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2-(Alkylthio)penem-3-carboxylic Acids. I. Synthesis of 6-Unsubstituted Penems[1]

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Treatment of 4-acetoxy-2-azetidinone (**9**) with various sodium alkyl trithiocarbonates gave 4-[(alkylthio)thiocarbonyl]thioazetidinones **10**, which were converted into the phosphoranes **8**. Intramolecular Wittig reactions of **8** followed by deblocking yielded penem-3-carboxylic acids **5**.

Keywords——antibiotics; β-lactam; penem-3-carboxylic acid; trithiocarbonate; intramolecular Wittig reaction

In addition to semi-synthetic studies of penicillin analogues centered on the C(6)-amide variants, a lot of works have recently been accumulated not only on chemical modification of the C(2), C(3) or C(6) substituent of penicillin, but also on alternation of the bicyclic nucleus itself.[3,4] Of particular interest among these nuclear analogues, because of their antibacterial potency, are the penem-3-carboxylic acids possessing thiazoline rings fused to β-lactams. Woodward and his co-workers[4] were the first to synthesize 6-acylaminopenem-3-carboxylic acids (**1**), by using an intramolecular Wittig reaction of 4-(acylthio)azetidinylphosphoranes (**2**) at the thiazoline ring formation stage. Further, they have recently announced the synthesis of the 6-unsubstituted 2-alkyl or 2-aryl penems (**3**) and also introduced 2,6-unsubstituted penem-3-carboxylic acid (**3**, R′=H), one of the simplest biologically active β-lactam antibiotics known to date.[5] Other synthetic approachs to penems have since been disclosed.[6] Meanwhile, the structure of thienamycin, a wide-spectrum β-lactam antibiotic of high antibacterial potency, has been determined as 2-(alkylthio)-1-carbapenem (**4**),[7] making the preparation of 2-(alkylthio)penem compounds (**5**) even more attractive on the basis of the contribution of the 2-substituent to bioactivity. Prompted by a recent report[8] which was also carried out on this line, we describe here the results of our studies on 6-unsubstituted 2-(alkylthio)-penem-3-carboxylic acids **5**.

In 1967, Corey and Märkl[9] reported that the trithiocarbonate **6** upon heating with tri-

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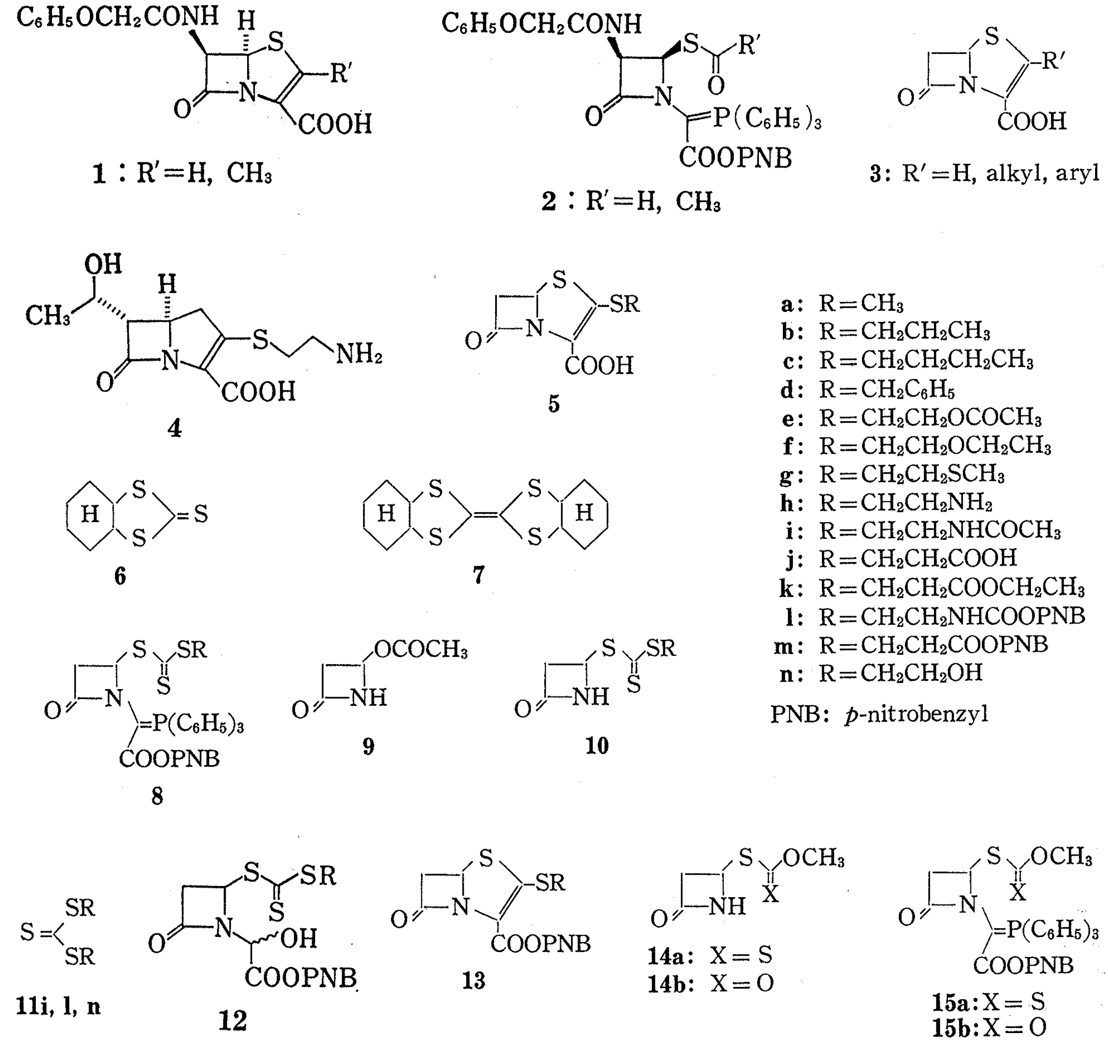

1 : R'=H, CH_3

2 : R'=H, CH_3

3: R'=H, alkyl, aryl

4

5

6

7

8

9

10

11i, l, n

12

13

14a: X=S
14b: X=O

15a: X=S
15b: X=O

a: $R=CH_3$
b: $R=CH_2CH_2CH_3$
c: $R=CH_2CH_2CH_2CH_3$
d: $R=CH_2C_6H_5$
e: $R=CH_2CH_2OCOCH_3$
f: $R=CH_2CH_2OCH_2CH_3$
g: $R=CH_2CH_2SCH_3$
h: $R=CH_2CH_2NH_2$
i: $R=CH_2CH_2NHCOCH_3$
j: $R=CH_2CH_2COOH$
k: $R=CH_2CH_2COOCH_2CH_3$
l: $R=CH_2CH_2NHCOOPNB$
m: $R=CH_2CH_2COOPNB$
n: $R=CH_2CH_2OH$

PNB: *p*-nitrobenzyl

Chart 1

methyl phosphite afforded the coupling product **7**, presumably by a Wittig reaction between an intermediate trimethoxyphosphonium ylide and **6**. This result indicates some reactivity of the thiocarbonyl group in **6** to ylides, suggesting that trithiocarbonates attached to azetidinonephosphoranes (**8**) might undergo the analogous intramolecular Wittig reaction which was proposed by Woodward and his co-workers as a general synthetic route for the bicyclic penem compounds.

