114. The Penems, a New Class of β-Lactam Antibiotics. 6. Synthesis of 2-Alkylthiopenem Carboxylic Acids

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Summary

A synthesis of 2-alkylthiopenems by an intramolecular *Wittig*-type reaction between a phosphorane and a trithiocarbonate ester is described.

In previous publications we described synthetic methods for the preparation of this new class of β-lactam antibiotics [1–4]. The approaches involved routes starting from penicillin V or penicillanic acid [1] [2] and total syntheses [3] [4] from 4-acetoxyazetidin-2-one [5].

The antibiotic potency and the wide spectrum of activity of the substances prepared so far warranted the search for the application of the methods to the synthesis of novel target structures. In view of the recent appearance of thienamycin [6] [7], epithienamycins [8] and PS-5 [9] we were particularly interested in combining common structural feature of these carbapenem antibiotics, an aliphatic side-chain attached in 2-position *via* a sulfur atom, with the penem nucleus.

In the present paper we describe the assembly of this system. The key reaction involved the intramolecular *Wittig*-type reaction between a carbonyl-stabi-

Table. *Antibacterial* in vitro *Activities of the Penemcarboxylic Acids* **8a** ($R = C_2H_5$) and **8b** ($R = (CH_2)_2NHCOCH_3$)

Microorganism	MIC [μg/ml]	
	8a	**8b**
Staphylococcus aureus (SMITH) 14	1	4
Staphylococcus aureus 2999 resistent	2	32
Streptococcus pyogenes ARONSON	0.5	2
Diplococcus pneumoniae	8	0.5
Neisseria meningitidis	8	1
Haemophilus influenzae	32	16
Escherichia coli 205	0.5	2
Salmonellae typhimurium 277	0.5	2
Proteus rettgeri K 856	2	> 128

[1]) Deceased July 8th, 1979.

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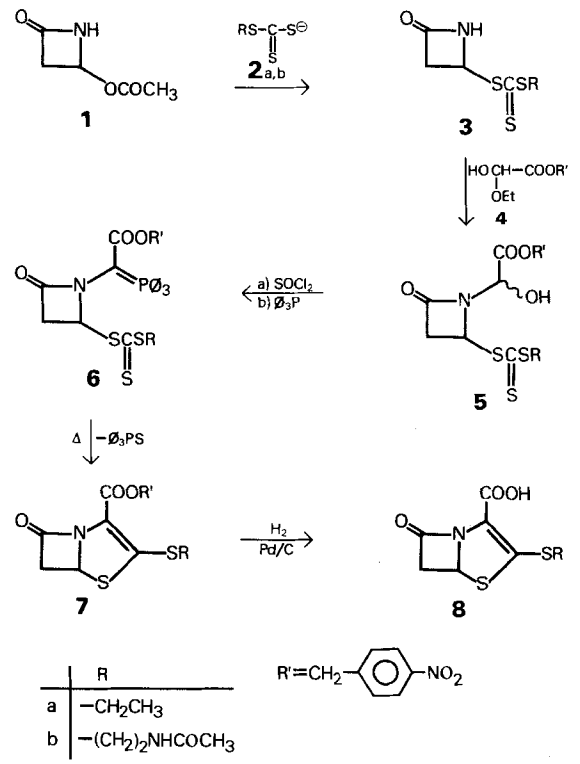
Scheme



lized phosphorane and a trithiocarbonate ester to form a dithioketenacetal [10] **6** to **7** and triphenylphosphinsulfide[2]). The precursor was built up in analogy to previous work, except that instead of a thiocarboxylate anion [3] or thioenolate salt [4] a trithiocarbonate salt was used as the displacing nucleophile in the reaction with 4-acetoxyazetidin-2-one.

The following scheme depicts the sequence of reactions leading to the title compounds **8**.

The acids **8** ($R=(CH_2)_2NHCOCH_3$ obtained only in crude form) showed antibiotic activity against the microorganisms summarized in the *Table*.

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[2]) To our knowledge this is the first reported case of a trithiocarbonate serving as a carbonyl-like component in a reaction with a phosphorane.

