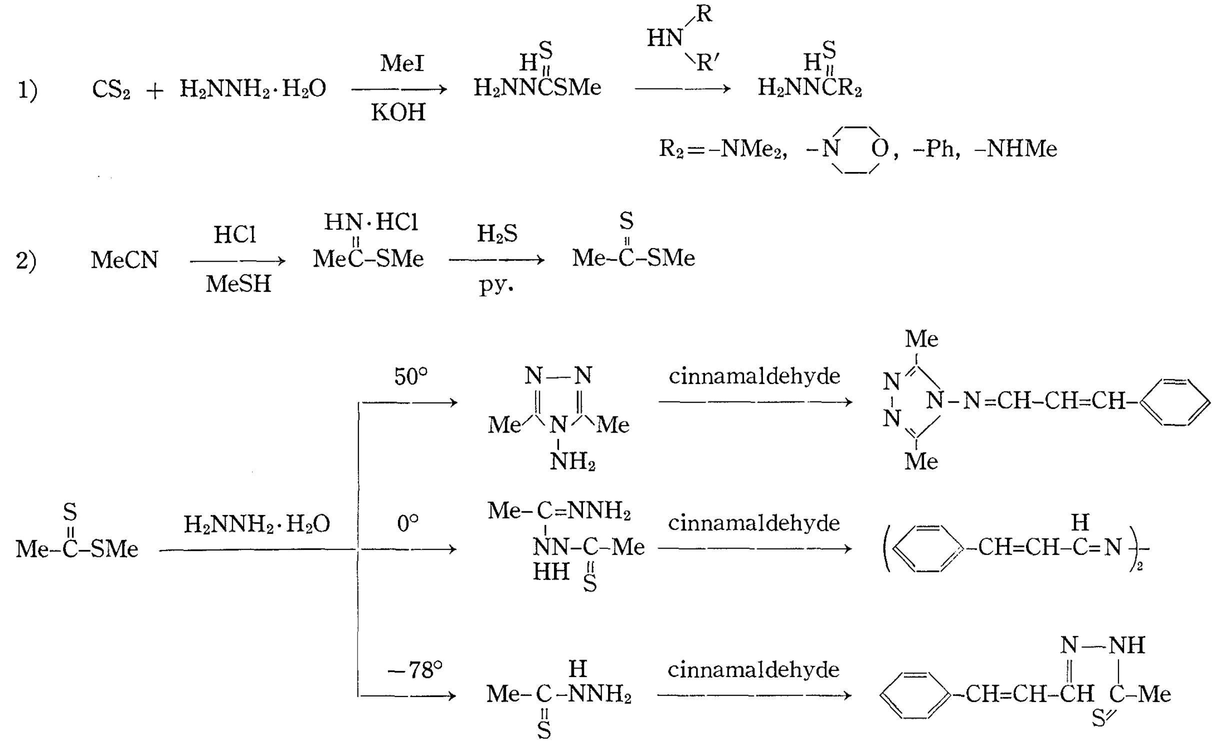

Chart 2

With cephalosporins, conventional reagents for accomplishing the transformation of thiocarbonylhydrazones (2) into the corresponding 1,3,4-thiadiazole derivatives (3), including ferric chloride ($FeCl_3$) in methanol at high temperature or peroxides,[14] often lead to side reactions such as β-lactam ring cleavage or other oxidations because of the strong reaction conditions employed.

It has been found that thiocarbonylhydrazones (**2a**—**d**) are readily cyclized to the corresponding thiadiazole derivatives (**3a**—**d**) by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane in good yields. Yields and spectral data for **3** are given in Table II. This method is mild enough to be used for cephalosporins containing sensitive functional groups and can also be successfully applied to other compounds. Some examples illustrating this reaction for benzaldehyde, α-picolinaldehyde and cinnamaldehyde thiocarbonylhydrazones are listed in Table III.

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10) R. Mayer, S. Scheithauer, and D. Kunz, *Chem. Ber.*, **99**, 1393 (1966).

11) Bülow reported that the reaction of acetonitrile and hydrazine hydrate at 180° gave 4-amino-3,5-dimethyl-1,2,4-triazole. *cf.* C. Bülow, *Chem. Ber.*, 39, 2618 (1906).

12) S. Ruhemann, *J. Chem. Soc.*, **89**, 1268 (1906).

13) Th. Curtius and R. Jay, *J. Prakt. Chem.*, [2], 39, 27 (1889).

14) *a*) S.C. De and S.K. Roy-chondhury, *J. Indian Chem. Soc.*, **5**, 269 (1928); *b*) P. Hemmerich, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **41**, 2058 (1958).

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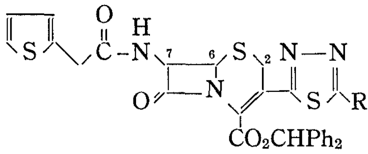
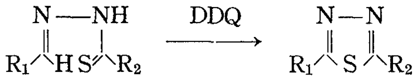
Table II. Yields and Spectral Data for Benzhydryl 7-Thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (3)

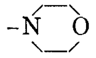
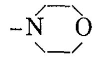


R_2	Yield (%)	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}	UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε)	NMR (DMSO-d_6, ppm) C_2-H[a]	C_6-H[b]	C_7-H[c]	CONH[d]	R_2
$-\mathrm{NMe}_2$	90	1785, 1727, 1663	343 (13100)	3.78, 4.05	5.23	5.81	9.21	2.89 (s)
	91	1778, 1720, 1641	338 (13700)	3.79, 4.03	5.23	5.83	9.23	3.2—3.9 (m)
-Me	93	1785, 1730, 1678	307 (11900)	3.80, 4.04	5.26	5.84	9.22	2.50 (s)
-Ph	90	1790, 1730, 1670	325 (18200)	3.97, 4.20	5.35	5.92	9.28	7.0—7.9 (m)
$-\mathrm{N}{<}^{\mathrm{H}}_{\mathrm{Ac}}$	71—78	1790, 1730, 1695, 1650	315 (13200)	3.82, 4.06	5.25	5.71	9.22	2.16 (s)
$-\mathrm{N}{<}^{\mathrm{Me}}_{\mathrm{Ac}}$	81[e] {72	1782, 1738, 1668	315 (12500)	3.86, 4.08	5.28	5.88	9.23	2.39 (s) 3.54 (s)
$-\mathrm{N}{<}^{\mathrm{Me}}_{\mathrm{H}}$	9	1783, 1725, 1663	333 (11600)	3.83, 4.03	5.26	5.84	9.20	2.79 (s)

a) ABq, J=18 Hz. b) d, J=5 Hz. c) q, J=5 Hz and 9 Hz. d) d, J=9 Hz.
e) Total yield without isolation of acetates.

Table III.



R_1	R_2	Yield (%)[a]	Product R_2	mp (°C)
-Ph	$-\mathrm{NMe}_2$	95	$-\mathrm{NMe}_2$	94—95 (pale yellow prisms)
-Ph	$-\mathrm{NH}_2$[b]	80	-NHAc	289—290 (colorless needles)[c]
2-Pyridyl	$-\mathrm{NH}_2$[b]	83	-NHAc	>300 (colorless needles)[d]
Stylyl	-NHMe	77	-NMeAc	161 (colorless prisms)
Stylyl		83		150—151 (colorless prisms)
Stylyl	$-\mathrm{NMe}_2$	95	$-\mathrm{NMe}_2$	133—135 (colorless flakes)
Stylyl	-SMe[b]	81	-SMe	95 (colorless needles)
Stylyl	$-\mathrm{NH}_2$[b]	95	-NHAc	307—309 (colorless flakes)
Stylyl	-Me	92	-Me	160—161 (colorless flakes)

a) Isolated after chromatography.
b) Cyclized to the corresponding thiadiazole derivatives after acetylation.
c) Lit., 297—299°.[15]
d) Lit., 320°.[14b]

In the cases of **2e** and **2f**, however, the thiadiazole derivatives were obtained in low yields by direct treatment with DDQ. It was found that the corresponding thiadiazole derivatives (**3e**—**g**) could be successfully obtained in high yields by treatment with DDQ after acetylation of the compounds (**2e** and **2f**) with $\mathrm{Ac_2O}$-AcOH.

