26. Reactions of Disulfides Derived from Penicillin Sulfoxides with Tertiary Phosphines in Presence of Carboxylic Acids

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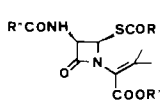
(15.X.80)

Summary

A novel method for the preparation of thioesters starting from Iso-*Fujisawa* disulfides is reported. The presence of an acylamino group *cis* to the disulfide function on the β-lactam nucleus seems to be an essential requirement for this reaction. In the absence of such a *cis*-acylamino group, desulfurization, is the preferred course.

Azetidinone thioesters of type **1** are used as key intermediates in the synthesis of penems **2** [1] and were generally made from benzothiazolyldisulfides **3** [2] in two steps: reduction to the corresponding thiol and acylation of the thiol using an activated carboxylic acid.



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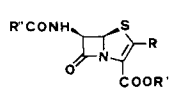

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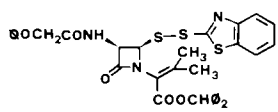

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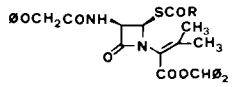
A convenient method for the preparation of thioesters, starting from aryldisulfides using carboxylic acids and tertiary phosphines, was reported by *Mukaiyama et al.* [3]. This method is claimed to be applicable only to aryl disulfides and not to alkyl disulfides [4].

In unsymmetrical disulfides of type **3** the two thio units could readily be differentiated from one another from the point of view of chemical reactivity,



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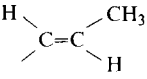
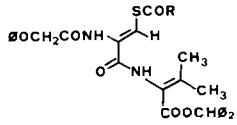
6 R = 



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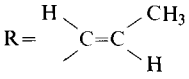
9 R = 

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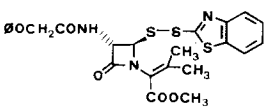
mercaptobenzothiazole being the 'inert partner'. This particular feature led us to investigate the reaction of these disulfides with carboxylic acids in the presence of tertiary phosphines. As expected, disulfide **3** reacted readily with acetic acid and triphenylphosphine in CH_2Cl_2 at 0° to give the thioesters **4** and **7**, mercaptobenzothiazole and triphenylphosphine oxide. Propionic and crotonic acids also reacted with disulfide **3** in a similar way yielding the corresponding thioesters **5**, **6**, **8** and **9**.

In contrast to the above mentioned disulfide in which the significant feature is the presence of a *cis*-acylamino group, the *trans*-acylamino compound **10** reacted in an entirely different way, sulfur extrusion resulting in the formation of product **11** and triphenylphosphine sulfide in almost quantitative yields.



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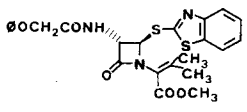

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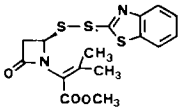

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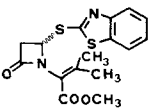

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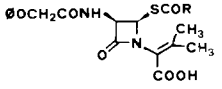
Desulfurization was also the main path in the reaction of disulfide **12** [5] with acetic acid and triphenylphosphine.

Azetidinone carboxylic acids **14**–**16** were obtained by trifluoracetic acid treatment of the corresponding benzhydryl esters. Dehydropeptide **17** was prepared from compound **8** using trifluoracetic acid.



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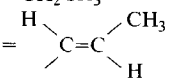
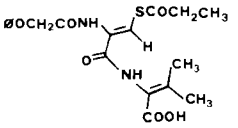
16 R = 



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The authors wish to express their gratitude to Mr. *O. Bammer* for skillful technical assistance.

Experimental Part

Disulfides **3** and **10** were prepared from the corresponding esters of (penicilin V)-*S*-oxide and (6-epipenicillin V)-*S*-oxide respectively by a two-step procedure of *Kamiya et al.* [2]. Disulfide **12** was prepared from the methyl penicillanate using the procedure of *Ernest et al.* [5].

Reactions with disulfide 3. - a) *With acetic acid.* To a solution of 2.34 g (3.44 mmol) of disulfide **3** and 0.21 g (3.44 mmol) of acetic acid in 30 ml of dry CH_2Cl_2 cooled in an ice/methanol bath, a solution of 0.9 g (3.44 mmol) of triphenylphosphine in 10 ml of dry CH_2Cl_2 was added dropwise over 10 min. After the addition, the reaction mixture was stirred for 1 h at RT., evaporated to dryness and the residue chromatographed on SiO_2 using toluene/EtOAc 4:1. First fractions yielded mercaptobenzothiazole, 500 mg (87%), identified by comparison with an authentic sample. The second group of fractions yielded *benzhydryl 2-[(3*R,*4*R*)-4-acetylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-*

3-methyl-2-butenoate (**4**): 960 mg (50%); colorless foam. – IR. (CH_2Cl_2): 3440, 1775, 1700 br., 1600, 1490, 1210, 1180 and 1160 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 2.12 (*s*, 3 H); 2.25 (*s*, 3 H); 2.27 (*s*, 3 H); 4.58 (*s*, 2 H); 5.25 (*d*×*d*, *J* = 5 and 8 Hz, 1 H); 5.90 (*d*, *J* = 5 Hz, 1 H); 6.80–7.60 (*m*, 17 H).

