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2-(Alkylthio)penem-3-carboxylic Acids. II.[1] Chemical Manipulation of Penem Side Chains

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The *tert*-butyldimethylsilyl group was found to be effective for protection of the hydroxyl group in penem synthesis. Manipulation of the side-chain hydroxyl group of base-sensitive penem-3-carboxylates was successfully conducted by means of a displacement reaction using a combination of triphenylphosphine-diethyl azodicarboxylate in the presence of a nucleophile.

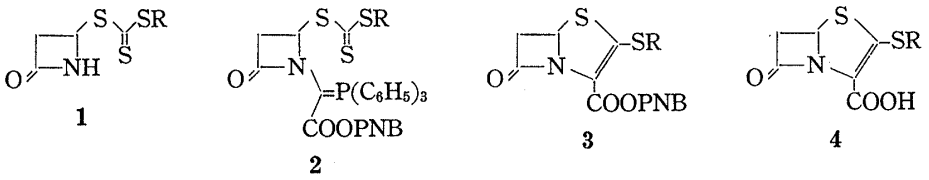
Keywords——antibiotics; β-lactam; penem-3-carboxylic acid; trithiocarbonate; intramolecular Wittig reaction; manipulation of penem side chain

In the preceding paper, we reported the transformation of azetidinone trithiocarbonates **1a** to their N-(phosphoranylidene)acetates **2a**, whose intramolecular Wittig reaction successfully resulted in the formation of penem esters **3a**,[1] and we also showed that penem-3-carboxylic acids **4a** derived from **3a** exhibited remarkable antibacterial activities against gram-positive and gram-negative bacteria.[3] Unfortunately, these penems were not only unstable to air and prolonged storage, but were also sensitive to both acid and base; therefore, the synthetic routes were designed to start from the phosphoranes **2a**, already provided with the requisite function in their side chains, and after penem ring formation, transformation to the final acids was achieved by a short procedure under mild conditions. This paper deals with the synthesis of penem compounds having a versatile side-chain hydroxyl function, and with chemical manipulations based on the hydroxyl groups to provide a supplementary route to penem derivatives.

In order to obtain a penem with a hydroxyl group in the side chain, we first chose a tetrahydropyranyl group (THP) for its protection and attempted the following reactions. This was because the thiazoline ring formation would presumably not be successful in the presence of a neighboring unmasked hydroxyl group (for instance, **2b**→**3b**), and also removal of the blocking group under basic conditions is not appropriate at the last stage of penem synthesis.[4]

2-(Tetrahydropyranyloxy)ethylmercaptan was prepared from the corresponding bromide[5] by treatment with disodium trithiocarbonate in aqueous methanol[6] followed by mild acidification. According to the method described earlier,[1] the mercaptan thus obtained was transformed to its sodium alkyl trithiocarbonate by treatment with sodium methoxide, then with carbon

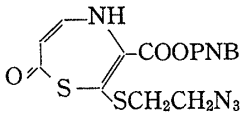
1) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, and E. Ohki, *Chem. Pharm. Bull.*, **28**, 3232 (1980).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
3) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, *J. Antibiotics*, **33**, 107 (1980).
4) Assuming that the N-(phosphoranilidene)acetate group is rather stable to basic hydrolysis (see L.D. Cama and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978)), we considered that the phosphorane **2c** having an acetoxy group in the side chain, which was reported earlier,[1] might be amenable to selective base hydrolysis, giving the hydroxy derivative **2b**; thus, **2c** was treated with sodium methoxide in methanol at low temperature. However, the yield of **2b** was low, presumably due to some attack on the trithiocarbonate function by bases.
5) D.T. Witiak, G.K. Poochikian, D.R. Feller, N.A. Kenfield, and H.A.I. Newman, *J. Med. Chem.*, **18**, 992 (1975).
6) The reaction in aqueous solution reported earlier did not give a satisfactory result. See D.J. Martin and C.C. Greco, *J. Org. Chem.*, 33, 1275 (1968).



1 2 3 4

a: R=alkyl
b: R=CH_2CH_2OH
c: R=$CH_2CH_2OCOCH_3$
d: R=CH_2CH_2OTHP
e: R=$CH_2CH_2OTBDMS$
f: R=$CH_2CH_2OSO_2CH_3$
g: R=$CH_2CH_2N_3$
h: R=$CH_2CH_2NH_2$
i: R=$CH_2CH_2NHCOCH_3$

b′: R=$CH_2CH_2CH_2OH$
c′: R=$CH_2CH_2CH_2OCOCH_3$
d′: R=$CH_2CH_2CH_2OTHP$
e′: R=$CH_2CH_2CH_2OTBDMS$
f′: R=$CH_2CH_2CH_2OSO_2CH_3$
g′: R=$CH_2CH_2CH_2N_3$
h′: R=$CH_2CH_2CH_2NH_2$
i′: R=$CH_2CH_2CH_2NHCOCH_3$
j′: R=$CH_2CH_2CH_2OCOCOOCH_3$
k′: R=$CH_2CH_2CH_2SCSNH_2$
l′: R=$CH_2CH_2CH_2SCSN$



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PNB: *p*-nitrobenzyl
THP: tetrahydropyranyl
TBDMS: *tert*-butyldimethylsilyl