Removal of the benzhydryl protecting group of **3** gave the corresponding free acids (**4**). The sodium salts of **4** were purified by chromatography on Amberlite XAD-2 after treatment

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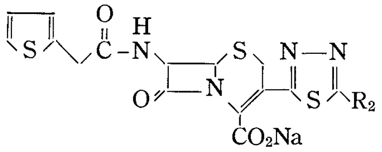
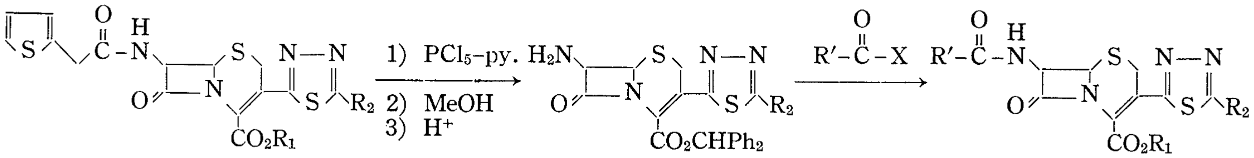
[15] S. Yoshida and M. Asai, *J. Pharm. Soc. Japan*, **74**, 946 (1954).

Table IV. Antibacterial Activity (*in Vitro*) of Sodium 7-Thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylates (**4e** and **4g**)



Organisms	$R_2=-N\langle^{H}_{Ac}$ (**4e**)	$R_2=-N\langle^{Me}_{Ac}$ (**4g**)	CET
S. aureus FDA 209p	≤ 0.2	≤ 0.2	≤ 0.2
E. coli NIHJ JC-2	12.5	6.25	12.5
P. aeruginosa pd 1	>100	>100	>100
S. marcescens IFO 12648	>100	>100	>100
P. vulgaris IFO 3988	0.78	3.13	3.13
P. mirabilis GN 4359	1.56	3.13	3.13
P. rettgeri GN 4733	3.13	50	>100
C. freundii GN 99	12.5	12.5	100



3: $R_1=-CHPh_2$
4: $R_1=-H, -Na$

5a: $R_2=-NMe_2$
5c: $R_2=-Me$
5d: $R_2=-Ph$
5e: $R_2=-NHAc$
5f: $R_2=-N\langle^{Ac}_{Me}$

6: $R_1=-CHPh_2$
7: $R_1=-H, -Na$

Chart 3

with an aqueous solution of sodium bicarbonate (pH~7). The antibacterial activity of these compounds (**4**) against gram-positive organisms was similar to that of cephalothin (CET), but their activity against gram-negative organisms was euperior to that of CET. Some antibacterial activities of the sodium salts of **4e** and **4g** are shown in Table IV.

As shown in Chart 3, cleavage of the thienylacetamido side chain by the imino-ether method[16] gave the corresponding 7-amino derivatives (**5**), which were transformed into various 7-acyl derivatives (**6**).

7-α-Substituted-phenylacetamido- and 7-[2-(2-aminothiazol-4-yl)acetamido]-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em derivatives (**6**) were synthesized by the usual coupling methods, such as the acid chloride, dicyclohexylcarbodiimide (DCC) and mixed anhydride methods. The 7-[2-(2-aminothiazol-4-yl)]acetamido side chain was synthesized according to the procedure of Numata *et al.*[17] Removal of the benzhydryl protecting group from **6** gave the corresponding free acids (**7**). Infrared (IR) and nuclear magnetic resonance (NMR) data for **7** are shown in Tables V and VI.[18]

The process mentioned above was also successfully applied to the C_4-carboxylic acid derivative. The 3-formylceph-3-em-4-carboxylic acid derivative (**8**), which was easily obtained

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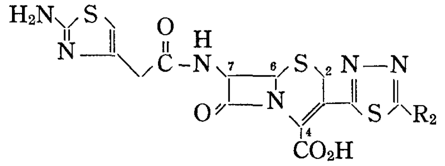
[16] Chapter 2 in reference 3).

[17] M. Numata, I. Minamida, M. Yamaoka, M. Shiraishi, T. Miyawaki, H. Akimoto, K. Naito, and M. Kida, *J. Antibiotics*, 31, 1262 (1978).

[18] Among them, 7-[2-(2-aminothiazol-4-yl)]acetamidocephalosporin derivatives showed strong antibacterial activity against gram-negative organisms. The antibacterial activities of these compounds will be reported elsewhere.

from desacetylcephalosporin C (DCPC),[19] was treated with thiocarbonylhydrazine derivatives to yield the corresponding thiocarbonylhydrazones (**9**) in about 80% yields. The compounds (**10**) were prepared by the reaction of **9** with DDQ, and 7-amino derivatives (**11**) were also prepared by the imino-ether method (Chart 4).

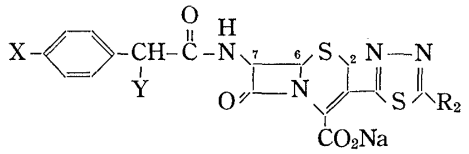
Table V. IR and NMR Spectral Data for 7-(2-Aminothiazolyl)-acetamido Cephalosporin Derivatives (7)



7	R_2	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, ppm)				
			C_2–H[b]	C_6–H[c]	C_7–H[d]	CONH[f]	R_2
7a	$-NMe_2$	1765, 1655, 1605	3.77, 4.05	5.18	5.74	8.93	3.07 (s)
7b[a]	–Me	1770, 1670, 1620	3.94, 4.18	5.38	5.86[e]	—	2.85 (s)
7c	–Ph	1785, 1765, 1620	3.94, 4.18	5.30	5.86	9.00	7.4—8.1 (m)
7d	$-N\langle^{H}_{Ac}$	1770, 1670, 1620	3.86, 4.17	5.29	5.84	9.14	2.22 (s)
7e[a]	$-N\langle^{Me}_{Ac}$	1765, 1685, 1610	3.91, 4.17	5.38	5.86[e]	—	2.55 (s) 3.79 (s)

a) NMR spectra were recorded in D_2O ($C_4=CO_2Na$).
b) ABq, *J*=18 Hz. *c*) d, *J*=5 Hz. *d*) q, *J*=5 Hz and 9 Hz. *e*) d, *J*=5 Hz. *f*) d, *J*=9 Hz.

Table VI. IR and NMR Spectral Data for 7-α-Substituted-phenylacetamido Cephalosporin Derivatives (7)



7	X	Y	R_2	IR ν_{max}^{KBr} cm^{-1}	NMR (D_2O, ppm)			
					C_2–H[b]	C_6–H[c]	C_7–H[d]	R_2
7f	–OH	$-NH_2$	$-NMe_2$	1770, 1685[a], 1610	3.60, 3.96	4.90	5.62[e]	3.02[a] (s)
7g	–H	$-NH_2$	$-NMe_2$	1762, 1685, 1610	3.70 (br. s)	5.16	5.80	3.30 (s)
7h	–H	$-NH_2$	–Me	1770, 1690, 1600	3.68, 3.91	5.20	5.80	2.72 (s)
7i	–H	$-NH_2$	–NHAc	1770, 1680, 1600	3.82, 4.04	5.32	5.90	2.38 (s)
7j	–H	–OH	–Me	1780, 1670, 1605	3.81, 4.03	5.20	5.85[e]	2.70[a] (s)
7k	–H	–OH	$-NMe_2$	1773, 1660, 1620	3.77, 4.01	5.18	5.75[e]	3.07 (s)
7l	–H	$-CO_2H$	$-NMe_2$	1764, 1660, 1603	3.71, 4.03	5.22	5.78	3.11 (s)
7m	–H	$-SO_3H$	$-NMe_2$	1762, 1672, 1608	3.63, 3.88	5.17	5.76	3.10 (s)

a) NMR spectra were recorded in DMSO-d_6 and IR spectra in nujol.
b) ABq, *J*=18 Hz. *c*) d, *J*=5 Hz. *d*) d, *J*=5 Hz. *e*) q, *J*=5 Hz and 9 Hz.

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19) Y. Fujisawa, H. Shirafuji, M. Kida, K. Nara, M. Yoneda, and T. Kanazaki, *Nature* (*London*) *New Biol.*, **246**, 154 (1973).

