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Studies on Lactams. VII.[1] 6-Isothiocyanatopenicillanate and 7-Isothiocyanatodeacetoxycephalosporanate and Their Reactions

Haruo Ogura, Kazuyoshi Takeda, and Koji Kajima

School of Pharmaceutical Sciences, Kitasato University[2]

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6-Isothiocyanatopenicillanate and 7-isothiocyanatodeacetoxycephalosporanate were prepared since they are valuable intermediates in the syntheses of penicillin and cephalosporin derivatives. When the reaction was carried out with those isothiocyanate compounds, addition products with dicyclohexylcarbodiimide were obtained as unexpected by-products. The isothiocyanate derivatives thus obtained were treated with benzylamine to give a penillic acid derivatives.

Keywords——6-isothiocyanatopenicillanate; 7-isothiocyanatocephalosporanate; isothiocyanate; ureide; DCC and isothiocyanate complex; esterification of penicillins and cephalosporins; dithiocarbamate; penillic acid

Derivatives of penicillin and cephalosporin have been prepared from acylations of 6-aminopenicillanic acid (6-APA) of 7-aminocephalosporanic acid (7-ACA). On the other hand, Perron *et al.*,[3] reported that the addition reactions of alkylisocyanates and alkylisothiocyanates with 6-APA gave derivatives of urea and thiourea.

The isocyanato- and isothiocyanato-compounds[4] are known as electrophillic reagents and react with various anions. In this report, we described the synthesis of 6-isothiocyanatopenicillanate and 7-isothiocyanatodeacetoxycephalosporanate derivatives and the reaction of those isothiocyanatoderivatives with benzylamine to form ureidoderivatives. 6-Isothiocyanatopenicillanates (**2a**, **b**) were prepared from phenacyl 6-aminopenicillanate[5] and pivaloyloxymethyl 6-aminopenicillanate[6] (pivaloyloxymethyl 6-APA). 7-Isothiocyanato-deacetoxycepharosporanates (**6a**, **b**) were prepared from phenacyl 7-aminodeacetoxycephalosporanate (phenacyl 7-ADCA) and pivaloyloxymethyl 7-aminodeacetoxycephalosporanate (pivaloyloxymethyl 7-ADCA).

The treatment of phenacyl 6-aminopenicillanate (phenacyl 6-APA) (**1a**) with carbon disulfide (CS_2) and dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (THF) in the presence of pyridine afforded phenacyl 6-isothiocyanatopenicillanate (**2a**) in a good yield. When the same reaction was carried out with pivaloyloxymethyl 6-aminopenicillanate (**1b**), phenacyl 7-aminodeacetoxycephalosporanate (**5a**) or pivaloyloxymethyl 7-aminodeacetoxycephalosporanate (**5b**) instead of **1a**, addition products with DCC were obtained as unexpected by-products. The structures of the by-products are not clear from nuclear magnetic resonance (NMR) and infrared (IR) spectra, and four probable structures[7,8] are shown in Chart 3.

1) Part VI: H. Ogura, K. Furuhata, and K. Furuhata, *Chem. Pharm. Bull.* (Tokyo), **23**, 2474 (1974); This constitutes Part XXII of a series entitled "Studies on Heterocyclic Compounds."
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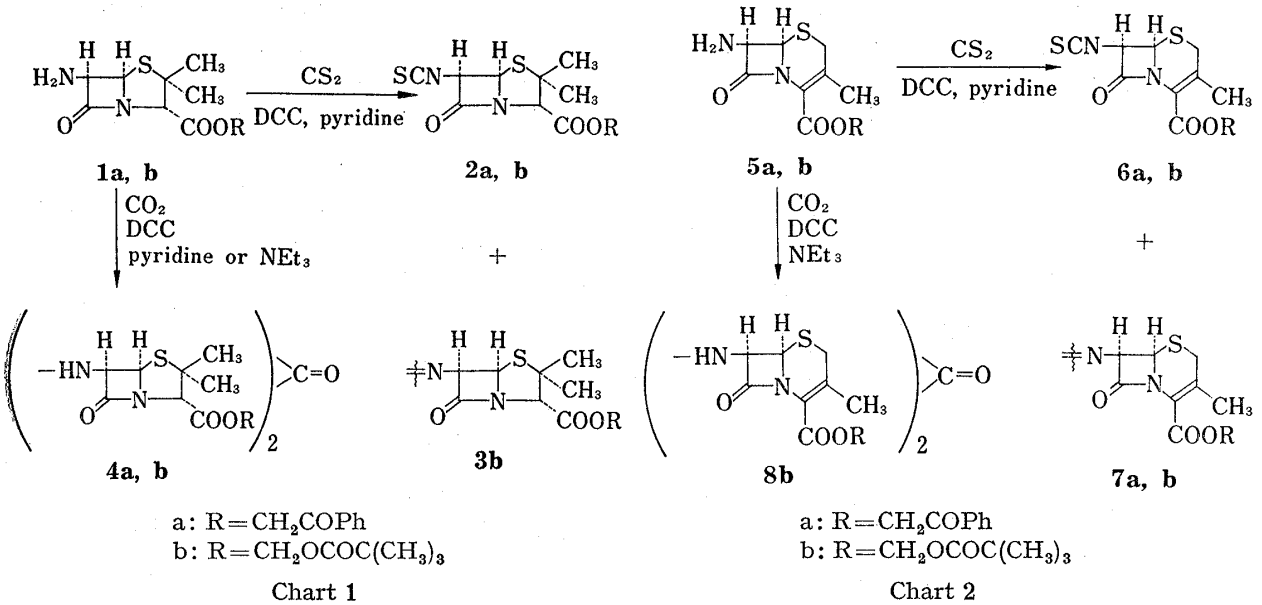