Chart 1

disulfide. Successive reaction with 4-acetoxy-2-azetidinone[7] resulted in a 76% yield of the azetidinone trithiocarbonate **1d**. Reflux of **1d** with *p*-nitrobenzyl glyoxylate in benzene gave the diastereomeric hemiaminal in 83% yield, and treatment of this product with thionyl chloride in the presence of 2,6-lutidine followed by reaction with triphenylphosphine afforded the phosphorane **2d** as a yellow powder in 51% yield over the two steps. The thiazoline ring formation from **2d** was carried out by heating in xylene at 125° for 23 hr; but the yield of the penem ester **3d** was rather low (26% yield) and the reaction seemed to be accompanied by removal of the THP group to give the 2-hydroxyethylthio derivative **3b** (5% yield) as a by-product. In addition, acid hydrolysis of the THP-masked penem ester **3d** was attempted by treatment with aqueous acetic acid or a dilute aqueous solution of *p*-toluenesulfonic acid at room temperature, but the desired hydroxy compound **3b** was obtained in an unsatisfactory yield (51% yield). Thus, the use of the THP group for protection in penem synthesis proved unsuitable and an alternative masking group for the hydroxyl functionality was sought.

The *tert*-butyldimethylsilyl (TBDMS) group has attractions for this purpose because of its stability to heat and its relative ease of removal with fluoride ions under neutral conditions.[8] Acid hydrolysis of the phosphorane THP-ether **2d** obtained above gave a quantitative yield of the phosphorane alcohol **2b** whose acetate **2c** was shown to be identical with the sample reported earlier.[1] The alcohol **2b** was converted into its TBDMS-ether **2e** on treatment with *tert*-butyldimethylchlorosilane in the presence of imidazole. The ether **2e** was subjected to Wittig cyclization in xylene (130—135°, 13 hr), giving a 69% yield of the penem ester **3e** along with 18% recovery of **2e**. Treatment of the penem ester **3e** with tetrabutylammonium fluoride in the presence of acetic acid[9] gave the desired 2-[(2-hydroxyethyl)thio]penem ester **3b** in good yield.

Next, we attempted to carry out displacement reactions of the restored hydroxyl function as follows. Treatment of the penem alcohol **3b** with mesyl chloride in the presence of triethyl-

7) K. Clauss, D. Grimm, and G. Prossel, *Liebigs Ann. Chem.*, **1974**, 539.
8) E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
9) G. Just and T.J. Liak, *Can. J. Chem.*, **56**, 211 (1978).

amine gave the mesylate **3f**. On treatment with sodium azide in dimethylsulfoxide in the usual manner, **3f** did not give any azide derivative **3g** even at low temperatures, but gave a thiazepine derivative **5** in 44% yield. The infrared spectrum of **5** showed the presence of the azide function at 2130 cm^{-1} but no absorption due to the β-lactam. The new absorption at 1590 cm^{-1}, probably due to the –NH–Ċ=Ċ–CO–S– system, in addition to a marked NH absorption at 3250 cm^{-1} supported the structure of **5**. Further, the nuclear magnetic resonance spectrum of **5** exhibited a characteristic doublet at 4.74 ppm, J=14 Hz, and a doublet of doublets at 7.42 ppm, J=14 and 9 Hz, reflecting the presence of a –CO–CH=CH–NH–conjugated system. In view of reports that ring conversion into thiazepine derivatives had also been carried out in penicillins,[10] under rather harsh conditions, the penem skeleton seems to be more sensitive to bases than that of penicillins and not amenable to ordinary displacement reactions.

In 1976, Loibner and Zbiral[11] reported a new displacement reaction of the hydroxyl group with many nucleophiles by the use of a combination of triphenylphosphine–diethyl azodicarboxylate, developed from the work of Mitsunobu *et al.*[12] Considering that this new displacement reaction proceeds under neutral conditions, we applied this method to the penem compounds in the following way. The penem alcohol **3b** was treated at room temperature with triphenylphosphine, diethyl azodicarboxylate and hydrogen azide in tetrahydrofuran. The displacement reaction proceeded smoothly to give an azide **3g** in 80% yield. Hydrogenolysis of **3g** with 10% palladium-charcoal in a mixture of tetrahydrofuran and a phosphate buffer solution gave 2-(aminoethylthio)penem-3-carboxylic acid **4h** along with a small amount of the sodium salt of 2-(azidoethylthio)penem **4g**. Acetylation of **4h** gave **4i**, which was shown to be identical with the sample reported earlier.[1] Thus, the displacement reaction using the combination of triphenylphosphine-azodicarboxylate does not affect the penem ring system and presumably substitution of the hydroxyl group in the penem side chain with other nucleophiles can be similarly carried out.

Starting from 3-(tetrahydropyranyloxy)propylmercaptan, we analogously prepared 2-[(3-hydroxypropyl)thio]penem-3-carboxylate **3b′** *via* the reaction sequence **1d′**→**2d′**→**2b′**→**2e′**→**3e′**→**3b′**, as described in "Experimental." The penem alcohol **3b′** formed its acetate **3c′**, its mesylate **3f′** and its oxalate **3j′** in the usual way. Further, **3b′** was similarly converted into an azide **3g′** by the displacement reaction described above. Hydrogenolysis of **3g′** gave the amino acid **4h′**, whose acetylation afforded **4i′**. On the other hand, the penem mesylate **3f′** was treated with ammonium dithiocarbamate to give the thiocarbamoylthio derivative **3k′** and with ammonium pyrrolidinedithiocarbamate to give pyrrolidine dithiocarbamate **3l′**. Hydrogenation of these penem esters with 10% palladium-charcoal in tetrahydrofuran gave the corresponding penem-3-carboxylic acids which were unstable to chromatographic purification on silica gel or, in some cases, even to recrystallization; therefore, they were washed briefly with appropriate solvent and immediately subjected to biological testing. In the case of hydrogenolysis with a mixture of tetrahydrofuran and a phosphate buffer solution as solvent, the penem acids were obtained as their sodium salts which proved to be more stable than the free acids. The antibacterial activities of these penem acids were communicated in our preceding paper.[3]