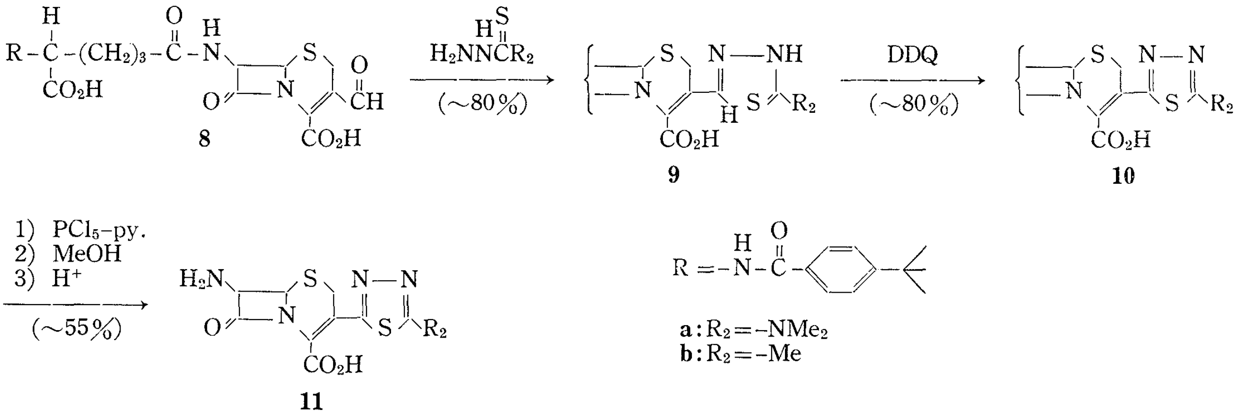

Chart 4

Recent studies[20] indicate that the antibacterial activity is closely correlated with instability of the β-lactam ring, and is enhanced by the introduction of an electron-withdrawing group into the C_3-position. The pK_a value of **4c** was 1.34±0.15, which was more acidic than that of usual cephalosporins (~2.1) or penicillins (~2.8). This indicates that the thiadiazole ring at the C_3-position acts as an electron-withdrawing group.

Experimental

All melting points were taken with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on Hitachi EPI-G2 and EPI-S2 spectrophotometers and mass spectra were obtained with a Hitachi RMU-6D or RMS-4 instrument. Ultraviolet (UV) spectra were measured on a Hitachi EPS-3T spectrophotometer. NMR spectra were recorded with a Varian T-60, HA-100 or XL-100-12 spectrophotometer using tetramethylsilane (TMS) as an internal (in DMSO-d_6) or external (in D_2O) standard. Abbreviations are as follows: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. For silica gel chromatography, Kieselgel G (0.05—0.2 mm, Merck) was used.

Benzhydryl 3-Formyl-7-thienylacetamidoceph-3-em-4-carboxylate (1)——Diphenyldiazomethane (2.3 g) was added to a solution of 3-formyl-7-thienylacetamidoceph-3-em-4-carboxylic acid (3.5 g) in tetrahydrofuran (THF, 100 ml). After stirring for 30 min at room temperature, the solvent was removed and the residue was thoroughly washed with pet. ether to afford **1** (4.9 g, 95%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1793, 1733, 1704, 1673. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 285 (19400). NMR (DMSO-d_6, ppm): 3.41 and 3.91 (2H, ABq, J=18 Hz, C_2-H), 3.74 (2H, s, $-CH_2-$), 5.25 (1H, d, J=5 Hz, C_6-H), 5.90 (1H, q, J=5 Hz and 8 Hz, C_7-H), 7.03 (1H, s, $-CHPh_2$), 7.2—7.5 (m, aromatic H), 9.22 (1H, d, J=8 Hz, $CON\underline{H}$), 9.44 (1H, s, $-C\underline{H}O$).

Benzhydryl 3-(4,4-Dimethylaminothiocarbonylhydrazonomethyl)-7-thienylacetamidoceph-3-em-4-carboxylate (2a)——A mixture of **1** (5 g) and 4,4-dimethylthiosemicarbazide (1.5 g) in DMSO (10 ml) was stirred at room temperature for 30 min. The reaction mixture was diluted with water and extracted with ethyl acetate (AcOEt). The AcOEt layer was washed with water and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on silica gel [elution with benzene–AcOEt (2: 1)] to give **2a** (5.45 g, 91%). Recrystallization from benzene–AcOEt gave pale yellow needles, mp 175—176°. *Anal.* Calcd for $C_{30}H_{29}N_5O_4S_2$: C, 61.31; H, 4.97; N, 11.92. Found: C, 60.99; H, 5.24; N, 12.03.

Benzhydryl 3-(4-Morpholinothiocarbonylhydrazonomethyl)-7-thienylacetamidoceph-3-em-4-carboxylate (2b)——A mixture of **1** (1.04 g) and morpholinothiocarbonylhydrazine (0.354 g) in DMSO (4 ml) was stirred at room temperature for 2 hr. After work-up as described for **2a**, the residue was chromatographed on silica gel [elution with AcOEt–n-hexane (5: 3)] to give **2b** (1.12 g, 84%).

Benzhydryl 7-Thienylacetamido-3-thioacetylhydrazonomethylceph-3-em-4-carboxylate (2c)——A mixture of **1** (11 g) and thioacetylhydrazine (2.1 g) in DMSO (30 ml) was stirred at room temperature for 3 hr. The reaction mixture was diluted with ice-water, and extracted with AcOEt. The AcOEt layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave **2c** (11.2 g, 89%) as pale yellow needles, mp 199—201° (dec.).

Benzhydryl 7-Thienylacetamido-3-thiobenzoylhydrazonomethylceph-3-em-4-carboxylate (2d)——A mixture of **1** (3 g) and thiobenzoylhydrazine (0.88 g) in DMSO (20 ml) was stirred for 4 hr at room temperature. After work-up as described above, **2d** (3.65 g, 97%) was obtained.

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20) J.M. Indelicato, T.T. Norvilas, R.R. Pfeiffer, W.T. Wheeler, and W.L. Wilham, *J. Med. Chem.*, **17**, 523 (1974); D.B. Boyd, R.B. Hermann, D.E. Presti, and M.M. Marsh, *J. Med. Chem.*, **18**, 986 (1975).

Benzhydryl 7-Thienylacetamido-3-(4-aminothiocarbonylhydrazonomethyl)ceph-3-em-4-carboxylate (2e)——A mixture of benzhydryl 3-formyl-7-thienylacetamidoceph-3-em-4-carboxylate (**1**, 2.4 g) and thiosemicarbazide (0.47 g) in DMSO (6 ml) was stirred for 1 hr at 45°. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water and then dried (Na_2SO_4). Evaporation of the solvent gave **2e** (2.7 g, 93%).

Benzhydryl 3-(4-Methylaminothiocarbonylhydrazonomethyl)-7-thienylacetamidoceph-3-em-4-carboxylate (2f)——A mixture of **1** (6.5 g) and 4-methylthiosemicarbazide (1.4 g) in DMSO (20 ml) was stirred at room temperature for 30 min. After work-up as described above, purification was carried out by column chromatography on silica gel [elution with benzene–AcOEt (3: 1)] to give **2f** (6.2 g, 81%).

7-(4-*p*-*tert*-Butylbenzenecarboxamido-4-carboxy-butanecarboxamido)-3-(4,4-dimethylaminothiocarbonylhydrazonomethyl)ceph-3-em-4-carboxylic Acid (9a) and 7-(4-*p*-*tert*-Butylbenzenecarboxamido-4-carboxybutanecarboxamido)-3-thioacetylhydrazonomethylceph-3-em-4-carboxylic Acid (9c)——These compounds (**9a** and **9c**) were also prepared in the manner described above.

9a; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1780, 1720, 1640, 1540. NMR (DMSO-d_6, ppm): 1.30 (9H, s, *tert*-Bu), 3.22 (6H, s, NMe_2), 5.12 (1H, d, $J=5$ Hz, C_6–H), 5.68 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 7.40 and 7.80 (4H, each d, $J=8$ Hz, aromatic H), 8.38 (1H, s, C_3–C$\underline{H}$=N–), 8.40 (1H, d, $J=9$ Hz, –N$\underline{H}$CO–), 8.86 (1H, d, $J=9$ Hz, CON$\underline{H}$).