a: R=CH_2COPh
b: R=$CH_2OCOC(CH_3)_3$

Chart 1

Chart 2

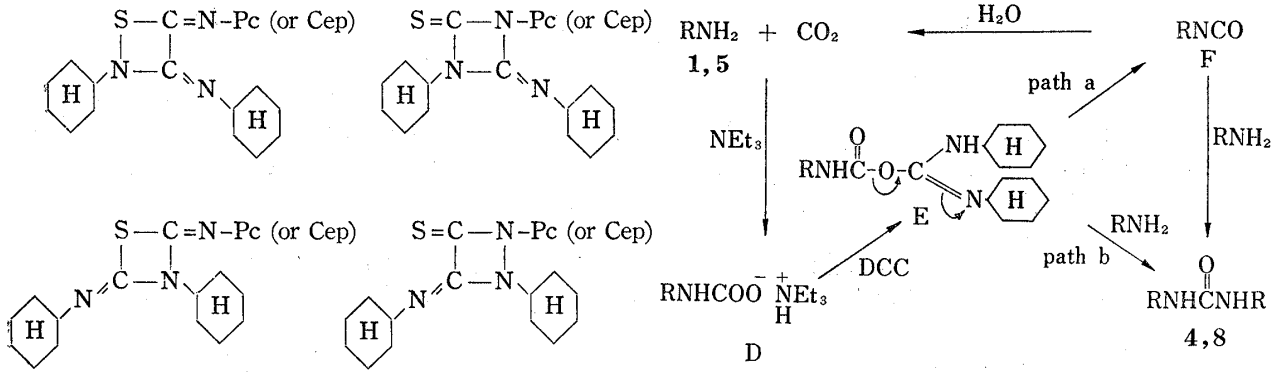

Chart 3

Chart 4

The configurations of phenacyl 6-isothiocyanatopenicillanate (**2a**) at 5-H and 6-H should have *cis* orientation from the *J*-value of 4.2 Hz. Hoppe *et. al.*[9] suggested the epimerization of isothiocyanate group in alkaline medium, though we could not obtain a 6α-epimer under reaction conditions mentioned above.

On the other hand, 6-APA and 7-ADCA were reacted with carbon dioxide (CO_2) and DCC with *tert.* amine to obtain urea derivatives. This method is a convenient direct synthesis of ureas from amines and CO_2.[10]

It is currently suggested that an intermediate salt (D) may play an important role in the formation of ureas (**4**, **8**), and two paths a and b are probable. When the intermediate salt (D) reacts with DCC, E is formed and following dehydration of amines (**1**, **5**) forms ureas (**4**, **8**) *via* isocyanate (F) (path a). This mechanism may be supported by an adsorption band due to the isocyanate group which appears around 2200 cm^{-1} on IR spectra of a crude reaction mixture. Another probable path b is the direct reaction of amines (**1**, **5**) with the intermediate carbamate (E) (Chart 4).