$C_{31}H_{30}N_2O_6$	Calc.	C 66.65	H 5.41	N 5.02	S 5.74%
(558.64)	Found	„ 66.63	„ 5.52	„ 5.03	„ 5.77%

The third group of fractions gave *benzhydral 2-(2-phenoxyacetamido-3-acetylthioacryloyl)amino-3-methyl-2-butenoate* (**7**): 300 mg (16%) colorless foam. – IR. (CH_2Cl_2): 3400, 1710, 1680, sh., 1600, 1580 and 1210 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.90 (*s*, 3 H); 2.23 (*s*, 3 H); 2.44 (*s*, 3 H); 4.58 (*s*, 2 H); 6.80–7.40 (*m*, 15 H); 7.61 (*s*, 1 H) and 8.31 (br., 1 H).

$C_{31}H_{30}N_2O_6S$	Calc.	C 66.65	H 5.41	N 5.02	S 5.74%
(558.64)	Found	„ 66.34	„ 5.46	„ 5.03	„ 5.44%

Further elution of the column gave triphenylphosphine oxide which was characterized by comparison with an authentic sample.

b) *With propionic acid.* The reaction was carried out as in the case of acetic acid using 7.26 g (10.5 mmol) of disulfide **3**, 0.78 g (10.5 mmol) of propionic acid and 2.76 g (10.5 mmol) of triphenylphosphine and worked up in the same fashion. Compounds **5** and **8** were isolated by column chromatography on SiO_2 (toluene/EtOAc 4:1).

Benzhydryl 2-[(3R,4R)-4-propionylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoate (**5**): 2.60 g (43%), m.p. 103–106° (from CH_2Cl_2/hexane). – IR. (KBr): 3310, 1780, 1690 br., 1600, 1520, 1490 and 1210 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.08 (*t*, *J* = 8 Hz, 3 H); 2.08 (*s*, 3 H); 2.24 (*s*, 3 H); 2.46 (*qa*, *J* = 8 Hz, 2 H); 4.55 (*s*, 2 H); 5.24 (*d*×*d*, *J* = 6 and 9 Hz, 1 H); 5.88 (*d*, *J* = 6 Hz, 1 H); 6.80–7.45 (*m*, 16 H).

$C_{32}H_{32}N_2O_6S$	Calc.	C 67.11	H 5.63	N 4.89	S 5.60%
(572.68)	Found	„ 67.28	„ 5.66	„ 4.97	„ 5.95%

Benzhydryl 2-(2-phenoxyacetamido-3-propionylthioacryloyl)amino-3-methyl-2-butenoate (**8**): 820 mg (13.4%), m.p. 159–163° (from CH_2Cl_2/hexane). – UV. (EtOH): 275 nm (ε 17,530). – IR. (KBr): 3290, 1726, 1716, 1675, 1642, 1600, 1520, 1490, 1325, 1315, 1210, 1075 cm^{-1}. – NMR. ($CDCl_3$): 1.20 (*t*, *J* = 8 Hz, 3 H); 1.88 (br. *s*, 3 H); 2.20 (br. *s*, 3 H); 2.66 (*qa*, *J* = 8 Hz, 2 H); 4.56 (*s*, 2 H); 6.80–7.40 (*m*, 15 H); 7.66 (*s*, 1 H) and 8.30 (br., 1 H).

$C_{32}H_{32}N_2O_6S$	Calc.	C 67.11	H 5.63	N 4.89	S 5.60%
(572.68)	Found	„ 66.91	„ 5.69	„ 4.85	„ 5.82%

c) *With crotonic acid.* The reaction was carried out with 2.42 g (3.5 mmol) of disulfide **3**, 0.30 g (3.5 mmol) of crotonic acid and 0.90 g (3.5 mmol) of triphenylphosphine, as in the earlier experiments and the following two new products were isolated.