9c; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1780, 1720, 1640, 1540. NMR (DMSO-d_6, ppm): 1.30 (9H, s, *tert*-Bu), 2.54 (3H, s, Me), 3.52 and 4.04 (2H, ABq, $J=18$ Hz, C_2–H), 5.16 (1H, d, $J=5$ Hz, C_6–H), 5.75 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 7.40 and 7.80 (4H, each d, $J=8$ Hz, aromatic H), 8.40 (1H, d, $J=9$ Hz, –N$\underline{H}$CO–), 8.42 (1H, s, C_3–C$\underline{H}$=N–), 8.90 (1H, d, $J=9$ Hz, CON$\underline{H}$).

Benzhydryl 3-(5-Dimethylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3a)——1) DDQ (2.75 g) was added to a solution of 4,4-dimethylaminothiocarbonylhydrazone (**2a**, 6.8 g) in dry dioxane (30 ml). The reaction mixture was stirred at room temperature for 10 min. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel [elution with benzene–AcOEt (3: 1)] to give **3a** (6.1 g, 90%).

2) A mixture of 4,4-dimethylaminothiocarbonylhydrazone (**2a**, 1.0 g) and chloranil (0.7 g) in dioxane (5 ml) was stirred at room temperature overnight. After work-up as described above, **3a** (0.73 g) was obtained as pale yellow plates, mp 190—191° (benzene–AcOEt). *Anal.* Calcd for $C_{30}H_{28}N_5O_4S_2$: C, 61.42; H, 4.81; N, 11.94; S, 10.93. Found: C, 59.98; H, 4.87; N, 11.59; S, 11.02.

Benzhydryl 3-(5-Morpholino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3b)——A mixture of morpholinothiocarbonylhydrazone (**2b**, 0.43 g) and DDQ (0.162 g) in dry dioxane (5 ml) was treated in the manner described above. Purification was carried out by chromatography on silica gel [elution with AcOEt–*n*-hexane (5: 3)] to give **3b** (0.39 g, 91%). Recrystallization from *n*-hexane–AcOEt gave colorless needles, mp 209—211°. *Anal.* Calcd for $C_{32}H_{29}N_5O_5S_3$: C, 58.25; H, 4.43; N, 10.61; S, 14.58. Found: C, 57.85; H, 4.13; N, 10.39; S, 14.56.

Benzhydryl 3-(5-Methyl-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3c)——A mixture of thioacetylhydrazone (**2c**, 7.89 g) and DDQ (3.2 g) in dry dioxane (70 ml) was stirred at 45° for 5 hr. After work-up as described above, purification was carried out by silica gel column chromatography [elution with AcOEt–benzene (1: 1)] to give **3c** (7.3 g, 93%). Recrystallization from *n*-hexane–AcOEt gave colorless needles, mp 192—194° (dec.). *Anal.* Calcd for $C_{29}H_{24}N_4O_4S_3$: C, 59.16; H, 4.11; N, 9.52; S, 16.34. Found: C, 58.94; H, 3.94; N, 9.64; S, 16.34.

Benzhydryl 3-(5-Phenyl-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3d)——A mixture of thiobenzoylhydrazone (**2d**, 1.0 g) and DDQ (0.28 g) in dry dioxane (10 ml) was stirred at room temperature for 30 min. After work-up as described above, the residue was recrystallized from AcOEt to give **3d** (0.9 g, 90%) as pale yellow needles, mp 226—228°.

Benzhydryl 3-(5-Acetylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3e)——A mixture of diacetate derivatives (2 g, roughly 1: 1 mixture of epimers prepared by the reaction of **2e** with Ac_2O–AcOH) and DDQ (1 g) in dry dioxane (30 ml) was stirred at 45° for 18 hr. After removing insoluble material by filtration, the filtrate was condensed under reduced pressure. The residue was purified by silica gel column chromatography [elution with CH_2Cl_2–AcOEt (3: 1)] to give **3e** (1.4 g, 75%). *Anal.* Calcd for $C_{30}H_{25}N_5O_5S_3$: C, 57.04; H, 3.99; N, 11.09; S, 15.23. Found: C, 56.80; H, 3.70; N, 10.83; S, 15.10.

Benzhydryl 3-(5-Acetylmethylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3f) and Benzhydryl 3-(5-Methylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (3g)——A mixture of ξ-acetyl-4-methylthiosemicarbazone derivatives (1.0 g, a mixture of monoacetate and diacetate prepared from **2f** and Ac_2O–AcOH) and DDQ (0.53 g) in dry dioxane (10 ml) was stirred at 45° for 12 hr. After work-up as described above, purification was carried out by silica gel column chromatography [elution with AcOEt–CH_2Cl_2 (1: 2)] to give **3f** (0.74 g, 72%) as colorless plates (mp 205—208°) and **9g** (0.09 g, 9%) as colorless prisms (mp 130—133°).

7-(4-*p*-*tert*-Butylbenzenecarboxamido-4-carboxy-butanecarboxamido)-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (10a) and 7-(4-*p*-*tert*-Butylbenzenecarboxamido-4-carboxy-butanecarboxamido)-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (10c)——Compounds **10a** and **10c** were also prepared in the manner described above.

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10a; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1780, 1720. NMR (DMSO-d_6, ppm): 1.28 (9H, s, *tert*-Bu), 3.08 (6H, s, NMe_2), 5.06 (1H, d, $J=5$ Hz, C_6–H), 5.80 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 7.38 and 7.80 (4H, each d, $J=8$ Hz, aromatic H).

10c; IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}; 1795, 1720, 1650, 1540. NMR (DMSO-d_6, ppm): 1.30 (9H, s, *tert*-Bu), 2.78 (3H, s, Me), 5.20 (1H, d, $J=5$ Hz, C_6–H), 5.78 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 7.42 and 7.80 (4H. each d, $J=8$ Hz, aromatic H), 8.90 (1H, d, $J=9$ Hz, CON$\underline{H}$).

Reaction of Methyl Dithioacetate with Hydrazine Hydrate——1) Methyl dithioacetate (21 g) was added dropwise to a solution of hydrazine hydrate (11 g) in ethanol (50 ml) at 50°. After evaporation of the solvent, the resulting crystals were collected and recrystallized from EtOH to give 10 g of 4-amino-3,5-dimethyl-1,2,4-triazole, mp 202—204°. *Anal.* Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 42.79; H, 7.16; N, 50.15. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3150, 1650, 1540, 1425. NMR (DMSO-d_6, ppm): 2.26 (6H, s, Me), 5.74 (2H, br. s, -N$\underline{H}_2$).

Cinnamaldehyde (4.4 g) and conc. HCl (2 drops) were added to a solution of 4-amino-3,5-dimethyl-1,2,4-triazole (3 g) in ethanol (20 ml). After stirring the reaction mixture for 1 hr at room temperature, the separated crystals were collected and recrystallized from ethanol to give cinnamylideneamino-3,5-dimethyl-1,2,4-triazole (5 g), mp 253—254° (colorless needles, lit.[12] mp 243°). *Anal.* Calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.08; H, 6.04; N, 25.00. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1625, 1415, 1018.

2) Methyl dithioacetate (5.3 g) was added dropwise to a solution of hydrazine hydrate (2.5 g) in ethanol (20 ml) at 0°. After stirring for 30 min, the separated crystals were collected by filtration and washed with ether to give N-thioacetylaminoacetamidrazone (5 g) as colorless prisms, mp 132—134° (dec.). *Anal.* Calcd for $C_4H_{10}N_4S$: C, 32.86; H, 6.89; N, 38.32. Found: C, 33.16; H, 6.95; N, 38.52. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1680, 1510, 1175.