The mechanisms of the formation of isothiocyanate derivatives (**2**, **6**) could be explained as shown in Chart 5. That is, DCC removes H_2S from an intermediate salt (A) *via* B. Reaction of phenacyl 6-isothiocyanatopencillanate (**2a**) with benzylamine produced a penillic acid

9) D. Hoppe and R. Follmann, *Chem. Ber.*, **109**, 3047 (1976).
10) H. Ogura, K. Takeda, R. Tokue, and T. Kobayashi, *Synthesis*, **5**, 394 (1978).

derivatives (**9**), and the desired thioureide derivative was not obtained. The reason might be that the β-lactam ring expansion causes the nucleophillic attack to the β-lactam. This is probably supproted by the fact that phenacyl 5,5-dimethyl-2-(1-phenacetamino)acetamido-thiazolidine-4-carboxylate is obtained from phenacyl benzylpenicillanate and ammonia.[11]

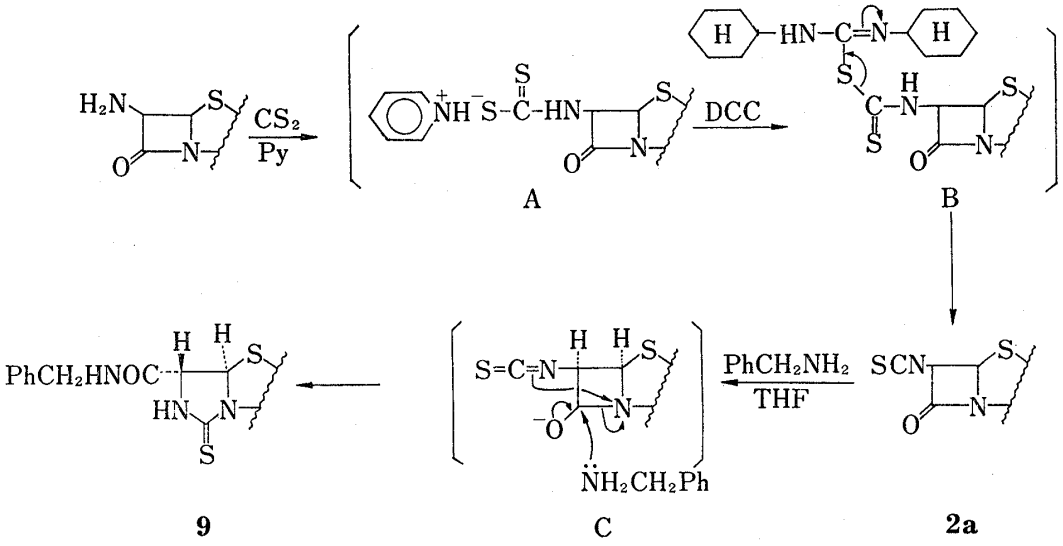

Chart 5

The structure of this compound (**9**) was proved by NMR spectrum and the configurations of 5-H and 6-H should have *trans* orientation from the J-value of 5.8 Hz. The J-values are summarized in Table I.

Table I. Coupling Constants of 6-Isothiocyanatopenicillanates ($J_{5,6}$) and 7-Isothiocyanatodeacetoxycephalosporanates ($J_{6,7}$)

Compound	$J_{5,6}$ ($J_{6,5}$) (Hz)	$J_{6,7}$ ($J_{7,6}$) (Hz)
1a	4.4	
1b	4.4	
2a	4.2	
2b	4.4	
3b	4.0	
4a	Broad	
4b	Broad	
5a		Broad
5b		Broad
6a		4.8
6b		5.0
7a		4.2
7b		5.0
8b		4.8
9	5.8	

Experimental

Temperatures are uncorrected. NMR spectra were measured in $CDCl_3$ at 60 MHz with Varian T-60, and Me_4Si was used as an internal reference. Mass spectra were determined with JEOL-01S spectrometer by a direct inlet system at 75 eV.

11) H. Ogura, K. Takeda, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2469 (1975).