The starting material for the synthesis of the phosphoranes **8** was provided by Clauss *et al.*,[10] who prepared 4-acetoxy-2-azetidinone (**9**) and showed that the acetoxy group in **9** could be readily displaced by a variety of nucleophiles. The azetidinone **9** was treated with various sodium alkyl trithiocarbonates, as described in the experimental section, and 4-[(alkylthio)-thiocarbonyl]thioazetidinones (**10a**—**g**, **i**, **k**—**n**) were obtained in 40—80% yields. Sodium alkyl trithiocarbonates were prepared *in situ* by mixing equimolar amounts of sodium methoxide, mercaptans and carbon disulfide, and were immediately allowed to react with the azetidinone **9** at room temperature. Most of the trithiocarbonates **10** were obtained in this way, but, in the case of 2-hydroxy-, 2-acetamido- and 2-*p*-nitrobenzyloxycarbonylamino-ethyl mercaptans, the reactions were carried out at low temperature and for a rather short time; otherwise the yields of the corresponding trithiocarbonates (**10i, l, n**) were considerably reduced.

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It was also observed by monitoring the progress of the reaction on thin-layer chromatograms that, under ordinary conditions, the azetidinonetrithiocarbonates (**10i**, **l**, **n**) formed initially were unstable and decomposed to give the symmetric trithiocarbonates (**11i**, **l**, **n**) composed of the corresponding mercaptans. The 2-acetoxyethylthio derivative **10e** was alternatively obtained from the hydroxy analogue **10n** by acetylation with acetic anhydride and boron trifluoride etherate.

Conversion of the trithiocarbonates (**10a**—**g**, **i**, **k**—**m**) thus obtained into the phosphoranes (**8a**—**g**, **i**, **k**—**m**) was carried out according to the traditional procedure developed by Woodward *et al.*4) Reflux of **10** with *p*-nitrobenzyl glyoxylate in benzene gave a 1: 1 diastereomeric mixture of the hemiaminal (**12a**—**g**, **i**, **k**—**m**) in good yield.11) These hemiaminals, on treatment with thionyl chloride and 2,6-lutidine and, without isolation of the resulting chlorides, with triphenylphosphine and 2,6-lutidine, were transformed into the corresponding phosphoranes (**8a**—**g**, **i**, **k**—**m**) in 40—70% yields.12,13)

Thiazoline ring formation of these phosphoranes (**8a**—**g**, **i**, **k**—**m**) to provide penem esters (**13a**—**g**, **i**, **k**—**m**) was easily conducted by heating at 130—135° (bath temp.) in xylene. The progress of the reaction was monitored by thin-layer chromatography, and these reaction conditions are shown in Table VII. In the case of the 2-acylaminoethylthio analogues (**8i**, **l**→ **13i**, **l**), addition of a catalytic amount of hydroquinone was necessary in order to suppress severe decomposition. The reaction products were chromatographed and/or recrystallized to yield the penem ester **13** along with triphenylphosphine sulfide and the remaining starting materials.14)

The ultraviolet spectra of these penem esters **13** display longer wavelength maxima, at about 340 nm, compared to the reported data on the 2-alkylpenem esters.4,5) Their infrared spectra showed typical short-wavelength bands between 1800—1780 cm^{-1} due to the strained β-lactam carbonyl group. The nuclear magnetic resonance absorptions were characteristic, with smaller coupling constants of both 5,6-*cis* hydrogens (3.5—4.0 Hz) and 5,6-*trans* hydrogens (2 Hz) than those of the monocyclic β-lactam compounds (5—5.5 Hz and 2.5 Hz). These penem esters are unstable on prolonged storage at room temperature, giving an unidentified resin.

These penem esters (**13a**, **b**, **d**—**g**, **i**, **k**—**m**) were deblocked by hydrogenolysis with 10% palladium–charcoal in tetrahydrofuran, giving the corresponding acids (**5**). The penem esters, **13l** and **13m**, were converted into penemcarboxylic acids, **5h** and **5j**, having amino or carboxyl functions in the side chain. These penem acids thus obtained were unstable to chromatographic purification on silica gel and some decomposition was also observed even on recrystallization; they were therefore washed briefly with appropriate solvents and immediately subjected to biological testing. In the case of hydrogenolysis using a mixture of tetrahydrofuran and a phosphate buffer solution as the solvent, the penem acids were obtained as their sodium salts which proved more stable than the free acids. The antibacterial activities of these penem acids (**5a**, **b**, **d**—**k**) have already been communicated in a preceding paper.1)

We also attempted to cyclize the azetidinonephosphorane with other carbonates in place of the trithiocarbonate, but without success. Treatment of 4-acetoxy-2-azetidin one (**9**) with sodium methyl xanthogenate gave the O-methyl dithiocarbonate 14**a**, while treatment of **9** with sodium methoxide and carbonyl sulfide gave the S-azetidinyl thiocarbonate **14b**. These

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11) In some cases, the hemiaminals (**12**) partly crystallized and their crystalline epimers were isolated and characterized as described in the experimental section.

12) Treatment of **12** with thionyl bromide gave the corresponding bromides which were transformed into the phosphoranes **8** under rather lower temperature conditions.

13) In the reactions of the intermediate chlorides with triphenylphosphine, formation of penems **13** was observed in some cases. This will be discussed in a forthcoming paper.

14) Considering the instability of the penem ester (**13**), we did not carry the reaction to completion but rather isolated the product **13** after partial cyclization of **8**.

compounds were then transformed to their corresponding phosphoranes, **15a** and **15b**, which we attempted to cyclize by heating. However, only slow decomposition occurred in both cases and no 2-methoxypenem or identifiable product could be isolated from the reaction mixture. The carbonyl or thiocarbonyl group in these phosphoranes, **15a** and **15b**, is presumably stabilized by the strong mesomeric electron release of the alkoxy group, and electrophilic attack on the phosphorane group does not occur.

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 a Hitachi-Perkin-Elmer R-24 spectrometer, with TMS as an internal standard, unless otherwise specified. 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

TABLE I. 4-[(Alkylthio)thiocarbonyl]thio-2-azetidinones (**10**)