A mixture of N-thioacetylaminoacetamidrazone (1.46 g) and cinnamaldehyde (1.32 g) in ethanol (10 ml) was warmed at 60° for 30 min. After cooling the reaction mixture, the separated yellow needles were collected and washed with a small amount of ethanol to give cinnamaldehydeazine (2 g), which was identical in mp and IR spectrum with an authentic sample obtained by Curtius' method.[13]

3) Methyl dithioacetate (5.3 g) was added dropwise to a solution of hydrazine hydrate (2.5 g) in ethanol (30 ml) at −78°. After 30 min, 30 ml of dry ether cooled to −78° was added to the reaction mixture and the separated crystals were collected and immediately dried under reduced pressure to give 2.1 g of thioacetylhydrazine, mp 73—75°. *Anal.* Calcd for $C_2H_6N_2S$: C, 26.65; H, 6.71; N, 31.07. Found: C, 26.49; H, 6.51; N, 30.88. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1640, 1540, 1180, 1128.

Synthesis of 5-Acetylmethylamino-2-styryl-1,3,4-thiadiazole——A mixture of cinnamylidene-ξ-acetyl-4-methylthiosemicarbazone (0.33 g, a 1 : 2 mixture of monoacetate and diacetate) and DDQ (0.3 g) in dry dioxane (8 ml) was stirred at 55° for 10 min. After evaporation of the solvent, the residue was chromatographed on silica gel [elution with *n*-hexane–AcOEt (1 : 1)] to give 5-acetylmethylamino-2-styryl-1,3,4-thiadiazole in 77% yield, mp 161° (colorless prisms, *n*-hexane–AcOEt). *Anal.* Calcd for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20; S, 12.36. Found: C, 59.87; H, 4.96; N, 16.16; S, 12.05. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1670. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 317 (28900), 327 (28400). NMR (DMSO-d_6, ppm): 2.40 (3H, s, Ac), 3.65 (3H, s, NMe). MS *m/e* (relative intensity, %): 216 (100), 217 (68), 259 (42), 260 (10). Other 2-styryl-5-substituted-1,3,4-thiadiazole derivatives were prepared in the same manner; their yields, melting points and spectral data are given below:

5-Methylthio-2-styryl-1,3,4-thiadiazole: 81% yield, mp 95° (colorless needles, *n*-hexane–AcOEt). *Anal.* Calcd for $C_{11}H_{10}N_2S_2$: C, 56.41; H, 4.27; N, 11.97; S, 27.74. Found: C, 56.05; H, 4.07; N, 11.97; S, 27.42. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1432, 1075. NMR (DMSO-d_6, ppm): 2.79 (3H, s, SMe), 7.2—7.7 (7H, m). MS *m/e* (relative intensity, %): 234 (M^+, 50), 233 (100).

5-Morpholino-2-styryl-1,3,4-thiadiazole: 83% yield, mp 150—151° (colorless prisms, *n*-hexane-AcOEt). *Anal.* Calcd for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.27; H, 5.34; N, 15.50; S, 11.56. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1500, 1276. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 338 (28200). NMR (DMSO-d_6, ppm): 3.3—4.0 (8H, m), 7.2—7.8 (8H, m). MS *m/e* (relative intensity, %): 273 (M^+, 100).

5-Dimethylamino-2-styryl-1,3,4-thiadiazole: 95% yield, mp 133—135° (colorless flakes, *n*-hexane–AcOEt). *Anal.* Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.17; H, 5.61; N, 18.19; S, 13.59. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1560, 1423, 1403. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 342 (29100). NMR (DMSO-d_6, ppm): 3.08 (6H, s, NMe), 7.2—7.8 (7H, m).

5-Methyl-2-styryl-1,3,4-thiadiazole: 92% yield, mp 160—161° (colorless flakes, *n*-hexane–AcOEt). *Anal.* Calcd for $C_{11}H_{10}N_2S$: C, 65.35; H, 4.95; N, 13.86; S, 15.84. Found: C, 65.58; H, 4.87; N, 13.81; S, 15.77. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1630, 1433. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 225 (10000), 308 (27200). NMR (DMSO-d_6, ppm): 2.75 (3H, s), 7.2—7.6 (7H, m). MS *m/e* (relative intensity, %): 201 (100), 202 (M^+, 27).

5-Acetylamino-2-styryl-1,3,4-thiadiazole: 95% yield, mp 307—309°. *Anal.* Calcd for $C_{12}H_{11}N_3OS$: C, 58.76; H, 4.52; N, 17.13; S, 13.07. Found: C, 58.52; H, 4.56; N, 17.01; S, 12.88. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3150, 1705, 1558, 955. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε): 317 (29100). NMR (DMSO-d_6, ppm): 2.20 (3H, s, NAc), 12.56 (1H, s, NHAc). This compound was identical in mp, IR and NMR spectra with an authentic sample which was prepared by treatment of 5-amino-2-styryl-1,3,4-thiadiazole (mp 245°)[14b] with Ac_2O–pyridine.

5-Acetylamino-2-phenyl-1,3,4-thiadiazole——A mixture of ξ-acetyl-benzylidenethiosemicarbazone (0.236g, prepared by the reaction of benzylidenethiosemicarbazone with Ac_2O–AcOH) and DDQ (0.23 g) in dry

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dioxane (20 ml) was stirred at 55° for 2 hr. The separated crystalline material was collected and washed with AcOEt and then with dry ether to give 5-acetylamino-2-phenyl-1,3,4-thiadiazole in 80% yield, mp 289—290°. *Anal.* Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.61; H, 4.04; N, 18.89; S, 14.51.

5-Dimethylamino-2-phenyl-1,3,4-thiadiazole——A mixture of benzaldehyde (1.06 g), 4,4-dimethylthiosemicarbazide (0.7 g) and its HCl salt (0.78 g) in DMSO (10 ml) was stirred at room temperature for 40 min. The reaction mixture was poured into ice-water and extracted with AcOEt–THF. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave benzylidene-4-dimethylthiosemicarbazone in quantitative yield. It was recrystallized from *n*-hexane–THF, mp 141—151° (dec.). A mixture of benzylidene-4-dimethylthiosemicarbazone (0.207 g) and DDQ (0.227 g) in dry dioxane (20 ml) was stirred at room temperature for 5 min. The separated crystals were collected to give 5-dimethylamino-2-phenyl 1,3,4-thiadiazole in 95% yield, mp 94—95°. *Anal.* Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.48; H, 5.01; N, 20.10; S, 15.58. IR ν_{max}^{KBr} cm^{-1}: 1550, 1410. NMR ($CDCl_3$, ppm): 3.19 (6H, s, NMe_2).

5-Acetylamino-2-(2′-pyridyl)-1,3,4-thiadiazole——2-Pyridylmethylene-ξ-diacetylthiosemicarbazone (0.212 g), DDQ (0.2 g) in dry dioxane (3.5 ml) was stirred at 60° for 15 min. The separated crystals were collected and washed with CH_2Cl_2. Recrystallization from DMF-ethanol gave 5-acetylamino-2-(2′-pyridyl)-1,3,4-thiadiazole in 83% yield, mp>300°, which was identical in IR with an authentic sample obtained by Hemmerich's method.[14b] *Anal.* Calcd for $C_9H_8N_4OS$: C, 49.08; H, 3.66; N, 25.44; S, 14.56. Found: C, 48.78; H, 3.60; N, 25.46; S, 14.55.

General Procedure for the Preparation of 7-Thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (4) and Their Sodium Salts——Benzhydryl ester (3, 0.05—0.20 g) was taken up in 1 ml of anisole, cooled to 0°, and treated with 3 ml of trifluoroacetic acid for 20 min. After evaporation of the solvent, the residue was washed with dry ether to give cephalosporin 4-carboxylic acid (**4**). The sodium salt was prepared as follows: the 4-carboxylic acid (**4**) was treated with dil. $NaHCO_3$ aq. solution (pH 6.5) and the solution was washed with AcOEt. The aqueous layer was charged on an Amberlite XAD-2 column and eluted with water then 5—10% ethanol. Lyophilization of the desired fraction gave sodium 7-thienylacetamido-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate in 75—85% yields. The following compounds were synthesized by the same procedure:

Sodium 3-(5-Dimethylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (**4a**; R_1= Na): IR ν_{max}^{KBr} cm^{-1}: 1770, 1660, 1603. UV $\lambda_{max}^{H_2O}$ nm (ε): 335 (15300). NMR (D_2O, ppm): 3.17 (3H, s, Me), 3.75 and 4.05 (2H, ABq, *J*=18 Hz, C_2–H), 3.95 (2H, s, $-CH_2-$), 5.24 (1H, d, *J*=5 Hz, C_6–H), 5.76 (1H, d, *J*=5 Hz, C_7–H), 7.05—7.45 (m, aromatic H).