Experimental

Melting points are not corrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton magnetic resonance spectra (NMR) on a Varian A-60 or Hitachi–Perkin–Elmer R-24 spectrometer,

10) J.R. Jackson and R.J. Stoodley, *J.S.C. Chem. Commun.*, **1970**, 14; O.K. Kovacs, B. Ekstrom, and B. Sjoberg, *Tetrahedron Lett.*, **1969**, 1863.
11) H. Loibner and E. Zbiral, *Helv. Chim. Acta*, **39**, 2100 (1976).
12) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967); O. Mitsunobu and E. Eguchi, *ibid.*, **44**, 3427 (1971).

using, unless otherwise specified, TMS as the internal standard. Thin-layer chromatography (TLC) was performed on TLC-plates, Silica gel F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by UV-irradiation or by spraying with vanadic acid–sulfuric acid followed by heating or with iodine. Chromatography columns were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and preparative TLC plates were provided with Silica gel $60F_{254}$ (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br., broad.

Mercaptans——2-(Tetrahydropyranyloxy)ethylmercaptan and 3-(tetrahydropyranyloxy)propylmercaptan were derived from their corresponding bromides[5,13] by treatment with disodium trithiocarbonate in aqueous methanol followed by mild acidification with dil. HCl according to Martin *et al.*[6]

4-[[[[2-[(Tetrahydropyran-2-yl)oxy]ethyl]thio]thiocarbonyl]thio]-2-azetidinone (1d) and Its [3-[(Tetrahydropyran-2-yl)oxy]propyl]thio Analogue (1d′)——To an ice-cold sodium methoxide solution prepared by dissolving sodium metal (1.63 g, 71 mmol) in MeOH (200 ml) were added 2-[(tetrahydropyran-2-yl)oxy]ethylmercaptan (11.7 g, 72 mmol) and then carbon disulfide (5.50 g, 72 mmol) with stirring and the mixture was stirred for 5 min with cooling. Then, a solution of 4-acetoxy-2-azetidinone[7] (9.29 g, 72 mmol) in MeOH (13 ml) was added and stirring was continued for 1 hr with cooling. The mixture was diluted with AcOEt, washed with brine and dried. The solvent was evaporated off *in vacuo*, and the resulting oil was chromatographed (150 g, benzene) to give **1d** (15.77 g, 74%) as a yellow oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250, 1780, 1065, 1020. NMR ($CDCl_3$) δ: 1.57 (6H, br.), 2.8—4.2 (8H, m), 4.57 (1H, br.), 5.54 (1H, dd, $J=5$, 3 Hz), 7.25 (1H, br.). *Anal.* Calcd for $C_{11}H_{17}NO_3S$: C, 43.00; H, 5.54; N, 4.56; S, 31.29. Found: C, 42.63; H, 5.72; N, 4.44; S, 31.56.

Starting from 3-[(Tetrahydropyran-2-yl)oxy]propylmercaptan, similar reactions were carried out to give **1d′** as an oil in 79% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3250, 1780. NMR ($CDCl_3+D_2O$) δ: 1.65 (6H, br.). 1.97 (2H, m), 2.96 (1H, dd, $J=15.5$, 2.5 Hz), 3.2—4.1 (7H, m), 4.56 (1H, br. s), 5.64 (1H, dd, $J=5$, 2.5 Hz).

***p*-Nitrobenzyl 2-[4-[[[[2-[(Tetrahydropyran-2-yl)oxy]ethyl]thio]thiocarbonyl]thio]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (2d) and Its [3-[(Tetrahydropyran-2-yl)oxy]propyl]thio Analogue (2d′)**——A solution of **1d** (17.0 g, 55.4 mmol) and *p*-nitrobenzyl glyoxylate (hydrate, 13.1 g, 57.7 mmol) in benzene (400 ml) was refluxed for 9 hr. The mixture was evaporated to dryness *in vacuo* and the residue was chromatographed (250 g, benzene–AcOEt, 10: 1) to give the hemiaminal (23.8 g, 83%) as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 1780, 1760. NMR ($CDCl_3$) δ: 1.3—2.0 (6H, m), 3.01 and 3.04 (1: 1, 1H, dd, $J=16$, 3 Hz), 3.3—4.2 (9H, m), 4.58 (1H, br. s), 5.28 and 5.33 (1: 1, 2H, s), 5.44 and 5.59 (1: 1, 1H, s), 5.90 and 6.00 (1: 1, 1H, dd, $J=6$, 3 Hz), 7.54 (2H, d), 8.23 (2H, d).

To a solution of the hemiaminal obtained as above (1: 1 isomeric mixture, 20.7 g, 40 mmol) in tetrahydrofuran (325 ml) were added dropwise 2,6-lutidine (4.71 g, 44 mmol) and then thionyl chloride (5.00 g, 42 mmol) at −10° with stirring. The mixture was stirred for 30 min at the same temperature, then triphenylphosphine (21.0 g, 80 mmol) and 2,6-lutidine (8.53 g, 80 mmol) were added. The whole mixture was stirred under an N_2 atmosphere for 11 hr at 50°, and then diluted with AcOEt, washed with water and dried. The product obtained by removal of the solvent was chromatographed (100 g, benzene, AcOEt, 6: 1) to give **2d** (15.6g, 51%) as fine yellow crystals, mp 103—110° (from hexane–AcOEt).