Phenacyl 6-Aminopenicillanate[5] (**1a**)——To an ice-cold stirred suspension of 6-APA (2.16 g; 0.01 mol) and phenacyl bromide (1.99 g; 0.01 mol) in an 1: 1 mixture of dry DMF–THF (30 ml), NEt_3 (1.01 g; 0.01 mol) was added dropwise in 15 min. The cold reaction mixture was stirred for 3 hr, EtOAc (50 ml) was added and the separated organic layer was washed successively with aqueous $NaHCO_3$ and NaCl. Then cold 2 N HCl (50 ml) was added under stirring to precipitate **1a**-HCl. This was collected, and washed with EtOAc giving 1.5 g (40%) of white needles, mp 158° (dec.). Recrystallization of **1a**-HCl from various solvents resulted in failure. *Anal.* Calcd. for $C_{16}H_{18}N_2O_4S \cdot HCl \cdot 1/2H_2O$: C, 50.59; H, 5.31; N, 7.37. Found: C, 50.85; H, 5.10; N, 7.09. IR ν_{max}^{KBr} cm^{-1}: 3000 (NH_3^+), 1780 (β-lactam), 1710 (ester), 1575 (phenyl). NMR (DMSO-d_6) δ (ppm): 1.74 (3H, s, α-CH_3), 1.80 (3H, s, β-CH_3), 4.68 (1H, s, 3-H), 5.12 (1H, d, $J_{5,6}$=4.4 Hz, 5-H), 5.64 (1H, d, $J_{6,5}$=4.4 Hz, 6-H), 5.70 (2H, bs, OCH_2), 7.54—8.17 (5H, m, phenyl).

1a was obtained as pale yellow syrup by treating **1a**-HCl with 10% Na_2CO_3 and used without further purification.

Pivaloyloxymethyl 6-Aminopenicillanate[6] (**1b**)——To a suspension of 6-APA (2.16 g; 0.01 mol) in DMF (50 ml) was added NEt_3 (1.01 g; 0.01 mol). After stirring for 0.5 hr, chloromethyl pivalate (1.5 ml; 0.01 mol) was added under stirring. After stirring at room temperature for 4 hr, the reaction mixture was diluted with EtOAc (50 ml) and the precipitated Et_3N-HCl was filtered off. The filtrate was washed with H_2O (100 ml × 3) to remove the greater part of DMF and unreacted 6-APA. The organic layer was dried and concentrated to about a half of the volume under reduced pressure (bath temperature 30—35°).

To the crude ester solution, 0.5 M *p*-toluenesulfonic acid in EtOAc (100 ml) was added at 25° to precipitate the crystalline *p*-toluenesulfonate. Recrystallization of *p*-toluenesulfonate of **1b** from MeOH–EtOAc afforded 4.1 g (81%) of colorless needles, mp 153° (dec.). *Anal.* Calcd. for $C_{21}H_{30}N_2O_8S_2$: C, 50.18; H, 6.02; N, 5.57. Found: C, 49.97; H, 5.89; N, 5.29. IR ν_{max}^{KBr} cm^{-1}: 3000 (NH_3^+), 1785 (β-lactam), 1740 (ester), 1580 (phenyl). NMR δ (ppm): 1.22 (9H, s, $(CH_3)_3$), 1.40 (3H, s, α-CH_3), 1.46 (3H, s, β-CH_3), 2.35 (3H, s, aromatic CH_3), 4.45 (1H, s, 3-H), 5.00 (1H, d, $J_{5,6}$=4.4 Hz, 5-H), 5.42 (1H, d, $J_{6,5}$=4.4 Hz, 6-H), 5.71, 5.85 (2H, dd, $J_{gem.}$=8.2 Hz, OCH_2), 7.48 (4H, dd, aromatic protons), 7.67 (3H, b, SO_3H, NH_2).

1b was obtained as pale yellow syrup by treating **1b**-*p*-toluenesulfonate with 10% Na_2CO_3 and used without further purification.

Phenacyl 6-Isothiocyanatopenicillanate (**2a**)——To a solution of **1a** (3.34 g; 0.01 mol) was added DCC (1.52 g; 0.02 mol), pyridine (0.79 g; 0.01 mol) and CS_2 (1.52 g; 0.02 mol) in dry THF (100 ml). After stirring at 0° for 3 hr, the reaction mixture was diluted with ether (30 ml), and precipitated DCU was filtered off. Evaporation of the filtrate left syrup and this was chromatographed on silica gel. Elution with benzene yielded 2.93 g (78%) of **2a** as white needles, mp 111—112° after recrystallization from ether. *Anal.* Calcd. for $C_{17}H_{16}N_2O_4S_2$: C, 54.24; H, 4.28; N, 7.44. Found: C, 54.46; H, 4.34; N, 7.40. IR ν_{max}^{film} cm^{-1}: 2075 (NCS), 1785 (β-lactam), 1750 (ester), 1600 (phenyl). NMR δ (ppm): 1.70 (3H, s, α-CH_3), 1.79 (3H, s, β-CH_3), 4.66 (1H, s, 3-H), 5.08 (1H, d, $J_{5,6}$=4.2 Hz, 5-H), 5.43 (2H, d, $J_{gem.}$=4.0 Hz, OCH_2), 5.58 (1H, d, $J_{6,5}$=4.2 Hz, (6-H), 7.46—7.98 (5H, m, phenyl).