Compd.	R	Appearance[a] mp, °C	Formula	Analysis, (%) Calcd (Found)				Reaction time (min)	Yield (%)
				C	H	N	S		
10a	CH_3	Leaflets 79—80 (E–P. E)	$C_5H_7NOS_3$	31.06 (31.04	3.65 3.46	7.25 7.23	49.76 49.38)	40	54
10b	$CH_2CH_2CH_3$	Leaflets 79—80 (B–E. A)	$C_7H_{11}NOS_3$	37.98 (38.12	5.01 4.93	6.33 6.24	43.36 43.32)	60	74
10c	$CH_2CH_2CH_2CH_3$	Leaflets 78—79 (B–H)	$C_8H_{13}NOS_3$	40.82 (40.87	5.57 5.34	5.95 5.89	40.87 40.61)	120	69
10d	$CH_2C_6H_5$	Needles 104—105 (B–H)	$C_{11}H_{11}NOS_3$	49.04 (49.18	4.11 4.19	5.19 5.09	35.70 35.55)	30	65
10e	$CH_2CH_2OCOCH_3$	Oil	$C_8H_{11}NO_3S_3$	—	—	—	—	50[c]	45
10f	$CH_2CH_2OCH_2CH_3$	Leaflets 65—66 (E–H)	$C_8H_{13}NO_2S_3$	38.22 (37.71	5.21 5.34	5.57 5.51	38.27 37.57)	30	64
10g	$CH_2CH_2SCH_3$	Prisms 76—77 (B–E. A)	$C_7H_{11}NOS_4$	33.18 (33.17	4.38 4.20	5.53 5.57	50.61 50.14)	40	72
10i	$CH_2CH_2NHCOCH_3$	Prisms 124—125 (E. A–Et)	$C_8H_{12}N_2O_2S_3$	36.34 (36.07	4.58 4.59	10.60 10.40	36.38 35.75)	40[b]	61
10k	$CH_2CH_2COOCH_2CH_3$	Prisms 85—86 (E–P. E)	$C_9H_{13}NO_3S_3$	38.69 (38.45	4.69 4.78	5.01 4.87	34.43 34.27)	90	60
10l	$CH_2CH_2NHCOOPNB$[d]	Prisms 116—118 (E. A–C)	$C_{14}H_{15}N_3O_5S_3$	41.88 (41.63	3.77 3.70	10.47 10.17)	—	60[b]	72
10m	$CH_2CH_2COOPNB$	Powder 135—136 (THF–H)	$C_{14}H_{14}N_2O_5S_3$	43.51 (43.48	3.65 3.66	7.25 7.10	24.89 24.55)	40	41
10n	CH_2CH_2OH	Prisms 79—81 (B–E. A)	$C_6H_9NO_2S_3$	32.26 (32.36	4.06 3.95	6.27 6.03	43.07 43.34)	15[b]	47

a) Yellow colored. Recrystallization solvents in parentheses: E, ether; P.E, petroleum ether; B, benzene; E.A, ethyl acetate; H, hexane; Et, ethanol; C, chloroform; THF, tetrahydrofuran.

b) The sodium alkyl trithiocarbonate was treated with **9** at −10° to 0°. After the reaction, the mixture was acidified by addition of a small amount of acetic acid.

c) The sodium alkyl trithiocarbonate was prepared at −78° and after addition of **9**, the mixture was stirred at −78° for 25 min, then further at 0° for 25 min.

d) PNB, *p*-nitrobenzyl.

the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; q, quartet; m, multiplet; br., broad.

Mercaptans——Methyl, propyl, butyl, benzyl and 2-hydroxyethylmercaptans were commercial products redistilled before use. 2-Acetoxyethylmercaptan was derived from 2-hydroxyethylmercaptan by partial acetylation according to Bliznyuk *et al.*,15) and 2-acetamidoethylmercaptan and 2-(*p*-nitrobenzyloxycarbonylamino)ethylmercaptan (mp 67—68°) were derived from 2-aminoethylmercaptan according to Martin *et al.*16) 2-Ethoxyethylmercaptan17) and 2-(methylthio)ethylmercaptan18) were prepared from the corresponding halides, and ethyl and *p*-nitrobenzyl *β*-mercaptopropionates were obtained by esterification of *β*-mercaptopropionic acid with the corresponding alcohols in the presence of acids.19)

4-[(Alkylthio)thiocarbonyl]thio-2-azetidinone (10a—g, i, k—n)——The preparation of 4-([propylthio)-thiocarbonyl]thioazetidin-2-one (**10b**) is described as a typical example. To an ice-cold sodium methoxide solution, prepared by dissolving sodium metal (460 mg, 20 mmol) in MeOH (40 ml), was added propylmercaptan (1.52 g, 20 mmol) and then carbon disulfide (1.52 g, 20 mmol). After the mixture was stirred for 5 min with cooling, 4-acetoxy-2-azetidinone10) (9) (2.58 g, 20 mmol) was added and stirring was continued for 1 hr at room temperature. The mixture was concentrated *in vacuo* to about half the initial volume, then diluted with AcOEt, washed with brine and dried. The solvent was evaporated off *in vacuo* and the resulting crystalline mass was recrystallized from benzene–hexane, giving **10b** (1.71 g, yellow leaflets, mp 79—80°). The mother liquors were collected, evaporated and chromatographed (30 g, benzene–AcOEt, (10: 1), giving the second crop (1.57 g). The total yield was 3.29 g (74%).

The other 4-[(alkylthio)thiocarbonyl]thio-2-azetidinones (**10a**, **c**—**g**, **i**, **k**—**n**) were similarly prepared; the reaction conditions being shown in Table I. The reaction products were purified by column or preparative thin-layer chromatography over silica gel using solvent systems of benzene and AcOEt. Elementary analysis

Table II. Spectral Data for 4-[(Alkylthio)thiocarbonyl]thio-2-azetidinones (**10**)

Compd.	IR. cm^{-1} (state)	NMR, δ a) ppm (solvent)
10a	3175, 1752 (KBr)	2.78 (3H, s), 3.10 (1H, dd, 16, 3), 3.51 (1H, dd, 16, 5), 5.67 (1H, dd, 5, 3) ($CDCl_3+D_2O$)
10b	3210, 1759 (Nujol)	1.04 (3H, t, 7), 1.8 (2H, m), 3.05 (1H, dd, 15.5, 2.5), 3.55 (1H, dd, 15.5, 5), 3.42 (2H, t, 7), 5.66 (1H, dd, 5, 2.5) ($CDCl_3+D_2O$)
10c	3170, 1755 (Nujol)	0.88 (3H, t, 6.5), 2.96 (1H, dd, 16, 3), 3.33 (2H, t, 6.5), 3.45 (1H, dd, 16, 5), 5.58 (1H, dd, 5, 3) ($CDCl_3+D_2O$)
10d	3300, 1751 (Nujol)	2.97 (1H, ddd, 15.5, 3, 1.5), 3.47 (1H, ddd, 15.5, 5, 2), 4.58 (2H, s), 5.57 (1H, dd, 5, 2), 6.88 (1H, br.), 7.29 (5H, s) ($CDCl_3$)
10e	3275, 1775, 1742 (liq.)	2.05 (3H, s), 3.07 (1H, dd, 15.5, 2.5), 3.62 (1H, dd, 15.5, 5) 3.69 (2H, t, 6.5), 4.37 (2H, t, 6.5), 5.66 (1H, dd, 5, 2.5) ($CDCl_3+D_2O$)
10f	3200, 1755 (Nujol)	1.20 (3H, t, 7), 3.54 (2H, q, 7), 3.01 (1H, dd, 16, 3), 3.55 (1H, dd, 16, 5), 3.65 (4H, s), 5.62 (1H, dd, 5, 3). ($CDCl_3+D_2O$)
10g	3450, 3200, 1770 (KBr)	2.25 (3H, s), 2.78 (2H, t, 7), 3.02 (1H, dd, 17, 3), 3.60 (1H, dd, 17, 6), 3.65 (2H, t, 7), 5.60 (1H, dd, 6, 3), 7.10 (1H, br.) ($CDCl_3$)
10i	3280, 3190, 1776, 1616 (Nujol)	1.90 (3H, s), 2.97 (1H, dd, 15.5, 2.5), 3.53 (1H, dd, 15.5, 5), 3.2—3.6 (4H, m), 5.70 (1H, dd, 5, 2.5) (CD_3OD)
10k	3200, 1763, 1750, 1730 (KBr)	1.28 (3H, t, 7), 2.78 (2H, t, 7), 3.07 (1H, ddd, 16, 3, 1.5), 3.57 (1H, ddd, 16, 5, 2), 3.67 (2H, t, 7), 4.22 (2H, q, 7), 5.67 (1H, dd, 5, 3), 7.20 (1H, br. s) ($CDCl_3$)
10l	3320, 1785, 1694, 1685 (sh.) (Nujol)	2.7—3.7 (6H, m), 5.13 (2H, s), 5.55 (1H, dd, 5, 2.5), 7.23 (1H, br.), 7.51 (2H, d, 8.5), 8.14 (2H, d, 8.5), 8.46 (1H, br.) (d_7-DMF+$CDCl_3$)
10m	3450, 1780, 1740, 1600 (Nujol)	2.98 (2H, t, 6), 3.08 (1H, dd, 13, 3), 3.63 (1H, dd, 13, 6), 3.73 (2H, t, 6), 5.40 (2H, s), 5.76 (1H, dd, 6, 3), 7.70 (2H, d, 7.5), 8.32 (2H, d, 7.5) (d_7-DMF)
10n	3270, 1740 (Nujol)	3.00 (1H, dd, 15.5, 2.5), 3.54 (1H, dd, 15.5, 5), 3.6 (4H, m), 5.65 (1H, dd, 5, 2.5) (CD_3CN+D_2O)

a) Chemical shifts are given with proton numbers, absorption patterns, and coupling constants in Hz in parentheses.