Similar treatment of **1d′** with *p*-nitrobenzyl glyoxylate gave the corresponding hemiaminal in 95% yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3370, 1778, 1760 (sh.). NMR ($CDCl_3$) δ: 1.60 (6H, br.), 1.96 (2H, m), 3.08 and 3.12 (1: 1, 1H, dd, $J=15.5$, 2.5 Hz), 3.2—4.1 (7H, m), 4.60 (1H, br.), 5.37 and 5.43 (1: 1, 2H, s), 5.63 (1H, d, $J=9$ Hz), 6.00 and 6.10 (1: 1, 1H, dd, $J=5$, 2.5 Hz), 7.65 (2H, d), 8.33 (2H, d). *Anal.* Calcd for $C_{21}H_{26}N_2O_8S_3$: C, 47.53; H, 4.94; N, 5.28; S, 18.13. Found: C, 47.21; H, 4.88; N, 5.37; S, 17.94.

The hemiaminal obtained above was similarly converted into **2d′** in 67% yield as fine yellow crystals, mp 96—98° (from hexane–AcOEt). Physical data for **2d** and **2d′** are given in Table I.

***p*-Nitrobenzyl 2-[4-[[[(2-Hydroxyethyl)thio]thiocarbonyl]thio]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (2b) and Its (3-Hydroxypropyl)thio Analogue (2b′) and Their Acetates (2c and 2c′)**——A solution of **2d** (11.40 g, 15 mmol), and *p*-toluenesulfonic acid (hydrate, 855 mg, 4.5 mmol) in a mixture of THF (205 ml) and water (80 ml) was kept at 50° for 7 hr with stirring. The mixture was then diluted with AcOEt, washed with water, dried and evaporated *in vacuo*. Thus, crude **2b** (10.0 g, 98%) was obtained. An analytical sample was obtained as fine crystals, mp 162—164°, by recrystallization from AcOEt. Treatment of **2b** with acetic anhydride and triethylamine in CH_2Cl_2 and work-up as usual afforded **2c**, which was identical with the sample obtained earlier.[1]

The (3-hydroxypropyl)thio analogue **2b′**, fine yellow crystals, mp 180—182° (from AcOEt), was obtained from **2d′** in 81% yield. Acetylation of **2d′** gave **2c′** in 90% yield, mp 168—170° (from hexane–AcOEt). Elementary and spectral data are given in Table I.

***p*-Nitrobenzyl 2-[4-[[[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]thiocarbonyl]thio]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (2e) and Its [3-(*tert*-Butyldimethylsilyloxy)propyl]thio Analogue (2e′)**——The crude **2b** (10.0 g, 14.8 mmol) obtained above was dissolved in dimethylformamide (50 ml), then imidazole (2.45 g, 36 mmol) and *tert*-butyldimethylchlorosilane (5.43 g, 36 mmol) were added with stirring and ice-cooling. After being stirred for 20 min, the reaction mixture was diluted with benzene, washed with water, dried and evaporated *in vacuo*. The residue was chromatographed (150 g, hexane–acetone, 3.5: 1) and the product was recrystallized from hexane–acetone to give **2e** (10.23 g, 88%) as fine yellow crystals, mp 125—

Table I. *p*-Nitrobenzyl 2-[4-[(Alkylthio)thiocarbonyl]thio]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetates (2)

Compd.	R[a]	IR ν_{max}^{Nujol} cm^{-1}	NMR δ[b] ppm ($CDCl_3$)	Formula	Analysis, (%) Calcd (Found) C	H	N	P
2b	CH_2CH_2OH	3470, 1762, 1660	—	$C_{33}H_{29}N_2O_6PS_3$	58.48 (58.36	4.46 4.45	4.13 4.34	4.57 4.71)
2b′	$CH_2CH_2CH_2OH$	3600, 3470, 1759, 1665	1.86 (2H, m), 2.8 (2H, br.), 3.44 (2H, t, 7), 3.61 (2H, q, 6.5), 4.90 and 5.24 (2H, s), 6.25 (1H, br.)	$C_{34}H_{31}N_2O_6PS_3$	59.11 (58.88	4.52 4.43	4.06 4.16	4.48 4.80)
2c′	$CH_2CH_2CH_2OCOCH_3$	1762, 1740, 1658	—	$C_{36}H_{33}N_2O_7PS_3$	59.00 (58.81	5.63 4.61	3.48 4.03	4.37 4.05)
2d	CH_2CH_2OTHP	1764, 1659, 1607	1.3—2.0 (6H, m), 2.5—4.2 (10H, m), 4.65 (1H, br. s), 4.90 and 5.22 (2H, s), 6.35 (1H, m)	$C_{38}H_{37}N_2O_7PS_3$	59.91 (59.96	5.03 4.95	3.68 3.80)	—
2d′	$CH_2CH_2CH_2OTHP$	1769, 1630[c]	1.65 (6H, br.), 1.99 (2H, m), 2.8 (2H, br.), 3.1—4.2 (6H, m), 4.65 (1H, br.), 4.92 and 5.25 (2H, s), 6.30 (1H, br.)	$C_{39}H_{39}N_2O_7PS_3$	60.45 (60.28	5.07 5.11	3.62 3.72	4.00 4.09)
2e	$CH_2CH_2OTBDMS$	1767, 1662, 1610	0.08 (6H, s), 0.92 (9H, s), 2.5—4.1 (2H, m), 3.54 (2H, t, 5), 3.88 (2H, t, 5), 4.93 and 5.25 (2H, s), 6.3 (1H, m)	$C_{39}H_{43}N_2O_6PS_3Si$	59.22 (59.23	5.48 5.42	3.54 3.46	3.92 4.27)
2e′	$CH_2CH_2CH_2OTBDMS$	1759, 1659	0.07 (6H, s), 0.87 (9H, s), 1.85 (2H, m), 2.7 (2H, br.), 3.35 (2H, t, 7.5), 3.63 (2H, t, 6), 4.82 and 5.14 (2H, s), 6.22 (1H, br.)	$C_{40}H_{45}N_2O_5PS_3Si$	59.67 (59.70	5.63 5.54	3.48 3.73	3.85 4.07)