Pivaloyloxymethyl 6-Isothiocyanatopenicillanate (**2b**) **and Addition Product with DCC** (**3b**)——To a solution of **1b** (1.0 g; 0.003 mol) was added DCC (0.62 g; 0.0033 mol), pyridine (0.4 g; 0.0033 mol) and CS_2 (0.76 g; 0.01 mol) in dry THF (50 ml). After stirring at 0° for 3 hr, reaction mixture was treated as described in the preparation of **2a** and 0.53 g (24%) of **2b** was obtained as white needles, mp 71—73°, after recrystallization from ether–hexane (1: 1). *Anal.* Calcd. for $C_{15}H_{20}N_2O_5S_2$: C, 48.37; H, 5.41; N, 7.52. Found: C, 48.73; H, 5.52; N, 7.61. IR ν_{max}^{film} cm^{-1}: 2150 (NCS), 1780 (β-lactam), 1750 (ester), NMR δ (ppm): 1.23 (9H, s, $(CH_3)_3$), 1.52 (3H, s, α-CH_3), 1.70 (3H, s, β-CH_3), 4.57 (1H, s, 3-H), 5.09 (1H, d, $J_{5,6}$=4.4 Hz, 5-H), 5.55 (1H, d, $J_{6,5}$=4.4 Hz, 6-H), 5.77, 5.88 (2H, dd, $J_{gem.}$=6.4 Hz, OCH_2).

From further elution of the column with benzene yielded 0.20 g (12%) of **3b** as white needles, mp 85—86° after recrystallization from ether. *Anal.* Calcd. for $C_{28}H_{42}N_4O_5S_2$: C, 58.10; H, 7.31; N, 9.68. Found: C, 58.20; H, 7.31; N, 9.52. IR ν_{max}^{film} cm^{-1}: 1780 (β-lactam), 1750 (ester), 1650 (amide). NMR δ (ppm): 1.22 (9H, s, $(CH_3)_3$), 1.49 (3H, s, α-CH_3), 1.65 (3H, s, β-CH_3), 0.8—2.6 (2OH, m, cyclohexyl), 2.70 (1H, b, cyclohexyl), 3.65 (1H, b, cyclohexyl), 4.60 (1H, s, 3-H), 4.70 (1H, d, $J_{5,6}$=4.0 Hz, 5-H), 5.49 (1H, d, $J_{6,5}$=4.0 Hz, 6-H), 5.73, 5.87 (2H, dd, $J_{gem.}$=8.4 Hz, OCH_2).

Ureylenedi-6-phenacyl Penicillanate (**4a**)——Excess dry ice was added to a solution of DCC (1.48 g; 0.0072 mol), **1a** (2.40 g; 0.0072 mol) and pyridine (0.57 g; 0.072 mol) in THF (60 ml) at −75° for 10 hr. After reaction mixture was concentrated to a half volume under reduced pressure, the resulting precipitates were filtered off. Ethyl acetate was added to the filtrate and the mixture was allowed to stand to precipitate **4a**. Recrystallization from benzene–acetone (1: 1) gave 2.15 g (86%) of **4a** as white needles, mp 109—113°. *Anal.* Calcd. for $C_{33}H_{34}N_4O_9S_2$: C, 57.04; H, 4.93; N, 8.06. Found: C, 57.49; H, 4.96; N, 7.69. IR ν_{max}^{film} cm^{-1}: 3350 (amide), 1780 (β-lactam), 1750 (ester), 1601 (phenyl). NMR (DMSO-d_6) δ (ppm): 1.60 (6H, s, $(\alpha\text{-}CH_3)_2$), 1.71 (6H, s, $(\beta\text{-}CH_3)_2$), 4.46 (2H, s, $(3\text{-}H)_2$), 5.20—5.75 (8H, m, $(5\text{-}H)_2$, $(6\text{-}H)_2$, $(OCH_2)_2$), 6.93—7.25 (2H, bd, J=10 Hz, $(NH)_2$), 7.42—8.10 (10H, m, $(phenyl)_2$).