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Table III. *p*-Nitrobenzyl 2-[4-[(Alkylthio)thiocarbonyl]thio-2-oxo-1-azetidinyl]-2-hydroxyacetates (**12**)

Compd.	R	Appearance[a] mp, °C	Formula	Analysis, (%) Calcd (Found) C	H	N	S	Reaction time (hr)	Yield (%)
12a	CH_3	Oil	$C_{14}H_{14}N_2O_6S_3$	41.78 (41.55	3.51 3.22	6.96 7.03	23.90 23.75)	5	71
12b	$CH_2CH_2CH_3$	Oil Cryst. isomer mp 92—93° (B–H)	$C_{16}H_{18}N_2O_6S_3$	44.63 (44.44	4.21 4.16	6.51 6.34	22.34 22.62[b])	8.5	75
12c	$CH_2CH_2CH_2CH_3$	Oil Cryst. isomer mp 95—97° (B–H)	$C_{17}H_{20}N_2O_6S_3$	45.93 (45.92	4.53 4.39	6.30 6.20	21.64 21.36[b])	4	86
12d	$CH_2C_6H_5$	Oil	$C_{20}H_{18}N_2O_6S_3$	—	—	—	—	3	87
12e	$CH_2CH_2OCOCH_3$	Oil	$C_{17}H_{18}N_2O_8S_3$	43.03 (43.03	3.82 3.75	5.90 5.95	20.27 20.07)	4.5	84
12f	$CH_2CH_2OCH_2CH_3$	Oil	$C_{17}H_{20}N_2O_7S_3$	44.33 (44.21	4.38 4.50	6.08 5.97	20.89 20.94)	2	95
12g	$CH_2CH_2SCH_3$	Oil	$C_{16}H_{18}N_2O_6S_4$	41.54 (41.21	3.92 3.95	6.06 5.87	27.73 27.91)	2	95
12i	$CH_2CH_2NHCOCH_3$	Oil	$C_{17}H_{19}N_3O_7S_3$	—	—	—	—	2	77
12k	$CH_2CH_2COOCH_2CH_3$	Oil Cryst. isomer mp 82—83° (B–H)	$C_{18}H_{20}N_2O_8S_3$	44.25 (44.00	4.13 4.07	5.73 5.82	19.69 19.77[b])	1.5	95
12l	$CH_2CH_2NHCOOPNB$[d]	Oil	$C_{23}H_{22}N_4O_{10}S_3$	—	—	—	—	5	95[c]
12m	$CH_2CH_2COOPNB$[d]	Oil	$C_{23}H_{21}N_3O_{10}S_3$	46.38 (46.18	3.55 3.63	7.05 7.12	16.15 16.24)	5.5	79

[a] Yellow colored. Recrystallization solvents in parentheses: B, benzene; H, hexane; E. A, ethylacetate.
[b] Crystalline isomers are used.
[c] The reaction was carried out in C_6H_6–THF (4: 1).
[d] PNB, *p*-nitrobenzyl

Table IV. Spectral Data for *p*-Nitrobenzyl 2-[4-[(Alkylthio)thiocarbonyl]-thio-2-oxo-1-azetidinyl]-2-hydroxyacetates (**12**)

Compd.	IR, cm^{-1} (state)	NMR, δ[a] ppm ($CDCl_3$)
12a	3410, 1778, 1760 (liq.)	2.72 (3H, s), 3.10 and 3.60 (1H, dd, 16, 3), 3.64 (1H, dd, 16, 5), 5.34 and 5.41 (2H, s), 5.45 and 5.53 (1H, s), 5.99 and 6.08 (1H, dd, 5, 3)[b]
12b[c]	3370, 1740(br.) (Nujol)	1.03 (3H, t, 6.5), 1.8 (2H, m), 3.32 (2H, t, 6.5), 3.11 (1H, dd, 15.5, 2.5), 3.62 (1H, dd, 15.5, 5), 5.37 3H, s), 5.95 (1H, dd, 5, 2.5)
12c[c]	3400, 1741, 1755 (sh.) (Nujol)	0.97 (3H, t, 6.5), 3.13 (1H, dd, 16, 2.5), 3.50 (2H, t, 7), 3.68 (1H, dd, 16, 5), 5.39 (1H, s), 5.43 (2H, s), 6.00 (1H, dd, 5, 2.5)[b]
12d	3400, 1780 (liq.)	3.08 and 3.13 (1H, dd, 16, 2.5), 4.58 (2H, s), 5.28 and 5.36 (2H, s), 5.35 and 5.60 (1H, s), 5.94 and 6.04 (1H, dd, 5, 2.5), 7.29 (5H, s)[b]
12e	3400, 1778, 1742 (liq.)	1.99 (3H, s), 3.05 (1H, br. d, 15.5), 3.62 (1H, dd, 15.5, 5), 3.57 (2H, t, 6.5), 4.25 (2H, t, 6.5), 5.29 and 5.33 (2H, s), 5.33 and 5.54 (1H, s), 5.91 and 6.01 (1H, dd, 5, 2.5)[b]
12f	3390, 1780, 1743 (liq.)	1.20 (3H, t, 7), 3.53 (2H, q, 7), 3.11 and 3.15 (1H, dd, 16, 2.5), 3.65 (1H, dd, 16, 5), 3.6 (4H, m), 5.34 and 5.39 (2H, s), 5.39 and 5.60 (1H, s), 5.97 and 6.08 (1H, dd, 5, 2.5)[b]
12g	3350, 1765, 1740 (KBr)	2.20 (3H, s), 2.7—3.8 (2H, m), 2.80 (2H, t, 9), 3.65 (2H, t, 9), 4.15 (1H, d, 8), 5.42 and 5.36 (2H, s), 5.4 and 6.6 (1H, d, 8), 6.0 (1H, m)
12i	3450, 1783, 1760 (sh.) 1677 (liq.)	1.97 (3H, s), 3.13 (1H, dd, 16, 2.5), 3.72 (1H, dd, 16, 5), 3.57 (4H, s), 5.39 and 5.43 (2H, s), 5.47 and 5.63 (1H, s), 5.97 and 6.10 (1H, dd, 5, 2.5)[b]
12k[c]	3400, 1777, 1758, 1744 (KBr)	1.24 (3H, t, 7), 2.73 (2H, t, 7), 3.13 (1H, dd, 16, 3), 3.62 (2H, t, 7), 3.64 (1H, dd, 16, 5), 4.17 (2H, q, 7), 4.30 (1H, br. s), 5.38 (3H, s), 5.96 (1H, dd, 5, 3)