a) THP, tetrahydropyranyl; TBDMS, *tert*-butyldimethylsilyl.
b) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons at 6.6—8.4 ppm (19H, m) are omitted.
c) Liquid film used.

Table II. *p*-Nitrobenzyl 3-(Alkylthio)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylates (3)

Compd.	R[a]	IR ν_{max}^{Nujol} cm^{-1}	NMR δ[b] ppm ($CDCl_3$)	Formula	Analysis, (%) Calcd (Found) C	H	N	S
3b	CH_2CH_2OH	3520, 1790, 1668	3.09 (2H, t-like, 6), 3.58 (1H, dd, 18, 2), 3.69 (2H, t-like, 6), 4.00 (1H, dd, 18, 4), 5.33 and 5.56 (1H each, ABq, 15), 5.86 (1H, dd, 4, 2)[c]	$C_{15}H_{14}N_2O_6S_2$	47.11 (46.99	3.69 3.77	7.33 7.15	16.77 16.76)
3b′	$CH_2CH_2CH_2OH$	3380, 1789, 1680	1.94 (2H, m), 3.10 (2H, t, 7), 3.75 (2H, t, 6), 3.46 (1H, dd, 15.5, 2), 3.86 (1H, dd, 15.5, 3.5), 5.23 and 5.49 (1H each, ABq, 14), 5.73 (1H, dd, 3.5, 2)	$C_{16}H_{16}N_2O_6S_2$	48.47 (48.33	4.07 3.93	7.07 6.90	16.18 16.10)
3c′	$CH_2CH_2CH_2OCOCH_3$	1801, 1738, 1679	2.05 (3H, s), 2.05 (2H, m), 3.03 (2H, t-like), 3.51 (1H, dd, 17, 2), 3.89 (1H, dd, 17, 3.5), 4.14 (2H, d, 6), 5.20 and 5.44 (1H each, ABq, 13.5), 5.68 (1H, dd, 3.5, 2)	$C_{18}H_{18}N_2O_7S_2$	49.30 (49.21	4.14 4.16	6.39 6.39	14.63 14.37)
3d	CH_2CH_2OTHP	1784, 1680	1.2—1.8 (6H, m), 3.14 (2H, t-like, 7), 3.41 (1H, dd, 17, 2), 3.81 (1H, dd, 17, 4), 4.58 (1H, br, s), 5.15 and 5.45 (1H each, ABq, 13.5), 5.78 (1H, dd, 4,2)	$C_{20}H_{22}N_2O_7S_2$	51.49 (51.28	4.75 4.67	6.00 5.94	13.75 13.96)
3e	$CH_2CH_2OTBDMS$	1790, 1683	0.05 (6H, s), 0.87 (9H, s), 3.11 (2H, t, 6), 3.49 (1H, dd, 17, 2), 3.78 (2H, t, 6), 3.91 (1H, dd, 17, 4), 5.25 and 5.51 (1H each ,ABq, 14.5), 5.75 (1H, dd, 4, 2)	$C_{21}H_{28}N_2O_6S_2Si$	50.78 (50.63	5.68 5.61	5.64 5.30	12.91 12.86)
3e′	$CH_2CH_2CH_2OTBDMS$	1797, 1695[d]	0.06 (6H, s), 0.85 (9H, s), 1.83 (2H, m), 3.00 (2H, t, 7.5), 3.64 (2H, t, 6), 3.41 (1H, dd, 16.5, 2), 3.80 (1H, dd, 16.5, 3.5), 5.15 and 5.42 (1H each, ABq, 14), 5.66 (1H, dd, 3.5, 2)	$C_{22}H_{30}N_2O_6S_2Si$	51.74 (51.65	5.92 5.98	5.49 5.37	12.56 12.62)
3f	$CH_2CH_2OSO_2CH_3$	1797, 1692[d]	2.99 (3H, s), 3.26 (2H, t, 7), 3.47 (1H, dd, 17, 2), 3.84 (1H, dd, 17, 4), 4.40 (2H, t, 7), 5.19 and 5.45 (1H each ,ABq, 13), 5.71 (1H, dd, 4, 2)	$C_{16}H_{16}N_2O_8S_3$	—	—	—	—
3f′	$CH_2CH_2CH_2OSO_2CH_3$	1800, 1695[d]	2.15 (2H, m), 2.99 (3H, s), 3.08 (2H, t-like), 3.49 (1H, dd, 16, 2), 3.84 (1H, dd, 16, 3.5), 4.32 (2H, t, 6), 5.22 and 5.48 (1H each, ABq, 14), 5.73 (1H, dd, 3.5, 2)	$C_{17}H_{18}N_2O_8S_3$	43.03 (42.80	3.82 3.81	5.90 5.94	20.27 20.57)
3g	$CH_2CH_2N_3$	2120, 1801, 1690	3.12 (2H, t, 6), 3.52 (1H, dd, 17, 2), 3.60 (2H, t, 6), 3.86 (1H, dd, 17, 4), 5.21 and 5.50 (1H, ABq, 14), 5.78 (1H, dd, 4, 2)	$C_{15}H_{13}N_5O_5S_2$	44.32 (44.44	3.22 3.12	17.19 17.06	15.74 15.93)
3g′	$CH_2CH_2CH_2N_3$	2110, 1802, 1683	2.0 (2H, m), 3.07 (2H, d-like, 7), 3.48 (2H, t, 6.5), 3.55 (1H, dd, 16.5, 2), 3.90 (1H, dd, 16.5, 3.5), 5.25 and 5.54 (1H each, ABq, 14.5), 5.78 (1H, dd, 3.5, 2), 5.75 (1H, dd, 3.5, 2)	$C_{16}H_{15}N_5O_5S_2$	45.59 (46.01	3.59 3.58	16.62 16.57	15.22 15.34)
3j′	$CH_2CH_2CH_2OCOCOOCH_3$	1799, 1778, 1749, 1695	2.15 (2H, m), 3.08 (2H, t-like), 3.50 (1H, dd, 16, 2), 3.86 (1H, dd, 16, 3.5), 3.89 (3H, s), 4.41 (2H, t, 6), 5.23 and 5.51 (1H each, ABq, 14.5)	$C_{19}H_{18}N_2O_9S_2$	—	—	—	—
3k′	$CH_2CH_2CH_2SCSNH_2$	3370, 3250, 3150, 1790, 1679	—	$C_{17}H_{17}N_3O_5S_3$	43.29 (43.41	3.63 3.84	8.91 8.42)	—
3l′	$CH_2CH_2CH_2SCSN$ 	1800, 1696[d]	1.8—2.3 (6H, m), 3.02 (2H, m), 3.37 (2H, t, 7), 3.43 (1H, dd, 16, 2), 3.79 (1H, dd, 16, 3.5), 3.5—4.0 (4H, m), 5.20 and 5.46 (1H each, ABq, 14), 5.70 (1H, dd, 3.5, 2)	$C_{21}H_{23}N_3O_5S_4$	—	—	—	—