Sodium 3-(5-Morpholino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (**4b**; R_1= Na): IR ν_{max}^{KBr} cm^{-1}: 1770, 1663, 1600. NMR (D_2O, ppm): 3.5—3.7 (4H, m, $-CH_2-$), 3.8—4.0 (4H, m, $-CH_2-$), 3.93 (2H, s, thienyl-CH_2-), 3.83 and 4.18 (2H, d, *J*=18 Hz, C_2–H), 5.27 (1H, d, *J*=5 Hz, C_6–H), 5.74 (1H, d, *J*=5 Hz, C_7–H), 7.1—7.2 and 7.4—7.6 (m, aromatic H).

Sodium 3-(5-Methyl-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (**4c**; R_1=Na): IR ν_{max}^{KBr} cm^{-1}: 1770, 1660, 1610. UV $\lambda_{max}^{H_2O}$ nm (ε): 305 (12800). NMR (D_2O, ppm): 2.75 (3H, s, Me), 3.78 and 4.02 (2H, ABq, *J*=18 Hz, C_2–H), 3.91 (2H, s, $-CH_2-$), 5.24 (1H, d, *J*=5 Hz, C_6–H), 5.73 (1H, d, *J*=5 Hz, C_7–H), 7.0—7.35 (m, aromatic H).

3-(5-Phenyl-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylic Acid (**4d**; R_1=H): mp 225—227° (pale yellow needles, *n*-hexane–AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1785, 1660. NMR (DMSO-d_6, ppm): 3.95 and 4.18 (2H, ABq, *J*=18 Hz, C_2–H), 4.75 (1H, br. s, $-CO_2H$), 5.32 (1H, d, *J*=5 Hz, C_6–H), 5.86 (1H, q, *J*=5 Hz and 9 Hz, C_7–H), 6.98, 7.37, 7.5—7.7 and 8.00 (m, aromatic H), 9.24 (1H, d, *J*=9 Hz, $CON\underline{H}$).

3-(5-Acetylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylic Acid (**4e**; R_1=H): IR ν_{max}^{KBr} cm^{-1}: 1783, 1700, 1695, 1660. UV λ_{max}^{EtOH} nm (ε): 254 (14100), 317 (13700). NMR (DMSO-d_6, ppm): 1.98 (3H, s, Me), 3.76 (2H, s, $-CH_2-$), 3.82 and 4.12 (2H, ABq, *J*=18 Hz, C_2–H), 5.22 (1H, d, *J*=4 Hz, C_6–H), 5.71 (1H, q, *J*=4 Hz and 8 Hz, C_7–H), 6.9—7.3 (m, aromatic H), 9.2 (1H, d, *J*=8 Hz, $CON\underline{H}$). **4e** (R_1=Na); IR ν_{max}^{KBr} cm^{-1}: 1770, 1665, 1610. NMR (D_2O, ppm): 2.47 (3H, s, Me), 3.96 and 4.20 (2H, ABq, *J*=18 Hz, C_2–H), 4.08 (2H, s, $-CH_2-$), 5.41 (1H, d, *J*=5 Hz, C_6–H), 5.89 (1H, d, *J*=5 Hz, C_7–H), 7.21—7.54 (3H, m, aromatic H).

Sodium 2-(5-Acetylmethylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (**4f**; R_1=Na): IR ν_{max}^{KBr} cm^{-1}: 1778, 1663, 1615. NMR (DMSO-d_6, ppm): 2.86 (3H, s, Ac), 3.66 (3H, s, Me), 3.78 (2H, s, $-CH_2-$), 4.14 (1H, a part of ABq, *J*=18 Hz, C_2–H), 5.12 (1H, d, *J*=5 Hz, C_6–H), 5.58 (1H, q, *J*=5 Hz and 9 Hz, C_7–H), 6.8—7.4 (m, aromatic H), 9.10 (1H, d, *J*=9 Hz, $CON\underline{H}$).

2-(5-Methylamino-1,3,4-thiadiazol-2-yl)-7-thienylacetamidoceph-3-em-4-carboxylate (**4g**; R_1=H): IR ν_{max}^{KBr} cm^{-1}: 1780, 1680.

Synthesis of Benzhydryl 7-Amino-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (5a)——Pyridine (3.16 g) was added with stirring to a suspension of pulverized phosphorus pentachloride (4.16 g) in CH_2Cl_2 (20 ml) at −15°, and then **3a** (3.04 g) was added with stirring to this reaction mixture at −5°. After stirring at 10° for 1 hr, methanol (7.5 ml) was added to the reaction mixture at −20°, and the solution was stirred for an additional 2 hr. The reaction mixture was poured into ice-water and neutralized with aq.

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$NaHCO_3$ solution (pH 7), and the CH_2Cl_2 layer was separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and then dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel [elution with AcOEt–*n*-hexane (5: 1)] to give **5a** (2.16 g, 89%). IR ν_{max}^{KBr} cm^{-1}: 3400, 1770 1720. UV λ_{max}^{EtOH} nm (ε): 340 (9900). NMR ($CDCl_3$, ppm): 2.23 (2H, br. s, $-N\underline{H}_2$), 2.90 (3H, s, Me), 3.67 and 4.15 (2H, ABq, $J=18$ Hz, C_2–H), 4.77 (1H, d, $J=5$ Hz, C_6–H), 4.97 (1H, d, $J=5$ Hz, C_7–H), 6.95 (1H, s, $-C\underline{H}Ph_2$), 7.1—7.4 (m, aromatic H).

The other 7-amino derivatives were also prepared by the same procedure, and their yields, melting points and spectral data are given below:

Benzhydryl 7-Amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**5c**): 78% yield, mp 162—164° (dec.) as pale yellow needles. IR ν_{max}^{KBr} cm^{-1}: 1790, 1735. UV λ_{max}^{EtOH} nm (ε): 307 (10500). NMR ($CDCl_3$, ppm): 2.3 (2H, br. s, $-N\underline{H}_2$), 2.46 (3H, s, Me), 3.68 and 4.06 (2H, ABq, $J=18$ Hz, C_2–H), 4.80 (1H, d, $J=5$ Hz, C_6–H), 4.97 (1H, d, $J=5$ Hz, C_7–H), 6.92 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.5 (m, aromatic H).

Benzhydryl 7-Amino-3-(5-phenyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**5d**): 76% yield, amorphous. IR ν_{max}^{KBr} cm^{-1}; 1780, 1730. UV ν_{max}^{EtOH} nm (ε): *ca.* 280 (8800, shoulder), 328 (16200). NMR (DMSO-d_6, ppm): 3.27 (2H, br. s, $-N\underline{H}_2$), 3.88 and 4.13 (2H, ABq, $J=18$ Hz, C_2–H), 4.99 (1H, d, $J=5$ Hz, C_6–H), 5.22 (1H, d, $J=5$ Hz, C_7–H), 6.89 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.9 (m, aromatic H).

Benzhydryl 7-Amino-3-(5-acetylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**5e**): 81% yield, mp 165—170° (dec.) as pale yellow needles. IR ν_{max}^{KBr} cm^{-1}: 1780, 1725, 1695. UV λ_{max}^{EtOH} nm (ε): 257 (6800), 317 (12200). NMR ($CDCl_3$, ppm): 1.80 (2H, br. s, $-N\underline{H}_2$), 2.30 (2H, s, Ac), 3.72 and 3.98 (2H, ABq, $J=18$ Hz, C_2–H), 4.86 (1H, d, $J=5$ Hz, C_6–H), 5.04 (1H, d, $J=5$ Hz, C_7–H), 6.94 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.4 (m, aromatic H).

Benzhydryl 7-Amino-3-(5-acetylmethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**5f**): 63.4% yield, amorphous. IR ν_{max}^{KBr} cm^{-1}: 1785, 1732. UV λ_{max}^{EtOH} nm (ε): *ca.* 256 (7900), 312 (10600). NMR ($CDCl_3$, ppm): 1.8 (2H, br. s, $-N\underline{H}_2$), 2.36 (3H, s, Ac), 3.60 (3H, s, Me), 3.70 and 4.05 (2H, ABq, $J=18$ Hz, C_2–H), 4.85 (1H, d, $J=5$ Hz, C_6–H), 5.04 (1H, d, $J=5$ Hz, C_7–H), 7.18 (s, aromatic H), 7.92 (1H, s, $-C\underline{H}Ph_2$).