Compd.	IR, cm^{-1} (state)	NMR, δ[a] ppm ($CDCl_3$)
12l	3460, 1788, 1762, 1732 ($CHCl_3$)	3.04 (1H, br. d, 16), 3.58 (1H, dd, 16, 5), 3.5 (4H, br.), 4.40 and 4.49 (1H, d, 7.5), 5.18 (2H, s), 5.30 and 5.34 (2H, s), 5.35 and 5.51 (1H, d, 7.5), 5.88 and 6.02 (1H, dd, 5, 2.5)
12m	3450, 1780, 1740 (sh.) 1600 (KBr)	2.80 (2H, t, 6), 3.00 (1H, dd, 16, 2), 3.67 (1H, dd, 16, 4), 5.20 (2H, s), 5.26 and 5.32 (1H, s), 5.52 (1H, d, 8), 5.88 and 6.00 (1H, dd, 4, 2), 7.10 (2H, d, 9)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of the aromatic protons are not given in the table: 7.54—7.66 (2H, d), 8.21—8.35 ppm (2H, d).

b) D_2O added.

c) Crystalline isomer was used.

and spectral data are shown in Tables I and II, respectively.

10e was alternatively obtained by acetylation of **10n** as follows. To a solution of **10n** (1.25 g) in CH_2Cl_2 (50 ml) was added acetic anhydride (2.5 g) and boron trifluoride etherate (0.5 g). The mixture was stirred for 1 hr at room temperature, then washed with dil. $NaHCO_3$, dried and evaporated. The residue was purified by chromatography (20 g, AcOEt–benzene, 1: 10), giving **10e** (1.07 g, 72%) as a syrup.

In the preparation of 2-(acetamido)ethyl, 2-(*p*-nitrobenzyloxycarbonylamino)ethyl and 2-hydroxyethyl derivatives (**10i**, **10l** and **10n**), the corresponding dialkyl trithiocarbonates were obtained as by-products in quantity under ordinary conditions (see Table I): di-2-(acetamido)ethyl trithiocarbonate (**11i**), yellow needles (from AcOEt–EtOH) mp 124—125° decomp.; di-2-(*p*-nitrobenzyloxycarbonylamino)ethyl trithiocarbonate

TABLE V. *p*-Nitrobenzyl 2-[4-[(Alkylthio)thiocarbonyl]thio-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetates (**8**)

Compd.	R	Appearance[a] mp, °C	Formula	Analysis (%) Calcd (Found) C	H	N	S	P	Reaction Temp. (°C)	Reaction Time (hr)	Yield (%) (from **12**)
8a	CH_3	Prisms 157—158 (E. A)	$C_{32}H_{27}N_2O_5PS_3$	59.43 (59.61	4.21 4.22	4.33 4.27	14.87 14.81	4.79 4.54)	55	10	39
8b	$CH_2CH_2CH_3$	Prisms 200—202 (E. A)	$C_{34}H_{31}N_2O_5PS_3$	60.52 (60.78	4.63 4.61	4.15 4.16	14.26 14.14	4.59 4.77)	60	6	50
8c	$CH_2CH_2CH_2CH_3$	Prisms 206—207 (E. A)	$C_{35}H_{33}N_2O_5PS_3$	61.03 (61.09	4.83 4.84	4.02 3.92	13.97 13.70	4.50 4.24)	55	2	61
8d	$CH_2C_6H_5$	Prisms 148—149 (E. A)	$C_{38}H_{31}N_2O_5PS_3$	63.14 (63.22	4.32 4.38	3.88 3.99)	—	—	55	7	59
8e	$CH_2CH_2OCOCH_3$	Prisms 193—194 (C–E. A)	$C_{35}H_{31}N_2O_7PS_3$	58.48 (58.40	4.35 4.38	3.90 3.71	13.38 13.24	4.31 4.03)	60	12	41
8f	$CH_2CH_2OCH_2CH_3$	Prisms 195—197 (E. A)	$C_{35}H_{33}N_2O_6PS_3$	59.64 (59.32	4.72 4.68	3.98 3.90	13.65 13.78	4.39 4.50)	55	6.5	58
8g	$CH_2CH_2SCH_3$	Powder 195—196 (C–E.A)	$C_{34}H_{31}N_2O_5PS_4$	57.79 (57.54	4.39 4.43	3.97 3.86	18.13 18.27	4.39 4.09)	60	12	44
8i	$CH_2CH_2NHCOCH_3$	Prisms 213 d (E. A)	$C_{35}H_{32}N_3O_6PS_3$	58.56 (57.49	4.49 4.47	5.85 5.80	13.40 13.31	4.31 4.03)	55	25	45
8k	$CH_2CH_2COOCH_2CH_3$	Prisms 162—163 (E. A)	$C_{36}H_{33}N_2O_7PS_3$	—	—	—	—	—	55	12	75
8l	$CH_2CH_2NHCOOPNB$	Oil	$C_{41}H_{35}N_4O_9PS_3$	—	—	—	—	—	70	7.5	64
8m	$CH_2CH_2COOPNB$	Powder 120—122 (C–E. A)	$C_{41}H_{34}N_3O_9PS$	58.64 (58.48	4.05 4.07	5.00 5.12	11.44 11.28)	—	55	12	62

a) Yellow colored. Recrystallization solvents in parentheses: E.A, ethyl acetate; C, chloroform; H, hexane.

Table VI. Spectral Data for p-Nitrobenzyl 2-[4-(Alkylthio)thiocarbonyl]thio-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetates (**8**)

Compd.	IR, cm^{-1} (state)	NMR, δ[a] ppm ($CDCl_3$)
8a	1764, 1660 (KBr)	2.70 (3H, s), 2.4—3.8 (2H, m), 4.94—5.28 (2H, s), 6.31 (1H, m), 6.7—8.4 (19H, m)
8b	1759, 1657 (Nujol)	1.02 (3H, t, 6.5), 1.8 (2H, m), 2.8 (2H, br.), 3.35 (2H, t, 7), 4.93 and 5.26 (2H, s), 6.3 (1H, br.), 6.7—8.4 (19H, m)
8c	1760, 1658 (Nujol)	0.95 (3H, t, 6.5), 2.82 (2H, br.), 3.39 (2H, t, 7), 4.95 and 5.28 (2H, s), 6.33 (1H, m), 6.8—8.4 (19H, m)
8d	1761, 1653 (Nujol)	2.8 (2H, br.), 4.54 (2H, s), 4.86 and 5.17 (2H, s), 6.2 (1H, br.), 6.7—8.3 (25H, m)
8e	1763, 1745, 1658 (Nujol)	2.09 (3H, s), 2.8 (2H, br.), 3.66 (2H, t, 6.5), 4.33 (2H, t, 6.5), 4.93 and 5.26 (2H, s), 6.25 (1H, br.), 6.7—8.4 (19H, m)
8f	1763, 1660 (Nujol)	1.16 (3H, t, 6.5), 2.8 (2H, br.), 3.54 (2H, q, 6.5), 3.6 (4H, m), 4.90 and 5.24 (2H, s), 6.25 (1H, br.), 6.7—8.4 (19H, m)
8g	1762, 1658 (KBr)	2.15 (3H, s), 2.6—3.8 (6H, m), 4.85 and 5.28 (2H, br. s), 6.15 (1H, m), 6.7—8.4 (19H, m)[b]
8i	3280, 1760, 1659 (Nujol)	1.92 (3H, s), 2.75 (2H, br.), 3.50 (4H, br. s), 4.90 and 5.25 (2H, s), 6.4 (1H, br.), 6.7—8.4 (19H, m)
8k	1762, 1735, 1657 (KBr)	1.23 (3H, t, 7), 2.70 (2H, t, 7), 2.4—3.7 (2H, m), 3.57 (2H, t, 7), 4.18 (2H, q, 7), 4.88 and 5.22 (2H, s), 6.26 (1H, m), 6.7—8.4 (19H ,m)
8l	3460, 1765, 1730, 1628 ($CHCl_3$)	2.7 (2H, br.), 3.45 (4H, br.), 4.83 and 5.17 (4H, s), 6.2 (1H, br.), 6.7—8.3 (32H, m)
8m	1760, 1740, 1650 (KBr)	2.85 (2H, t, 7), 2.5—3.4 (2H, m), 3.65 (2H, t, 7), 5.3 (4H, br. s), 5.6 and 6.3 (1H, m), 6.7—8.4 (23H, m)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.