a) THP, tetrahydropyranyl; TBDMS, *tert*-butyldimethylsilyl.
b) Chemical shifts are given with roton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons at 7.6—8.3 ppm are omitted.
c) d_6-DMSO used as a solvent.
d) $CHCl_3$ used as a solvent.

126.5°. The (3-hydroxypropyl)thio analogue **2b′** was similarly converted into **2e′** fine powder, mp 127—130° (from hexane–AcOEt) in quantitative yield. Elementary analysis and spectral data are shown in Table I.

***p*-Nitrobenzyl 3-[[2-(*tert*-Butyldimethylsilyloxy)ethyl]thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3e) and Its [3-(*tert*-Butyldimethylsilyloxy)propyl]thio Analogue (3e′)**——A solution of **2e** (101 mg, 0.13 mmol) and hydroquinone (7 mg) in xylene (10 ml) was kept at 130—135° (bath temp.) for 13 hr under an N_2 atmosphere with stirring. The reaction mixture was evaporated to dryness *in vacuo* and the residue was purified by preparative TLC (benzene–AcOEt, 5: 1). Thus, along with recovery of **2e** (18 mg, 18%), **3e** was obtained as a crystalline mass (44 mg, 69%), which was recrystallized from hexane–ethanol to provide needles, mp 94.5—95.5°. Heating **2e′** gave **3e′** in 52% yield as fine needles, mp 113—115° (from hexane–AcOEt). Elementary and spectral data are given in Table II.

***p*-Nitrobenzyl 3-[[2-[(Tetrahydropyran-2-yl)oxy]ethyl]thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3d)**——A solution of **2d** (5.0 g) in xylene (300 ml) was heated at 125° (bath temp.) for 23 hr and the product was chromatographed (40 g, benzene–AcOEt, 8: 1), giving **3d** (798 mg, 26%) as needles, mp 120—122° (from acetone–ethanol) and **3b** (136 mg, 5%) (see Table II), along with recovery of **2d** (1.17 g, 23%).

***p*-Nitrobenzyl 3-[(2-Hydroxyethyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3b) and Its (3-Hydroxypropyl)thio Analogue (3b′)**——i) To an ice-cold solution of **3e** (1.77 g, 3.57 mmol) in THF (15 ml) were added acetic acid (0.64 g, 10.7 mmol) and a solution of tetrabutylammonium fluoride (1.21 g, 4.64 mmol) in THF (5 ml) with stirring. The mixture was stirred for 2.5 hr at room temperature, then diluted with AcOEt and shaken with water. The organic layer was collected, washed with dil. $NaHCO_3$, then with water, dried and concentrated *in vacuo*, giving **3b** (1.21 g) as fine crystals. The mother liquor was evaporated and chromatographed ($CHCl_3$–AcOEt, 1: 1) to give a second crop (76 mg). The total yield was 94.5%. An analytical sample was obtained by recrystallization from $CHCl_3$–AcOEt, needles, mp 163.5—165.5°. Similar conversion of **3e′** into **3b′** was carried out in 75% yield, prisms, mp 127—129° (from AcOEt). Analytical and spectral data for these compounds are shown in Table II.

ii) A mixture of **3d** (335 mg), *p*-toluenesulfonic acid (hydrate, 335 mg), THF (18 ml) and water (9 ml) was stirred for 4.5 hr at room temperature. The mixture was extracted with AcOEt, washed with water, dried and evaporated to dryness *in vacuo*. The residue was recrystallized from AcOEt to give **3b′** (80 mg). The mother liquor of the recrystallization was subjected to TLC ($CHCl_3$–AcOEt, 3: 1) to provide a second crop (60 mg). The total yield was 140 mg (51%).