Experimental Part

Melting points were determined on a *Reichert* micro hot stage and are uncorrected. UV. (EtOH 96%, λ_{max} in nm, ε in parentheses) and IR. spectra (CH_2Cl_2, wave lenght in μ) were recorded on *Beckman* DB-GT and *Perkin-Elmer* 137 spectrophotometers respectively. ^{1}H-NMR. spectra were measured in $CDCl_3$ (unless stated otherwise), containing TMS as internal standard on a *Varian* HA-100D spectrometer; shifts are given in δ values. Mass spectra were recorded with a *Varian* CH 7 spectrometer. *Merck* silica gel 60 F_{254} was used for thin layer chromatography (TLC.) Abbreviations: RT. = room temperature, i.V. = *in vacuo* (water pump).

Potassium trithiocarbonates **2**. Potassium ethyl-trithiocarbonate (**2**, R = C_2H_5) was prepared according to a literature procedure [11].

Potassium *N*-acetyl-β-aminoethyl trithiocarbonate was prepared from *N*-acetylcysteamine [12] by the following procedure: To a solution of 0.8 g of potassium hydroxide in 5 ml of abs. ethanol, 1.708 g (1 mol-equiv.) *N*-acetylcysteamine in 2 ml of abs. ethanol was added dropwise over 0.5 h, with stirring and cooling at 10–15°. After stirring for an additional 0.5 h, 1.09 g (1 mol-equiv.) of carbon disulfide in 3 ml of abs. ethanol was added while maintaining the temp. at 10–15°. The reaction mixture was then stirred for 3 h at RT., cooled on ice for 20 min and the bright yellow crystalline solid was collected by filtration and washed once with abs. ethanol. There resulted 2.83 g of pure trithiocarbonate **2** (R = $(CH_2)_2NHCOCH_3$): yield 84%, m.p. 171–174°. – IR. (KBr): 2.95, 6.18, 6.50, 7.0, 7.32, 7.43, 7.79, 8.33, 9.09, 11.83.

$C_5H_8KNOS_3$	Calc.	C 25.73	H 3.46	N 6.00	S 41.21%
(233.41)	Found	„ 25.87	„ 3.66	„ 6.07	„ 41.01%

Ethyl 2-oxo-azetidin-4-yl trithiocarbonate (**3**, R = Ethyl). 4-Acetoxy-2-azetidinone (**1**, 1.32 g) was dissolved in 1 ml of acetone and 3.5 ml of water. A solution of potassium ethyl trithiocarbonate (2.25 g, 1.28 mol-equiv) in 12 ml of water was then added dropwise at RT. and under N_2 to the mixture. Precipitation of a yellow solid started readily and after 30 min the mixture was extracted 4 times with CH_2Cl_2. The combined organic extracts were washed with brine and after drying (Na_2SO_4) and evaporation of the solvent i.V. afforded 1.76 g of pure yellow **3** (R = Ethyl): yield 83%. Crystallization from ether gave yellow needles: m.p. 99.5–101.5°. – IR.: 2.95, 5.6, 8.12, 9.15 and 9.3. – ^{1}H-NMR.: 6.85 (br., NH); 5.55 (*d*×*d*, 1 H); 3.35 (*qa*, 2 H); 3.6–2.9 (*m*, 2 H); 1.35 (*t*, 3 H).

$C_6H_9NOS_3$	Calc.	C 34.76	H 4.38	N 6.76	S 46.39%
(207.3)	Found	„ 34.88	„ 4.48	„ 6.75	„ 46.51%

N-*Acetyl-β-aminoethyl 2-oxo-azetidin-4-yl trithiocarbonate* (**3**, R = *N*-Acetyl-β-aminoethyl). To a stirred solution of 1.29 g of 4-acetoxy-2-azetidinone in 2 ml of dioxane 2.33 g (1 mol-equiv.) of potassium *N*-acetyl-β-aminoethyltrithiocarbonate in 20 ml of phosphate buffer (pH-7) solution was added dropwise at 0°. After the addition stirring was continued at RT. and a yellow precipitate started separating. The reaction mixture was then cooled on ice, filtered and the precipitate was washed with cold water. The combined filtrates were extracted with 2× 100 ml CH_2Cl_2 and the organic phase was washed with brine, dried and evaporated. The residue thus obtained was redissolved in a small quantity of CH_2Cl_2 and on cooling yellow crystals started separating. The product was filtered off and combined with the one obtained earlier. Recrystallization from acetone/CH_2Cl_2 gave crystals (yield 0.82 g, 31%): m.p. 119–120°. – IR.: 2.92, 2.96, 5.63, 6.01, 6.65, 7.91, 9.56, 12.19. – ^{1}H-NMR. (DMSO d_6): 8.90 (br., 1 H); 8.10 (br., 1 H); 5.63 (*d*×*d*, *J* = 2 and 5 Hz, 1 H); 3.70–2.90 (*m*, 6 H); 1.82 (*s*, 3 H).