b) d_6-DMSO was used as a solvent.

(**11l**), yellow needles (from AcOEt–benzene), mp 73—74.5°; 2-hydroxyethyl trithiocarbonate (**11n**), yellow oil. *Anal.* for **11i**: Calcd for $C_9H_{16}N_2O_2S_3$: C, 38.54; H, 5.75; N, 9.99; S, 34.30. Found: C, 38.60; H, 5.66; N, 9.94; S, 33.75.

***p*-Nitrobenzyl 2-[4-[(Alkylthio)thiocarbonyl]thio-2-oxo-1-azetidinyl]-2-hydroxyacetate (12a—g, i, k, l—m)**——A typical procedure is as follows. A solution of **10b** (1.40 g, 6.3 mmol) and *p*-nitrobenzyl glyoxylate (1.60 g, 7.7 mmol) in benzene (25 ml) was refluxed for 8.5 hr. The mixture was evaporated to dryness *in vacuo* and the residue was chromatographed (30 g, AcOEt–benzene, 1: 20) to provide **12b** (20.4 g, 75%) as a yellow oil, which, on the basis of NMR analysis, was a 1: 1 isomeric mixture. Recrystallization from benzene–hexane gave one isomer as a yellow powder, mp 92—93°. The other glyoxylate adducts were similarly prepared. Reaction conditions, elementary analysis data and spectral data are shown in Tables III and IV.

***p*-Nitrobenzyl 2-[4-[(Alkylthio) thiocarbonyl] thio-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)-acetate (8a—g, i, k—m)**——As a typical example, the preparation of the 4-[propylthio)thiocarbonyl]thio derivative **8b** is described. To a solution of **12b** (1: 1 isomeric mixture, 2.13 g, 4.95 mmol) in tetrahydrofuran (THF) (70 ml) was added dropwise 2,6-lutidine (1.59 g, 14.8 mmol) and then thionyl chloride (1.77 g, 14.8 mmol) at −15° with stirring. Stirring was continued for 20 min. The mixture was then evaporated to dryness *in vacuo* at room temperature. The resulting chloride was dissolved in THF (60 ml) and triphenylphosphine (2.59 g, 9.9 mmol) and 2,6-lutidine (10.6 g, 9.9 mmol) were added. The mixture was stirred for 6 hr at 60° under an N_2 atmosphere, then diluted with AcOEt, washed with water and dried. The product obtained by removal of the solvent was chromatographed (50 g, benzene–AcOEt, 7: 3). Recrystallization from AcOEt gave **8b** (1.67 g, 50%, yellow prisms, mp 200—202°). The other phosphoranes were similarly synthesized. Their reaction conditions and physical data, including those for **8b**, are shown in Tables V and VI.

***p*-Nitrobenzyl 3-(Alkylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (13a—g, i, k—m)**——A solution of **8b** (200 mg) and hydroquinone (9 mg) in xylene (15 ml) was kept at 130—135° (bath temp.) for 14 hr with stirring under an N_2 atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the residue was purified by preparative TLC (AcOEt–benzene, 1: 7). Thus, **13b** (64 mg, 57%) was obtained as a crystalline mass along with recovered **8b** (21 mg, 11%). An analytical sample (fine needles, mp 150—151°) was obtained by recrystallization from benzene–hexane. The other penem esters were similarly prepared and their reaction conditions and physical data, including those for **13b**, are shown in Tables VII and VIII.

3-Alkylthio-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid (5a, b, d—k)——i) The synthesis of the 3-propylthio derivative **5b** is described below as a typical example of the preparation of a

TABLE VII. *p*-Nitrobenzyl 3-Alkylthio-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (13)

Compd.	R	Appearance[a] mp, °C	Formula	Analysis (%) Calcd (Found) C	H	N	S	Reaction Starting material (recovery %)	Reaction time (hr)	Yield (%)
13a	CH_3	Needles 165—166 (A)	$C_{14}H_{12}N_2O_5S_2$	47.71 (47.77	3.43 3.45	7.95 7.83	18.20 18.14)	**8a** (44)	11	34
13b	$CH_2CH_2CH_3$	Needles 150—151 (B–H)	$C_{16}H_{16}N_2O_5S_2$	50.51 (50.70	4.24 4.24	7.36 7.28	16.86 16.55)	**8b** (11)	14	57
13c	$CH_2CH_2CH_2CH_3$	Needles 128—129 (E. A–H)	$C_{17}H_{18}N_2O_5S_2$	51.76 (51.75	4.50 4.45	7.10 7.07	16.26 16.35)	**8c** (43)	8	25[b]
13d	$CH_2C_6H_5$	Prisms 138—140 (E. A–E)	$C_{20}H_{16}N_2O_5S_2$	56.06 (56.12	3.76 3.64	6.54 6.75	14.97 15.14)	**8d** (21)	12	48
13e	$CH_2CH_2OCOCH_3$	Prisms 124—125.5 (M–E. A)	$C_{17}H_{16}N_2O_7S_2$	48.12 (48.37	3.80 3.70	6.60 6.71	15.08 15.27)	**8e** (12)	7	22[b]
13f	$CH_2CH_2OCH_2CH_3$	Needles 94—95.5 (E. A–H)	$C_{17}H_{18}N_2O_6S_2$	49.74 (49.78	4.42 4.31	6.83 6.81	15.62 15.90)	**8f** (23)	7.5	47
13g	$CH_2CH_2SCH_3$	Powder 129—130 (B–C)	$C_{16}H_{16}N_2O_5S_3$	46.59 (46.56	3.91 3.98	6.79 7.06	23.32 23.39)	**8g** (26)	12	45
13i	$CH_2CH_2NHCOCH_3$	Oil	$C_{17}H_{17}N_3O_6S_2$	48.21 (48.48	4.05 4.33	9.92 9.60)	—	**8i** (20)	10	48
13k	$CH_2CH_2COOCH_2CH_3$	Fine crystals 94—95 (E. A–E)	$C_{18}H_{18}N_2O_7S_2$	49.30 (49.18	4.14 3.96	6.39 6.38	14.63 14.69)	**8k** (29)	9	62
13l	$CH_2CH_2NHCOOPNB$[c]	Powder 179—180.5 (E. A)	$C_{23}H_{20}N_4O_9S_2$	49.28 (49.35	3.60 3.79	10.00 9.74	11.82 11.73)	**8l** (—)	10	69
13m	$CH_2CH_2COOPNB$[c]	Powder	$C_{23}H_{19}N_3O_9S_2$	50.64 (49.55	3.51 3.41	7.70 7.58	11.75 11.45)	**8m** (32)	8	59