***p*-Nitrobenzyl 3-[(3-Acetoxypropyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3c′) and Its (3-Methoxalyloxypropyl)thio Analogue (3j′)**——To a solution of **3b′** (60 mg, 0.15 mmol) in CH_2Cl_2 (1 ml) were added triethylamine (50 mg, 0.5 mmol) and acetic anhydride (50 mg, 0.5 mmol) and the mixture was stirred for 2 hr at room temperature. Work-up in the usual manner and recrystallization of the product from AcOEt–hexane gave **3c′** (62 mg, 93%), mp 111—112°.

To a solution of **3b′** (50 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added triethylamine (50 mg, 0.5 mmol) and methyl chloroglyoxylate (50 mg, 0.41 mmol) at −10° with stirring. After being stirred for 30 min, the mixture was diluted with AcOEt and worked up as usual. Preparative TLC of the product (benzene–hexane, 3: 1) gave **3j′** (56 mg, 92%) as an oil.

***p*-Nitrobenzyl 3-[(2-Mesyloxyethyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3f) and Its (3-Mesyloxypropyl)thio Analogue (3f′)**——To an ice-cold suspension of **3b** (59 mg, 0.15 mmol) in CH_2Cl_2 (10 ml) were added triethylamine (34 mg, 0.34 mmol) and mesyl chloride (38 mg, 0.33 mmol) with stirring. The mixture was stirred for 1 hr with cooling, then worked up as usual. The product was chromatographed (3 g, benzene–AcOEt, 4: 1) to afford **3f** (48 mg, 68%) as an oil.

Similar treatment of **3b′** with triethylamine and mesyl chloride afforded the (3-mesyloxypropyl)thio homolog **3f′** in 89% yield as prisms, mp 111—112° (from AcOEt).

***p*-Nitrobenzyl 3-[[3-[(Thiocarbamoyl)thio]propyl]thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3k′) and Its (1-Pyrrolidinylcarbothioyl)thio Analogue (3l′)**——To a solution of **3f′** (50 mg, 0.105 mmol) in DMSO (1 ml) was added ammonium dithiocarbamate (25 mg, 0.23 mmol). The mixture was stirred for 1 hr at room temperature, and worked up as usual. Recrystallization of the product from AcOEt gave **3k′** (30 mg, 60%) as prisms, mp 134—135°.

Similarly, **3f′** (50 mg, 0.105 mmol) was treated with ammonium pyrrolidinedithiocarbamate (20 mg, 0.122 mmol) in DMSO (0.5 ml). Preparative TLC of the product (benzene–AcOEt, 3: 1) gave **3l′** (49 mg, 88%) as an oil.

***p*-Nitrobenzyl 3-[(2-Azidoethyl)thio]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3g) and Its (3-Azidopropyl)thio Analogue (3g′)**——To a stirred suspension of **3b** (1.28 g, 3.35 mmol) in THF (130 ml) were successively added triphenylphosphine (1.23 g, 4.69 mmol), a 0.7 M hydrogen azide benzene solution (8.2 ml, 5.74 mmol) and diethyl azodicarboxylate (0.82 g, 4.71 mmol) at room temperature. After being stirred for 15 min, the mixture was diluted with AcOEt and was worked up. The product was purified by chromatography (23 g, benzene–AcOEt, 12: 1), then by recrystallization from ethanol–acetone, giving **3g** (1.10 g, 80%) as needles, mp 98.5—100°.

In a similar way, **3b′** (349 mg, 0.88 mmol) was treated with triphenylphosphine (460 mg, 1.76 mmol), a 0.7 M hydrogen azide benzene solution (3.1 ml, 2.17 mmol) and diethyl azodicarboxylate (306 mg, 1.76

mmol) at room temperature for 15 min, giving **3g′** (264 mg, 71%) as fine needles, mp 98—99° (from AcOEt–hexane). Elementary analysis and spectral data are given in Table II.

3-(Alkylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acids (4b, 4g—i, 4b′, 4c′, 4f′, 4h′—l′)——i) A mixture of **3b** (100 mg), THF (10 ml), 0.1 M phosphate buffer solution (pH 7, 5 ml) and 10% palladium-charcoal (250 mg) was shaken under an H_2 atmosphere at room temperature for 2 hr. The catalyst was filtered off and washed with a mixture of ethanol and phosphate buffer solution. The filtrate and washings were combined, washed with AcOEt and concentrated *in vacuo* to about 10 ml at room temperature. The concentrate was charged on Diaion HP 20 AG (Mitsubishi Chemical Industries, Ltd., 20 ml), washed with water and eluted with 1% acetone-water. The fractions were collected and lyophilized to give the sodium salt of **4b** (32 mg, 45.5%) as an amorphous powder. UV $\lambda_{max}^{H_2O}$ nm (ε): 251 (4970), 321 (6820). IR ν_{max}^{KBr} cm^{-1}: 3400 (br.), 1766, 1587.