7-Amino-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (11a) and 7-Amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (11c)——Compounds **11a** and **11c** were prepared by the method described above.

11a: IR ν_{max}^{KBr} cm^{-1}: 1740, 1630, 1560. NMR (DMSO-d_6, ppm): 3.00 (6H, s, NMe_2), 3.60 and 4.02 (2H, ABq, $J=18$ Hz, C_2–H), 4.58 (1H, d, $J=5$ Hz, C_6–H), 4.95 (1H, d, $J=5$ Hz, C_7–H). NMR (CF_3CO_2D, ppm): 3.44 (6H, s, NMe_2), 3.90 and 4.14 (2H, ABq, $J=18$ Hz, C_2–H), 5.46 (2H, br. s, C_6–H and C_7–H).

11c: IR ν_{max}^{KBr} cm^{-1}: 1805, 1608, 1550. NMR (CF_3CO_2D, ppm): 3.18 (3H, s, Me), 4.16 (2H, s, C_2–H), 5.58 (2H, br. s, C_6–H and C_7–H).

Synthesis of 7-(2-Aminothiazolyl)acetamido Cephalosporin Derivatives (6 and 7)

7-[2-(2-Aminothiazol-2-yl)acetamido]-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic Acid (7a)——Bromine (0.224 g) in CH_2Cl_2 (7.25 ml) was added dropwise at −40° to a solution of diketene (0.103 g) in CH_2Cl_2 (2 ml) and the mixture was stirred for 15 min. The reaction mixture was added dropwise at −30° to a solution of **5b** (0.439 g) and triethylamine (0.101 g) in CH_2Cl_2 (7 ml). After removal of the solvent, the residue (0.540 g) was dissolved in acetone (20 ml). Thiourea (0.0836 g), $NaHCO_3$ (0.0924 g) and water (5 ml) were added to the above acetone solution and the solution was allowed to stand overnight. After evaporation of the acetone, the aqueous layer was extracted with AcOEt. The extracts was washed with water and dried (Na_2SO_4). The organic solvent was evaporated off, and the residue was purified by column chromatography on silica gel [elution with AcOEt–acetone (3: 1)] to give benzhydryl 7-[2-(2-aminothiazol-4-yl)acetamido]-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6a**). Recrystallization from AcOEt–acetone gave colorless needles (0.362 g, 66%), mp 197—198°. IR ν_{max}^{KBr} cm^{-1}: 1779, 1721, 1660. UV λ_{max}^{EtOH} nm (ε): 259 (12200), 342 (12800). NMR ($CDCl_3$, ppm): 3.42 (2H, s, $-CH_2-$), 3.92 (6H, s, NMe_2), 3.69 and 4.10 (2H, ABq, $J=18$ Hz, C_2–H), 5.10 (1H, d, $J=5$ Hz, C_6–H), 5.87 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.18 (1H, s, thiazole-H), 7.1—7.4 (m, aromatic H), 8.81 (1H, d, $J=9$ Hz, $CON\underline{H}$).

1) A mixture of benzhydryl 7-[2-(2-aminothiazol-4-yl)acetamido]-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6a**, 0.2 g), anisole (3 ml) and trifluoroacetic acid (2 ml) was stirred at room temperature for 20 min. After evaporation of the solvent, the residue was taken up in 50 ml of water and treated with Amberlite IR-45 (2 ml). After stirring for 10 min, followed by removal of the resin by filtration, the aqueous solution was lyophilized to give **7a** (0.04 g), mp 225° (dec.).

2) After treating **6a** with anisole and trifluoroacetic acid, the residue was neutralized with dil. $NaHCO_3$ aq. solution and charged on an Amberlite XAD-2 column. The desired fraction was lyophilized to give the sodium salt. IR ν_{max}^{KBr} cm^{-1}: 1760, 1660, 1600. NMR (D_2O, ppm): 3.06 (6H, s, NMe_2), 3.54 (2H, s, $-CH_2-$), 3.68 and 3.96 (2H, ABq, $J=18$ Hz, C_2–H), 5.17 (1H, d, $J=5$ Hz, C_6–H), 5.67 (1H, d, $J=5$ Hz, C_7–H), 6.42 (1H, s, thiazole-H).

Other benzhydryl 7-[2-(2-aminothiazol-4-yl)acetamido]-3-(5-substituted-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylates (**6b**—**e**) and their carboxylic acids or sodium salts (**7b**—**e**) were prepared in the same manner; their yields, melting points and spectral data are given below and in Table V.

Benzhydryl 7-[2-(2-Aminothiazol-4-yl)acetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl) ceph-3-em-4-carboxylate (**6b**): IR ν_{max}^{KBr} cm^{-1}: 1782, 1735, 1675. NMR ($CDCl_3$, ppm): 2.65 (3H, s, Me), 3.47 (2H, s, $-CH_2-$),

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3.98 and 4.20 (2H, ABq, $J=18$ Hz, C_2–H), 5.07 (1H, d, $J=5$ Hz, C_6–H), 5.50 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 8.08 (1H, d, $J=9$ Hz, CON$\underline{H}$).

Benzhydryl 7-[2-(2-Aminothiazol-4-yl)acetamido]-3-(5-phenyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6c**): mp 160—164° (pale yellow needles). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1785, 1725. NMR (DMSO-d_6, ppm): 3.44 (2H, s, $-CH_2-$), 3.98 and 4.21 (2H, ABq, $J=18$ Hz, C_2–H), 5.34 (1H, d, $J=5$ Hz, C_6–H), 5.94 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.30 (1H, s, thiazole-H), 9.04 (1H, $J=9$ Hz, CON$\underline{H}$).

Benzhydryl 3-(5-Acetylamino-1,3,4-thiadiazol-2-yl)-7-[2-(2-aminothiazol-4-yl)acetamido]ceph-3-em-4-carboxylate (**6d**): IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1785, 1725, 1680. NMR (DMSO-d_6, ppm): 2.20 (3H, s, Ac), 3.42 (2H, s, $-CH_2-$), 3.86 and 4.10 (2H, ABq, $J=18$ Hz, C_2–H), 5.29 (1H, d, $J=5$ Hz, C_6–H), 5.87 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.29 (1H, s, thiazole-H), 6.81 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.4 (m, aromatic H).

Benzhydryl 3-(5-Acetylmethylamino-1,3,4-thiadiazol-2-yl)-7-[2-(2-aminothiazol-4-yl)acetamido]ceph-3-em-4-carboxylate (**6e**): IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1785, 1730, 1675. NMR (DMSO-d_6, ppm): 2.39 (3H, s, Ac), 3.42 (2H, s, $-CH_2-$), 3.54 (3H, s, Me), 3.86 and 4.08 (2H, ABq, $J=18$ Hz, C_2–H), 5.29 (1H, d, $J=5$ Hz, C_6–H), 5.84 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.28 (1H, s, thiazole-H), 6.79 (1H, s, $-C\underline{H}Ph_2$), 7.29 (s, aromatic H), 9.00 (1H, d, $J=9$ Hz, CON$\underline{H}$).

Synthesis of 7-α-Substituted-phenylacetamido Cephalosporin Derivatives

1) **The Acid Chloride Method**——α-Sulfophenylacetyl chloride (0.197 g, $[\alpha]_D$ −49.5°) in CH_2Cl_2 (10 ml) and N,N-dimethylaniline (0.102 g) in CH_2Cl_2 (10 ml) were added dropwise with stirring at 2° to a solution of benzhydryl 7-amino-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6m**, 0.46 g) in CH_2Cl_2 (30 ml). After 30 min, the reaction mixture was washed with dil. HCl aqueous solution and then with water, and the organic layer was dried (Na_2SO_4). After evaporation of the solvent, the residue was suspended in anisole (3 ml) and treated with trifluoroacetic acid (2 ml) at 0°. After stirring at room temperature for 20 min, the solvent was evaporated off and the residue was washed with dry ether to give a pale yellow powder, which was neutralized with aqueous $NaHCO_3$ solution (pH 6.5). Purification was carried out on an Amberlite XAD-2 column. Lyophilization of the desired fractions gave sodium 3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)-7-D-α-sulfophenylacetamidoceph-3-em-4-carboxylate (**7m**, 0.233 g).