[a] Recrystallization solvents in parentheses. A, acetone; B, benzene; H, hexane; E.A, ethyl acetate; E, ether; C, chloroform.
[b] No special effort was made to optimize isolated yields.
[c] PNB, *p*-nitrobenzyl.

free carboxylic acid; a solution of **13b** (88 mg) in THF (4 ml) was shaken with 10% palladium–charcoal (200 mg) under an H_2 atmosphere for 15 hr at room temperature. The mixture was filtered, and evaporated to dryness *in vacuo* to give crude **5b** (50 mg) which was recrystallized from chloroform-AcOEt to give yellow crystals, mp 138—141°. The other carboxylic acids (**5a, d—f, k**) were similarly prepared. The physical data for these compounds are given in Table IX.

ii) Sodium salts of carboxylic acids (**5b, f, g, i, j**) were obtained by hydrogenolysis of the corresponding esters in a buffer solution as exemplified by the preparation of the sodium salt of **5b**: a solution of **13b** (46 mg) in a mixture of THF (3.5 ml) and 0.1 M phosphate buffer solution (pH 7.1) (3.5 ml) was shaken with 10% palladium–charcoal (120 mg) under an H_2 atmosphere for 4 hr. The catalyst was filtered off and washed with a buffer solution (5 ml). The filtrate and washings were washed with AcOEt and concentrated *in vacuo* at room temperature to half the initial volume and chromatographed on Diaion HP20AG(20) (15 ml). Fractions eluted with 2% acetone–water were collected and lyophilized, giving the sodium salt of **5b** (16 mg, 50%) as a powder. Using the same procedure described above, the amino acid **5h** was obtained from the protected penem ester **13l**. The physical data for these compounds are given in Table IX.

4-[(Methoxy)thiocarbonyl]thio-2-azetidinone (14a) and 4-(Methoxycarbonyl)thio-2-azetidinone (14b)——To a 0.5 M methanolic $NaOCH_3$ solution (6 ml), was added carbon disulfide (228 mg, 3.0 mmol) at room temperature. The mixture was stirred for 15 min, then **9** (387 mg, 3.0 mmol) was added. The whole was stirred at room temperature for 40 min and then worked-up as usual to yield **14a** (370 mg, 70%, mp 48—49°).

TABLE VIII. Spectral Data for *p*-Nitrobenzyl 3-Alkylthio-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (13)

Compd.	IR, cm^{-1} (state)	UV, λ(EtOH), nm (ε)	NMR, δ[a] ppm ($CDCl_3$)
13a	1800, 1683 (KBr)	260(16400) 340(10900)	2.54 (3H, s), 3.51 (1H, dd, 16, 2), 3.84 (1H, dd, 16, 3.5), 5.24 and 5.47 (1H each, ABq, 14), 5.73 (1H, dd, 3.5, 2)
13b	1790, 1685 (Nujol)	262(16500) 339(11500)	1.05 (3H, t, 6.5), 1.8 (2H, m), 2.98 (2H, t, 7), 3.51 (1H, dd, 16, 2), 3.90 (1H, dd, 16, 3.5), 5.26 and 5.56 (1H each, ABq, 14), 5.77 (1H, dd, 3.5, 2)
13c	1786, 1677 (Nujol)	262(16200) 339(11100)	0.93 (3H, t, 6), 2.98 (2H, t, 7), 3.50 (1H, dd, 17, 2), 3.91 (1H, dd, 17, 3.5), 5.26 and 5.55 (1H each, ABq, 14) 5.77 (1H, dd, 3.5, 2)
13d	1788, 1683 (KBr)	262(16400) 340(10400)	3.45 (1H, dd, 16.5, 2), 3.82 (1H, dd, 16.5, 3.5), 4.20 (2H, s), 5.20 and 5.43 (1H each, ABq, 14), 5.71 (1H, dd, 3.5, 2), 7.30 (5H, s)
13e	1795, 1743, 1695 ($CHCl_3$)	—	2.10 (3H, s), 3.25 (2H, t, 6.5), 3.53 (1H, dd, 17, 2), 3.91 (1H, dd, 17, 3.5), 4.35 (2H, t, 6.5), 5.26 and 5.53 (1H each, d, 13.5), 5.77 (1H, dd, 3.5, 2)
13f	1770, 1682 (Nujol)	262(16400) 339(11300)	1.19 (3H, t, 6.5), 3.53 (2H, q, 6.5), 3.2 (2H, m), 3.7 (2H, m), 3.50 (1H, dd, 17, 2), 3.53 (2H, q, 6.5), 3.88 (1H, dd, 17, 3.5), 5.27 and 5.55 (1H each, ABq, 14.5), 5.78 (1H, dd, 3.5, 2)
13g	1780, 1680 (KBr)	—	2.18 (3H, s), 2.8 (2H, m), 3.2 (2H, m), 3.51 (1H, dd, 16, 2), 3.92 (1H, dd, 16, 4), 5.22 and 5.57 (1H each, ABq, 15), 5.80 (1H, dd, 4, 2)
13i	3460, 1796, 1678 ($CHCl_3$)	—	1.93 (3H, s), 3.10 (2H, m), 3.47 (2H, t, 6), 3.46 (1H, dd, 16.5, 2), 3.84 (1H, dd, 16.5, 3.5), 5.18 and 5.48 (1H each, ABq, 14), 5.72 (1H, dd, 3.5, 2)
13k	1786, 1730, 1672 (KBr)	261(16200) 338(11100)	1.21 (2H, t, 7), 2.5—3.4 (4H, m), 3.49 (1H, dd, 16, 2), 3.83 (1H, dd, 16, 4), 4.15 (2H, q, 7), 5.23 and 5.47 (1H each, ABq, 14), 5.72 (1H, dd, 4, 2)
13l	3310, 1800, 1687 (Nujol)	264(25460)[b] 338(10760)	3.1 (2H, m), 3.44 (2H, m), 3.45 (1H, dd, 15.5, 2), 3.82 (1H, dd, 15.5, 3.5), 5.18 (2H, s), 5.18 and 5.45 (1H each ABq, 14), 5.67 (1H, dd, 3.5, 2)
13m	3450, 1790, 1740, 1680 (KBr)	—	2.85 (2H, t, 6), 3.28 (2H, t, 6), 3.50 (1H, dd, 16, 2), 3.90 (1H, dd, 16, 4), 5.32 (2H, s), 5.25 and 5.50 (1H each, ABq, 14), 5.87 (1H, dd, 4, 2)

[a] Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons are not given in the table: *ca.* 7.6 (2H, d) and *ca.* 8.2 ppm (2H, d).

[b] THF was used as a solvent.