Similar treatments of **3b′** and **3k′** gave the sodium salts of **4b′** and **4k′** in 47% and 36% yields respectively. IR ν_{max}^{KBr} cm^{-1} for **4b′** (sodium salt): 3400, 1767, 1586. IR ν_{max}^{Nujol} cm^{-1} for **4k′** (sodium salt): 3290, 3160, 1770, 1595. UV $\lambda_{max}^{H_2O}$ nm (ε) for **4k′** (sodium salt): 247 (8260), 275 (9980), 321.1 (7370). NMR (D_2O) δ for **4k′** (sodium salt): 2.15 (2H, m), 3.09 (2H, t, J=7.5 Hz), 3.33 (2H, t, J=7 Hz), 3.54 (1H, dd, J=17, 1.5 Hz), 3.88 (1H, dd, J=17, 3.5 Hz), 5.82 (1H, dd, J=3.5, 1.5 Hz).

ii) A mixture of **3c′** (52 mg), THF (3 ml) and 10% palladium-charcoal (120 mg) was shaken for 15 hr at room temperature under an H_2 atmosphere. The mixture was filtered and evaporated to dryness *in vacuo*, and the residue was dissolved in ether–AcOEt (2: 1). The resulting yellow resin was filtered off and the filtrate was evaporated *in vacuo*. The crystals thus obtained were washed with ether to give **4c′** (17 mg, 48%), mp 120—130°. IR ν_{max}^{Nujol} cm^{-1}: 2600 (br.), 1788, 1735, 1650.

Similarly, hydrogenolysis of **3f′**, **3j′**, and **3l′** in THF gave **4f′**, mp 117—125°, **4j′**, mp 105—110°, and **4l′**, mp 117—122°, respectively. IR ν_{max}^{Nujol} cm^{-1} for **4f′**: 2600 (br.), 1788, 1650; for **4j′**: 2600, 1784, 1778 (sh.), 1744, 1651; for **4l′**: 2600 (br.), 1786, 1650.

iii) A mixture of **3g** (600 mg, 1.47 mmol), THF (40 ml), 0.1 M phosphate buffer solution (pH 7, 40 ml) and 10% palladium-charcoal (1.7 g) was shaken at room temperature under an H_2 atmosphere for 3 hr. Work-up followed by chromatographic purification using Diaion HP 20 AG as described above afforded **4h** (101 mg, 28%, from fractions eluted with 1% aqueous acetone) which was identical with the sample obtained earlier.[1] Further elution of the column with 2—4% acetone-water followed by removal of the solvent gave the sodium salt of **4g** (6 mg, 1.4%). IR ν_{max}^{KBr} cm^{-1}: 3420 (br.), 2120, 1778, 1600. NMR (D_2O) δ: 3.0—4.0 (4H, m), 3.46 (1H, dd, J=17, 2 Hz), 3.89 (1H, dd, J=17, 4 Hz), 5.79 (1H, dd, J=4, 2 Hz).

To a solution of **4h** (10 mg), obtained as described above, in 50% aqueous THF (2 ml) were added $NaHCO_3$ (7 mg) and acetic anhydride (5 mg) and the mixture was stirred for 30 min. The mixture was diluted with 0.5 M phosphate buffer solution (pH 7, 2 ml) and washed with AcOEt. The aqueous layer was concentrated, charged on Diaion HP 20 AG (5 ml), eluted with 2% acetone-water and lyophilized to give the sodium salt of **4i** (62% yield).

Similarly, hydrogenolysis of **3g′** gave **4h′** in 30% yield, as an amorphous powder, mp 150° (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 251 (4300), 320 (5800). IR ν_{max}^{KBr} cm^{-1}: 3430 (br.), 1775, 1567. NMR (D_2O) δ: 2.15 (2H, m), ~3.1 (2H, m), 3.25 (2H, t, J=7.5 Hz), 3.71 (1H, dd, J=15, 2 Hz), 4.03 (1H, dd, J=15, 3.5 Hz), 5.91 (1H, dd, J=3.5, 2 Hz).

Acetylation of **4h′** afforded **4i′** (sodium salt) in 43% yield. UV $\lambda_{max}^{H_2O}$ nm (ε): 252 (4100), 322 (5500). IR ν_{max}^{KBr} cm^{-1}: 3430 (br.), 1789, 1640, 1560. NMR (D_2O) δ: ~2.0 (2H, m), 2.05 (3H, s), ~3.2 (4H, m), 3.65 (1H, dd, J=15, 2 Hz), 3.97 (1H, dd, J=15, 3.5 Hz), 5.93 (1H, dd, J=3.5, 2 Hz).

2-(2-Azidoethylthio)-3-*p*-nitrobenzyloxycarbonyl-7-oxo-4,7-dihydro-1,4-thiazepine (5)——Sodium azide (3 mg) was added to a solution of **3f** (23 mg) in dimethylsulfoxide (0.6 ml). The mixture was stirred for 2 hr at room temperature, then diluted with AcOEt, washed with water, dried and evaporated. The residue was purified by preparative TLC (benzene–AcOEt, 1.5: 1) to give **5** (9 mg, 44%). An analytical sample was obtained by recrystallization from AcOEt–cyclohexane as orange prisms, mp 138—139° (dec.). IR ν_{max}^{KBr} cm^{-1}: 3250, 2130, 1690, 1662, 1590, 1517. NMR ($CDCl_3$) δ: 3.1—3.6 (4H, m), 4.74 (1H, d, J=14 Hz), 5.16 (2H, s), 6.00 (1H, d, J=9 Hz), 7.40 (2H), 7.43 (1H, dd, J=14, 9 Hz), 8.10 (2H). *Anal.* Calcd for $C_{15}H_{13}N_5O_5S_2$: C, 44.22; H, 3.21; N, 17.19. Found: C, 44.33; H, 3.33; N, 16.79.