Ureylenedi-6-pivaloyloxymethyl Penicillanate (**4b**)——A similar method described above in **4a** applied to **1b**, **4b** was obtained in 66% yield after recrystallization from ether-benzene (1: 1) as white needles, mp 90—95°. *Anal.* Calcd. for $C_{29}H_{42}N_4O_{11}S_2$: C, 50.72; H, 6.16; N, 8.16. Found: C, 50.46; H, 6.13; N, 8.05. IR ν_{max}^{KBr} cm^{-1}: 3300 (amide), 1795 (β-lactam), 1750 (ester). NMR δ (ppm): 1.25 (18H, s, $((CH_3)_3)_2$), 1.52 (6H,

s, (α-CH_3)$_2$), 1.60 (6H, s, (β-CH_3)$_2$), 4.42 (2H, s, (3-H)$_2$), 5.45—5.96 (8H, m, (5-H)$_2$, (6-H)$_2$, (OCH_2)$_2$), 6.87 (2H, d, J=7.0 Hz, $(NH)_2$).

Phenacyl 7-Aminodeacetoxycephalosporanate (5a)——To a suspension of 7-ADCA (2.14 g; 0.01 mol) in DMF–THF (1: 1) (50 ml) and NEt_3 (1.01 g; 0.01 mol) phenacyl bromide (1.99 g; 0.01 mol) was added. After stirring at 0° for 4 hr, the mixture was added to EtOAc (100 ml), and the solution was washed with aqueous $NaHCO_3$ and following with H_2O to remove DMF and unreacted 7-ADCA. The organic layer was dried and concentrated to about a half volume under reduced pressure. A solution of p-toluenesulfonic acid (0.01 mol) in EtOAc (50 ml) was added to the concentrated solution at 0° to precipitate p-toluenesulfonate. Separation and washing with EtOAc and later with ether afforded 3.53 g (70%) of colorless needles, mp 176—178° (dec.) after recrystallization from EtOH–ether (1: 1). *Anal.* Calcd. for $C_{23}H_{24}N_2O_{11}S_2$: C, 54.74; H, 4.79; N, 5.55. Found: C, 54.77; H, 4.77; N, 5.48. IR ν_{max}^{film} cm^{-1}: 3340 (amide), 1780 (β-lactam), 1750 (ester), 1600 (phenyl). NMR (CD_3OD) δ (ppm): 2.02 (3H, s, 3-CH_3) 2.25 (3H, s, aromatic CH_3), 3.46 (2H, s, 2-CH_2–), 4.90—5.23 (2H, m, 6-H, 7-H), 5.50 (2H, d, $J_{gem.}$=4.2 Hz, OCH_2), 7.14—8.10 (11H, m, aromatic protons, NH_2), 8.45 (1H, b, SO_3H).

5a was obtained as pale yellow syrup by treating p-toluenesulfonate of **5a** with 10% Na_2CO_3 and used without further purification.

Pivaloyloxymethyl 7-Aminodeacetoxycephalosporanate (5b)——To a suspension of 7-ADCA (5.35 g; 0.025 mol) in DMSO (100 ml) and NEt_3 (3.58 g; 0.035 mol) chloromethylmethyl pivalate (7.4 ml; 0.05 mol) was added. After stirring at room temperature for 5 hr, the mixture was diluted with EtOAc (150 ml) and washed with saturated $NaHCO_3$ (150 ml×2) and H_2O (100 ml×2) to remove DMSO and unreacted 7-ADCA. The organic layer was dried and evaporated to about a half volume and a solution of p-toluenesulfonic acid (0.01 mol) in EtOAc was added at 0° to precipitate 8.03 g (64%) of p-toluenesulfonate of **5b** as colorless needles, mp 174—176° (dec.) after recrystallization from EtOH–ether (1: 1). *Anal.* Calcd. for $C_{21}H_{28}N_2O_8S_2$: C, 50.38; H, 5.63; N, 5.59. Found: C, 50.50; H, 5.64; N, 5.48. IR ν_{max}^{film} cm^{-1}: 3450 (amide), 1780 (β-lactam), 1735 (ester), 1605 (phenyl). NMR δ (ppm): 1.23 (9H, s, $(CH_3)_3$), 3.10 (3H, s, 3-CH_3), 2.30 (3H, s, aromatic CH_3), 2.76 (1H, d, $J_{gem.}$=18.0 Hz, 2β-H), 3.48 (1H, d, $J_{gem.}$=18.0 Hz, 2α-H), 4.90 (2H, bs, 6-H, 7-H), 5.77 (2H, bs, OCH_2), 7.32 (4H, dd, aromatic protons), 8.60 (3H, b, SO_3H, NH_2).