Benzhydryl 2-[(3R,4R)-4-crotonoylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoate (**6**): 400 mg (20%), colorless foam; $[\alpha]_D^{25} = -25.3°$ (*c* = 1.4, $CHCl_3$). – UV. (EtOH): 275 nm (ε 6090), 268 nm (ε 8120) and 260 nm (ε 9340). – IR. (KBr): 3320, 1775, 1725, 1680, 1630, 1600, 1525, 1495 and 1215 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.87 (*d*×*d*, *J* = 7 and 1.5 Hz, 3 H); 2.10 (*s*, 3 H); 2.25 (*s*, 3 H); 4.56 (*s*, 2 H); 5.30 (*d*×*d*, *J* = 5 and 8 Hz, 1 H); 5.96 (*d*, *J* = 5 Hz, 1 H); 6.00 (*m*, 1 H); 6.70–7.50 (*m*, 17 H).

$C_{33}H_{32}N_2O_6S$	Calc.	C 67.80	H 5.52	N 4.79%	
(584.70)	Found	„ 68.62	„ 5.92	„ 4.59%	

Benzhydryl 2-(2-phenoxyacetamido-3-crotonoylthioacryloyl)amino-3-methyl-2-butenoate (**9**): 100 mg (5%), colorless foam. – UV. (EtOH): 290 (ε 13,600), 276 (ε 9490) and 268 nm (ε 9230). – IR. (KBr): 3340, 1690, 1675, 1655, 1635, 1615, 1598, 1515, 1495, 1320 and 1245 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 1.90 (*s*, 3 H); 1.94 (*d*×*d*, *J* = 7 and 1.5 Hz, 3 H); 2.22 (*s*, 3 H); 4.59 (*s*, 2 H); 6.16 (*m*, 1 H); 6.80–7.50 (*m*, 16 H); 7.77 (*s*, 1 H) and 8.34 (br., 1 H).

Methyl 2-[(3S,4R)-4-(2-benzothiazolylthio)-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoate (**11**). To a solution of 9.95 g (20 mmol) of disulfide **10** and 1.20 g (20 mmol) of acetic acid in 100 ml of dry CH_2Cl_2, cooled in an ice/methanol bath, was added 5.24 g (20 mmol) of triphenylphosphine in 50 ml of dry CH_2Cl_2. The reaction mixture was stirred for 1 h at RT., evaporated and the residue was chromatographed on SiO_2 using toluene/EtOAc 4:1. First fraction yielded triphenylphosphine sulfide. The following fractions yielded compound **11**, 7.47 g (92%), colorless foam;

$[\alpha]_D^{25} = +125.5°$ ($c = 1.3$, $CHCl_3$). – IR. (CH_2Cl_2): 3430, 1780, 1720, 1690, 1600, 1510, 1490, 1380, 1360 and 1220 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 2.00 (*s*, 3 H); 2.20 (*s*, 3 H); 3.80 (*s*, 3 H); 4.60 (*s*, 2 H); 5.37 (*d*×*d*, $J = 3$ and 9 Hz, 1 H); 6.13 (*d*, $J = 3$ Hz, 1 H); 6.90–8.00 (*m*, 10 Hz).

Methyl 2-[4-(2-benzothiazolyldithio)-2-azetidinon-1-yl]-3-methyl-2-butenoate (**12**). The disulfide **12** (2.25 g, 5.9 mmol) was treated as in the earlier experiment with 0.36 g (6 mmol) of acetic acid and 1.57 g (6 mmol) of triphenylphosphine. Triphenylphosphine sulfide and compound **12** were isolated. Compound **12**: 1.64 g (80%). – IR. (KBr): 1765, 1725, 1427 and 1225 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 2.00 (*s*, 3 H); 2.16 (*s*, 3 H); 3.18 (*d*×*d*, $J = 3$ and 16 Hz, 1 H); 3.66 (*d*×*d*, $J = 6$ and 16 Hz, 1 H); 3.85 (*s*, 3 H); 6.13 (*d*×*d*, $J = 3$ and 6 Hz, 1 H); 7.20–7.50 (*m*, 2 H); 7.68–7.90 (*m*, 2 H).

A similar result was obtained when the reaction was carried out in the absence of acetic acid.

2-[(3R,4R)-4-Acetylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoic acid (**14**). To an ice-cold solution of 800 mg (1.4 mmol) of compound **4** in 8 ml of CH_2Cl_2 were added 2 ml of trifluoroacetic acid. The reaction mixture was stirred for 30 min in an ice-bath and diluted with ether/hexane. Compound **14** was obtained as a crystalline solid, m.p. 169–170°, 500 mg (91%); $[\alpha]_D^{25} = +9.5°$ ($c = 1.06$, acetone). – UV. (EtOH): 275 (ε 1740) and 268 nm (ε 2380). – IR. (KBr): 3360, 1748, 1740, 1700 br., 1628, 1600, 1510, 1485, 1438, 1415, 1365, 1240, 1200, 1130, 1070 and 1060 cm^{-1}. – ^{1}H-NMR. (DMSO): 2.97 (*s*, 3 H); 2.14 (*s*, 3 H); 2.30 (*s*, 3 H); 4.58 (*s*, 2 H); 5.18 (*d*×*d*, $J = 6$ and 8 Hz, 1 H); 5.90 (*d*, $J = 6$ Hz, 1 H), 6.85–7.40 (*m*, 5 H); 8.84 (br. *d*, $J = 8$ Hz, 1 H).