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TABLE IX. 3-Alkylthio-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-3-carboxylic Acids (**5**)

Compd.	R	Appearance[a] mp, °C	IR, cm^{-1} (state)	UV, $\nu_{max}^{H_2O}$ nm (ε)	NMR, δ[b] ppm (solvent)	Yield (%)
5a	CH_3	135—140 (C–E. A)	2600 (br.), 1780, 1640 (Nujol)	—	2.57 (3H, s), 3.58 (1H, dd, 17, 2), 3.95 (1H, dd, 17, 4), 5.88 (1H, dd, 4, 2) (d_6-DMSO)	37
5b	$CH_2CH_2CH_3$	138—141 (C–E. A)	2600 (br.), 1787, 1650 (KBr)	—	1.04 (3H, t, 7), 1.7 (2H, m), 2.97 (2H, t, 7), 3.48 (1H, dd, 16, 1.5), 3.87 (1H, dd, 16, 3.5), 5.74 (1H, dd, 3.5, 1.5) ($CDCl_3$)	35
	Na salt	Powder	1763, 1590 (KBr)	252(5360) 322(7470)	0.96 (3H, t, 6.5), 1.6 (2H, m), 2.85 (2H, t-like), 3.47 (1H, dd, 17, 2), 3.80 (1H, dd, 17, 3.5), 5.71 (1H, dd, 3.5, 2) (D_2O)	50[c]
5d	$CH_2C_6H_5$	149—152 (E. A)	2600 (br.), 1782, 1646 (Nujol)	—	3.48 (1H, dd, 17, 1.5), 3.84 (1H, dd, 17, 3.5), 4.23 (2H, s), 5.72 (1H, dd, 3.5, 1.5), 7.34 (5H, s)	40
5e	$CH_2CH_2OCOCH_3$	115—123 (C–E. A)	2600 (br.), 1785, 1742 1646 (Nujol)	—	2.10 (3H, s), 3.27 (2H, t, 6.5), 3.56 (1H, d-like, 16), 3.93 (1H, dd, 16, 3.5), 4.40 (2H, t, 6.5), 5.80 (1H, br.) ($CDCl_3$)	42
5f	$CH_2CH_2OCH_2CH_3$	133—134 (C–E. A)	2600 (br.), 1782, 1650 (KBr)	—	1.14 (3H, t, 7), 3.11 (2H, t, 6.5), 3.3—4.0 (6H, m), 5.68 (1H, br.) ($CDCl_3$)	44
	Na salt	Powder	1765, 1590 (KBr)	251(5390) 320(7240)	1.19 (3H, t, 7), 3.13 (2H, m), 3.48 (1H, dd, 17, 2), 3.84 (1H, dd, 17, 3.5), 3.60 (2H, q, 7), 3.77 (2H, t, 6), 5.73 (1H, dd, 3.5 ,2) (D_2O)	55[c]
5g	$CH_2CH_2SCH_3$, Na salt	Powder	1760, 1590 (KBr)	253(5230) 320(6570)	2.01 (3H, s), 2.70 (3H, m), 2.95 (3H, m), 3.31 (1H, dd, 16, 2), 3.70 (1H, dd, 16, 3.5), 5.64 (1H, dd, 3.5, 2) (D_2O)	44[c]
5h	$CH_2CH_2NH_2$	Powder	3400 (br.), 1772, 1570 (br.) (KBr)	250(4600) 319(6260)	3.3 (4H, m), 3.68 (1H, dd, 17, 2), 4.03 (1H, dd, 17, 4), 5.97 (1H, dd, 4, 2) (D_2O)	36[c]
5i	$CH_2CH_2NHCOCH_3$, Na salt	Powder	3400 (br.), 1767, 1640, 1582 (KBr)	253(3800) 320(5000)	2.06 (3H, s), 2.9—3.7 (4H, m), 3.60 (1H, dd, 17, 2), 3.93 (1H, dd, 17, 3.5), 5.83 (1H, dd, 3.5, 2) (D_2O)	62[c]
5j	CH_2CH_2COOH, Na salt	Powder	3430 (br.), 1770, 1590 (br.) (KBr)	251(3290) 321(3760)	2.70 (2H, t, 6) 3.20 (2H, t, 6), 3.55 (1H, dd, 17, 2), 3.92 (1H, dd, 17, 4), 5.84 (1H, dd, 4, 2) (D_2O)	48[c]
5k	$CH_2CH_2COOCH_2CH_3$	110—115 (E)	1783, 1732, 1648 (Nujol)	—	1.24 (3H, t, 7), 2.6—3.4 (4H, m), 3.55 (1H, dd, 17, 2), 3.92 (1H, dd, 17, 4), 4.19 (2H, q, 7), 5.90 (1H, dd, 4, 2) (d_6-acetone–d_7-DMF)	59

[a] Recrystallization solvents in parentheses: E.A, ethyl acetate; C, chloroform; E, ether.
[b] Chemical shifts were obtained with TMS as an external standard. Proton numbers, absorption patterns and coupling constants in Hz are given in parentheses.
[c] Carried out in buffer solutions.

To a 0.88 M methanolic $NaOCH_3$ solution (6.0 ml) was added a 0.5 M methanolic carbonyl sulfide solution (66 ml) with ice-cooling and stirring. Next, a solution of **9** (689 mg, 5.3 mmol) in MeOH (2 ml) was added and the whole was stirred for 4 hr at 10°. This was worked-up as usual and chromatography of the reaction product (10 g, benzene–AcOEt, 3—2: 1) and recrystallization from hexane–ether gave **14b** (623 mg, 73%, prisms, mp 72—73°). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} for **14a**: 3200, 1786; $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} for **14b**: 3210, 1760, 1722. NMR ($CDCl_3$) δ for **14a**: 3.05 (1H, ddd, $J=16$, 5, 3 Hz), 3.56 (1H, ddd, $J=16$, 5, 2 Hz), 4.27 (3H, s), 5.52 (1H, dd, $J=5$, 3 Hz), 7.66 (1H, br.); for 14b 2.87 (1H, ddd, $J=15$, 3, 1 Hz), 3.46 (1H, ddd, $J=15$, 5.5, 2 Hz), 3.86 (3H, s), 5.25 (1H, dd, $J=5.5$, 3 Hz), 7.36 (1H, br. s). *Anal.* for **14a**. Calcd for $C_5H_7NO_2S_2$: C, 33.88, H, 3.98; N, 7.90; S, 36.18. Found: C, 33.86; H, 3.85; N, 7.76; S, 36.05; for **14b**. Calcd for $C_5H_7NO_3S$: C, 37.26; H, 4.38; N, 8.69; S, 19.89. Found: C, 37.33; H, 4.41; N, 8.75; S, 20.04.

***p*-Nitrobenzyl 2-[4-[(Methoxy)thiocarbonyl]thio- and 2-[4-(Methoxycarbonyl)thio-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetate (15a and 15b)**——As described earlier, reflux of **14a** and *p*-nitrobenzyl glyoxylate in benzene for 5 hr gave the hemiaminal quantitatively. This product was treated with thionyl chloride and 2,6-lutidine in THF, then with triphenylphosphine, giving **15a**, mp 132—124° (dec.), in 71% yield. Similar treatment of **14b** afforded **15b**, as a powder, in 74% yield. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} for **15a**: 1760, 1658; for **15b**: 1763, 1717, 1624. NMR ($CDCl_3$) δ for **15a**: 2.3—3.6 (2H, m), 4.12 (3H, s), 4.88 and 5.22 (2H, s), 5.87 (1H, m), 6.7—8.4 (19H, m). *Anal.* for **15a**. Calcd for $C_{32}H_{27}N_2O_6PS_2$: C, 60.94; H, 4.32; N, 4.44. Found: C, 60.35; H, 4.47; N, 4.46; for **15b**. Calcd for $C_{32}H_{27}N_2O_7PS$: C, 62.53; H, 4.42; N, 4.56. Found: C, 62.85; H, 4.51; N, 4.39.

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