5b was obtained as pale yellow syrup by treating p-toluenesulfonate of **5b** with 10% Na_2CO_3 and used without further purification

Phenacyl 7-Isothiocyanatodeacetoxycephalosporanate (6a) and the Adduct with DCC (7a)——A solution of **5a** (3.32 g; 0.01 mol), DCC (2.06 g; 0.01 mol), pyridine (0.79 g; 0.01 mol) and CS_2 (1.52 g; 0.02 mol) in dry THF (100 ml) was stirred at 0° for 4 hr. After filtration of DCU which precipitated with addition of ether, the filtrate was evaporated and chromatographed on silica gel. From the benzene eluate was obtained 0.19 g (5.2%) of **6a** as white needles, mp 135—137° after recrystallization from hexane–ether (2: 3). *Anal.* Calcd. for $C_{17}H_{14}N_2O_4S_2$: C, 54.53; H, 3.77; N, 7.48. Found: C, 54.87; H, 3.91; N, 7.29. IR ν_{max}^{film} cm^{-1}: 3300 (amide), 2050 (NCS), 1780 (β-lactam), 1705 (ester), 1600 (phenyl). NMR δ (ppm): 2.30 (3H, s, 3-CH_3), 3.26 (1H, d, $J_{gem.}$=19.0 Hz, 2β-H), 3.63 (1H, d, $J_{gem.}$=19.0 Hz, 2α-H), 5.01 (1H, d, $J_{6,7}$=4.8 Hz, 6-H), 5.25 (1H, d, $J_{7,6}$=4.8 Hz, 7-H), 5.52 (2H, d, $J_{gem.}$=4.2 Hz, OCH_2), 7.30—8.10 (5H, m, phenyl).

From the further elution of the column 1.38 g (24%) of the adduct (7a) was obtained as white needles, mp 119° after recrystallization from ether. *Anal.* Calcd. for $C_{30}H_{36}N_4O_4S_2$: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.81; H, 6.19; N, 9.55. IR ν_{max}^{film} cm^{-1}: 3350 (amide), 1780 (β-lactam), 1740 (ester), 1680 (C=N–), 1605 (phenyl). NMR δ (ppm): 0.85—2.09 (2OH, m, cyclohexyl), 2.24 (3H, s, 3-CH_3), 3.20 (1H, $J_{gem.}$=19.0 Hz, 2β-H), 2.65 (1H, b, cyclohexyl), 3.63 (1H, d, $J_{gem.}$=19.0 Hz, 2α-H), 3.80 (1H, b, cyclohexyl), 4.83 (1H, d, $J_{6,7}$=4.2 Hz, 6-H), 5.07 (1H, d, $J_{7,6}$=4.2 Hz, 7-H), 5.53 (2H, d, $J_{gem.}$=4.8 Hz, OCH_2), 7.32—8.10 (5H, m, phenyl).

Pivaloyloxymethyl 7-Isothiocyanatodeacetoxycephalosporanate (6b) and the Adduct with DCC (7b)——To a solution of **5b** (1.05 g; 0.0032 mol) was added DCC (0.66 g; 0.0032 mol), pyridine (0.25 g; 0.0032 mol), and CS_2 (0.48 g; 0.0064 mol) in dry THF (50 ml) and stirred at 0° for 4 hr. The reaction mixture was treated similarly as described above, 0.22 g (12%) of **6b** was obtained as pale yellow liquid. *Anal.* Calcd. for $C_{15}H_{18}N_5O_2S_2$: C, 48.63; H, 4.89; N, 7.56. Found: C, 48.75; H, 4.94; N, 7.39. IR ν_{max}^{film} cm^{-1}: 2150 (NCS), 1790 (β-lactam), 1750 (ester). NMR δ (ppm): 1.29 (9H, s, $(CH_3)_3$), 2.26 (3H, s, 3-CH_3), 3.23 (1H, d, $J_{gem.}$=18.0 Hz, 2β-H), 3.40 (1H, d, $J_{gem.}$=18.0 Hz, 2α-H), 4.98 (1H, d, $J_{6,7}$=5.0 Hz, 6-H), 5.29 (1H, $J_{7,6}$=5.0 Hz, 7-H), 5.84, 5.98 (2H, dd, $J_{gem.}$=7.6 Hz, OCH_2).