$C_{18}H_{20}N_2O_6S$	Calc.	C 55.10	H 5.14	N 7.14%
(392.36)	Found	„ 55.09	„ 5.05	„ 6.99%

2-[(3R,4R)-4-Propionylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoic acid (**15**). Compound **5** (700 mg, 1.2 mmol) was treated as in the earlier experiment. Compound **15**: 370 mg (74%); m.p. 165–168°, $[\alpha]_D^{25} = +10.1$ ($c = 1.3$, acetone). – UV. (EtOH): 275 (ε 2180), 268 (ε 2720). – IR. (KBr): 3360, 1755 sh., 1740, 1700, 1675, 1630, 1595, 1495, 1410, 1240 and 1200 cm^{-1}. – ^{1}H-NMR. (DMSO): 1.00 (*t*, $J = 8$ Hz, 3 H); 1.98 (*s*, 3 H); 2.15 (*s*, 3 H); 2.60 (*qa*, $J = 8$ Hz, 2 H); 4.60 (*s*, 2 H); 5.19 (*d*×*d*, $J = 6$ and 8 Hz, 1 H); 5.94 (*d*, $J = 6$ Hz, 1 H); 6.85–7.45 (*m*, 6 H); 9.00 (*d*, $J = 8$ Hz, 1 H).

$C_{19}H_{22}N_2O_6S$	Calc.	C 56.70	H 5.52	N 6.75	S 8.00%
(406.45)	Found	„ 56.15	„ 5.46	„ 6.89	„ 7.88%

2-[(3R,4R)-4-Crotonoylthio-3-phenoxyacetamido-2-azetidinon-1-yl]-3-methyl-2-butenoic acid (**16**). As in the earlier experiments 750 mg (1.3 mmol) of compound **6** were treated with trifluoracetic acid. Compound **16**, 440 mg (83%); amorphous; $[\alpha]_D^{25} = +30.1$ ($c = 1.08$, acetone). – UV. (EtOH): 274 (ε 5010), 268 nm (ε 6740). – IR. (KBr): 3350, 1775 br., 1760 br., 1700 sh., 1670 br., 1630, 1595, 1530, 1490, 1440, 1370, 1210 and 1165 cm^{-1}. – ^{1}H-NMR. (DMSO): 1.84 (*d*×*d*, $J = 8$ and 2 Hz, 3 H); 1.98 (*s*, 3 H); 2.14 (*s*, 3 H); 4.58 (*s*, 2 H); 5.20 (*d*×*d*, $J = 6$ and 8 Hz, 1 H); 5.98 (*d*, $J = 6$ Hz, 1 H); 6.18 (*m*, 1 H); 6.70–7.40 (*m*, 7 H); 8.90 (br. *d*, $J = 8$ Hz, 1 H).

$C_{20}H_{22}N_2O_6S \cdot H_2O$ (436.48) Calc. C 55.05 H 5.50% Found C 55.02 H 4.98%

2-(2-phenoxyacetamido-3-propionylthioacryloyl)amino-3-methyl-2-butenoic acid (**17**). As in earlier experiments 820 mg of compound **8** were treated with trifluoracetic acid. Compound **17**: 520 mg (90%); amorphous. – UV. (EtOH): 275 nm (ε 17,600). – IR. (KBr): 3230 br., 1700 br., 1655, 1595, 1490, 1210 and 1170 cm^{-1}. – ^{1}H-NMR. (DMSO): 1.10 (*t*, $J = 8$ Hz, 3 H); 1.72 (*s*, 3 H); 2.04 (*s*, 3 H); 2.74 (*qa*, $J = 8$ Hz, 2 H); 4.66 (*s*, 2 H); 6.80–7.40 (*m*, 5 H); 7.62 (*s*, 1 H); 8.00 (br., 1 H); 9.20 (br. *s*, 1 H); 9.58 (br. *s*, 1 H).

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[4] *S. Masamune, S. Kamata, J. Diakur, Y. Sugihara & G. S. Bates,* Can. J. Chem. *53*, 3693 (1975).

[5] Compound **12** and **13** were described by *Ernest et al.*, J. Am. Chem. Soc. *101*, 6301 (1979); **13** was obtained employing different conditions.