The compound (**7l**) was prepared by the same procedure.

2) **The DCC Method**——A mixture of benzhydryl 7-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (0.464 g), D-α-(−)-*tert*-butyloxycarboxamido-phenylacetic acid (0.378 g) and 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide *metha-p*-toluenesulfonate (CMC *metha-p*-toluenesulfonate, Aldrich) (0.670 g) in dry THF (10 ml) was stirred for 2 hr at room temperature. After removal of the solvent, the residue was dissolved in AcOEt and the solution was washed with water and dried (Na_2SO_4). After removing the solvent *in vacuo*, the residue was chromatographed on a silica gel column [elution with benzene–AcOEt (3: 1)] to give benzhydryl 7-[D-α-*tert*-butyloxycarboxamido)phenylacetamido]-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6h**, 0.564 g, 81%). Recrystallization from *n*-hexane–AcOEt gave colorless prisms, mp 207—210° (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1790, 1730, 1665. NMR ($CDCl_3$, ppm): 1.40 (9H, s, *tert*-Bu), 2.48 (3H, s, Me), 3.57 and 4.01 (2H, ABq, $J=18$ Hz, C_2–H), 4.98 (1H, d, $J=5$ Hz, C_6–H), 5.25 (1H, s, $-C\underline{H}$-NH–), 5.65 (1H, d, $J=7$ Hz, –CH–N$\underline{H}$–), 5.88 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.92 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.5 (15H, m, aromatic H).

A mixture of **6h** (0.30 g), anisole (3 ml) and trifluoroacetic acid (9 ml) was stirred for 20 min at room temperature. After removal of the solvent, the residue was triturated with addition of absolute ether. The precipitates were collected by filtration, and washed with ether to give the trifluoroacetic acid salt of the corresponding carboxylic acid. The salt was chromatographed on an Amberlite XAD-2 column [elution with 10% ethanol] to give 0.117 g of 7-D-(−)-α-amino-phenylacetamido-3-(5-methyl-1,3,4-thiadiazol-2-yl)-ceph-3-em-4-carboxylic acid (**7h**).

The following compounds (**6f**, **6g** and **6i**) were prepared by the same procedure, and physical data for their sodium salts (**7f**, **7g** and **7i**) are given in Table VI.

Benzhydryl 7-[D-(−)-α-(*tert*-Butyloxycarboxamido)-*p*-hydroxyphenylacetamido]-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6f**): IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1785, 1720. NMR (DMSO-d_6, ppm): 1.40 (9H, s, *tert*-Bu), 2.90 (6H, s, NMe_2), 3.57 and 3.97 (2H, ABq, $J=18$ Hz, C_2–H), 5.16 (1H, d, $J=4$ Hz, C_6–H), 5.20 (1H, d, $J=7$ Hz, Ph–C$\underline{H}$–), 5.84 (1H, q, $J=4$ Hz and 9 Hz, C_7–H), 6.85 (1H, s, $-C\underline{H}Ph_2$), 7.1—7.4 (m, N$\underline{H}$ and aromatic H), 9.14 (1H, d, $J=9$ Hz, CON$\underline{H}$).

Benzhydryl 7-[D-(−)-α-(*tert*-Butyloxycarboxamido)-phenylacetamido]-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6g**): mp 175—178° (dec. *n*-hexane–AcOEt). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1790, 1725, 1695, 1665. NMR ($CDCl_3$, ppm): 1.40 (9H, s, *tert*-Bu), 2.90 (6H, s, NMe_2), 3.57 and 4.06 (2H, ABq, $J=18$ Hz, C_2–H), 4.94 (1H, d, $J=5$ Hz, C_6–H), 5.22 (1H, d, $J=7$ Hz, Ph–C$\underline{H}$–), 5.68 (1H, d, $J=7$ Hz, N$\underline{H}$–CO_2–), 5.82 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.75 (1H, d, $J=9$ Hz, CON$\underline{H}$), 6.95 (1H, s, $-C\underline{H}Ph_2$), 7.0—7.5 (m, aromatic H).

Benzhydryl 7-[D-(−)-α-(*tert*-Butyloxycarboxamido)-phenylacetamido]-3-(5-acetylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6i**): mp 213—215° (benzene–AcOEt). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1790, 1720, 1700. NMR ($CDCl_3$+DMSO-d_6 (trace), ppm): 1.45 (9H, s, *tert*-Bu), 2.23 (3H, s, Ac), 3.63 and 3.95 (2H, ABq, $J=18$ Hz, C_2–H), 5.05 (1H, d, $J=5$ Hz, C_6–H), 5.42 (1H, d, $J=7$ Hz, Ph–C$\underline{H}$–), 5.86 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.10 (1H, d, $J=7$ Hz, Ph–CH–N$\underline{H}$–), 6.91 (1H, s, $-C\underline{H}Ph_2$), 12.2 (1H, br. s, AcN$\underline{H}$–).

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3) **The Mixed Anhydride Method**——A mixture of benzhydryl 7-amino-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (0.439 g) and 2,4-dioxo-5-phenyl-1,3-dioxolane (0.200 g) in dry CH_2Cl_2 (5 ml) was stirred at room temperature for 15 hr. After removal of the solvent, the residue was chromatographed on a silica gel column [elution with AcOEt–benzene (1: 1)] to give benzhydryl 7-D-(−)-α-hydroxyphenylacetamido-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6k**, 0.400 g). Recrystallization from AcOEt–benzene gave colorless cubes. mp 189—190°. *Anal.* Calcd for $C_{32}H_{29}N_5O_5S_2$: C, 61.23; H, 4.66; N, 11.16; S, 10.22. Found: C, 61.12; H, 4.60; N, 11.11; S, 9.62. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300, 1799, 1721, 1679. NMR (DMSO-d_6, ppm): 2.90 (6H, s, NMe_2), 3.30 (1H, br. s, OH), 3.75 and 4.01 (2H, ABq, J=18 Hz, C_2–H), 5.09 (1H, s, Ph–C$\underline{H}$–), 5.20 (1H, d, J=5 Hz, C_6–H), 5.82 (1H, q, J=5 Hz and 9 Hz, C_7–H), 6.84 (1H, s, –C$\underline{H}$$Ph_2$), 7.0—7.5 (15H, m, aromatic H), 8.87 (1H, d, J=9 Hz, CON$\underline{H}$).

A mixture of benzhydryl ester (**6k**, 0.1 g), anisole (2 ml) and trifluoroacetic acid (1 ml) was stirred at 0° for 10 min and then at room temperature for 20 min. After removal of the solvent, the residue was triturated with absolute ether to give 0.065 g of the trifluoroacetic acid salt of 7-D-(−)-α-hydroxyphenylacetamido-3-(5-dimethylamino-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylic acid (**7k**) as pale yellow needles, mp 152—162° (dec.).

The following compound (**6j**) was prepared by the same procedure.

Benzhydryl 7-D-(−)-α-Hydroxyphenylacetamido-3-(5-methyl-1,3,4-thiadiazol-2-yl)ceph-3-em-4-carboxylate (**6j**): mp 188—190° (dec. benzene–AcOEt). *Anal.* Calcd for $C_{31}H_{26}N_4O_5S_2$: C, 62.19; H, 4.38; N, 9.36; S, 10.71. Found: C, 62.36; H, 4.31; N, 9.40; S, 10.46. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1770, 1718, 1670. NMR ($CDCl_3$, ppm): 2.48 (3H, s, Me), 3.67 and 4.10 (2H, ABq, J=18 Hz, C_2–H), 5.05 (1H, d, J=5 Hz, C_6–H), 5.14 (1H, s, Ph-C$\underline{H}$-), 5.85 (1H, q, J=5 Hz and 9 Hz, C_7–H), 6.92 (1H, s, –$CHPh_2$), 7.0—7.6 (15H, m, aromatic H), 8.06 (1H, d, J=9 Hz, CON$\underline{H}$).

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