From the further eluate of the column, 0.11 g (9.5%) of adduct (**7b**) was obtained as colorless liquid. *Anal.* Calcd. for $C_{28}H_{40}N_4O_5S_2$: C, 58.30; H, 6.99; N, 9.71. Found: C, 58.01; H, 6.96; N, 9.41. IR ν_{max}^{film} cm^{-1}: 3300 (amide), 1780 (β-lactam), 1740 (ester). NMR δ (ppm): 1.23 (9H, s, $(CH_3)_3$), 2.15 (3H, s, 3-CH_3), 0.90—2.22 (2OH, m, cyclohexyl), 2.76 (1H, b, cyclohexyl), 3.11 (1H, $J_{gem.}$=19.0 Hz, 2β-H), 3.58 (1H, d, $J_{gem.}$= 19.0 Hz, 2α-H), 3.70 (1H, b, cyclohexyl), 4.79 (1H, d, $J_{6,7}$=5.0 Hz, 6-H), 4.99 (1H, d, $J_{7,6}$=5.0 Hz, 7-H), 5.87 (2H, bs, OCH_2).

Ureylenedi-7-pivaloyloxymethyl Deacetoxycephalosporanate (8b)——**5b** (3.28 g; 0.01 mol) was treated similarly as described in **4a**. Recrystallization from benzene–acetone (1: 1) yielded 2.72 g (78%) of **8b** as colorless needles, mp 251—253° (dec.). *Anal.* Calcd. for $C_{29}H_{38}N_4O_{11}S_2$: C, 51.02; H, 5.61; N, 8.21. Found: C, 50.95; H, 5.58; N, 8.23. IR ν_{max}^{film} cm^{-1}: 3300 (amide), 1780 (β-lactam), 1740 (ester). NMR δ (ppm):

1.23 (18H, s, $((CH_3)_3)_2$), 2.12 (6H, s, 3-$(CH_3)_2$), 3.18 (2H, $J_{gem.}=19.0$ Hz, $(2\beta\text{-H})_2$), 3.61 (2H, d, $J_{gem.}=19.0$ Hz, $(2\alpha\text{-H})_2$), 4.93 (2H, d, $J_{6,7}=4.8$ Hz, $(6\text{-H})_2$), 5.78 (2H, d, $J_{7,6}=4.8$ Hz, $(7\text{-H})_2$), 5.88 (4H, d, $J_{gem.}=4.0$ Hz, $(OCH_2)_2$), 6.72 (2H, d, $J=9.0$ Hz, $(NH_2)_2$).

Reaction of Phenacyl 6-Isothiocyanatopenicillanate (2a) with Benzylamine——To a solution of **2a** (3.76 g; 0.01 mol) in THF (50 ml) was added freshly distillated benzylamine (1.07 g; 0.01 mol) under stirring at 0°. After 10 min, the reaction mixture was evaporated to dryness under reduced pressure. Crystallization of the residue from benzene gave 4.30 g (89%) of **9** as colorless needles, mp 153—155°. *Anal.* Calcd. for $C_{24}H_{25}O_4N_3S_2$: C, 59.61; H, 5.21; N, 8.69. Found: C, 59.67; H, 5.27; N, 8.68. IR ν_{max}^{KBr} cm^{-1}: 3350 (amide), 1750 (ester), 1600 (phenyl). NMR (DMSO-d_6) δ (ppm): 2.60 (3H, s, $2\alpha\text{-CH}_3$), 2.66 (3H, s, $2\beta\text{-CH}_3$), 4.50 (1H, s, 3-H), 4.68 (2H, d, $J_{gem.}=6.2$ Hz, $PhCH_2$), 5.57 (1H, d, $J_{5,6}=5.8$ Hz, 5-H), 5.59 (2H, s, OCH_2), 5.96 (1H, $J_{6.5}=5.8$ Hz, 6-H), 7.32 (5H, s, phenyl), 7.46—8.35 (7H, m, phenyl, CONH, CSNH).