$C_8H_{12}N_2O_2S_3$	Calc.	C 36.35	H 4.58	N 10.60	S 36.38%
(264.38)	Found	„ 36.49	„ 4.31	„ 10.57	„ 35.52%

Ethyl [N-(p-nitrobenzyloxycarbonyl-triphenylphosphoranylidene-methyl)-2-oxo-azetidin-4-yl] trithiocarbonate (**6**, R = C_2H_5). Azetidinone **3** (R = C_2H_5, 621 mg, 3 mmol) and the ethyl hemiacetal of *p*-nitrobenzylglyoxylate (**4**, R′ = *p*-nitrobenzyl [1], 1.7 g) were dissolved in 35 ml of dry toluene and 9 ml of dry dimethylformamide. After addition of freshly activated molecular sieves (3 or 4 Å) the mixture was stirred under N_2 at RT. overnight and for 2 h at 50°. The sieves were filtered off and the solvent evaporated under reduced pressure to give 1.8 g of a yellow oily material. Column chromatography of this residue on 80 g of silica gel afforded (with toluene/ethyl acetate 9:1) compound **5** (R = C_2H_5) as a mixture of diastereomers: 1.1 g (88%). – IR.: 2.85, 5.62, 5.7,

6.55, 7.45. – ^{1}H-NMR.: 8.3–8.15 (*m*, 2 H); 7.6–7.45 (*m*, 2 H); 6.1–5.9 (*m*, 1 H); 5.55 (*d*, 1 H); 5.4–5.3 (*m*, 2 H), 4.2–4 (*m*, 1 H: exchanges with D_2O); 3.8–3 (*m*, 4 H); 1.35 (*t*, 3 H).

A solution of 1.1 g crude **5** ($R=C_2H_5$) in 23 ml of abs. dioxane was added to 4.55 g of polymeric *Hünig* base [1] that had previously been stirred for 30 min in 11 ml of the same solvent. Thionyl chloride (0.8 ml) was added and the mixture was then stirred at RT. under N_2 for 3 h. The insoluble polymeric base was filtered off and the filtrate evaporated i.V. to give the crude corresponding halides. Redissolution of this material in 54 ml of abs. dioxane and addition of polymeric base (4.55 g) was followed by treatment of the resulting solution with 1.42 g of triphenylphosphine at 50° for 15 h under N_2. Filtration and evaporation of the solvent under reduced pressure gave crude **6** ($R=C_2H_5$) which was purified by column chromatography. Yield 1.1 g (62.3%), Rf = 0.4 (toluene/ethyl acetate 2:3). – IR.: 5.67, 6.15, 6.57, 6.97, 7.43 and 9.05.

*2-Acetylaminoethyl [*N*-(p-nitrobenzyloxycarbonyl-triphenylphosphoranylidenemethyl)-2-oxo-azetidin-4-yl] trithiocarbonate* (**6**, $R=(CH_2)_2NHCOCH_3$). Azetidinone **3** ($R=(CH_2)_2NHCOCH_3$, 0.88 g) and *p*-nitrobenzyl glyoxylate ethyl hemiacetal (**4**, 0.926 g) were processed for 3 h as described for **5** ($R=C_2H_5$). The crude mixture of diastereomers **5** ($R=(CH_2)_2NHCOCH_3$) thus obtained was triturated with ether in order to remove the excess of glyoxylate. The residue was used in the following step without further purification: yield 1.6 g (quant.), Rf = 0.16 (AcOEt). – IR.: 2.98, 2.93, 5.64, 5.73, 5.99, 6.58, 7.43 and 9.22.

A solution of 1.6 ml **5** ($R=(CH_2)_2NHCOCH_3$) in 10 ml dry THF was cooled to −15° and treated successively with thionyl chloride (0.31 ml, 1.25 mol-equiv.) and triethylamine (0.58 ml, 1.25 mol-equiv.). The reaction mixture was then stirred at 0° for 20 min, diluted with 40 ml of precooled CH_2Cl_2 and finally washed with precooled 1N HCl. The organic phase was dried and the solvent was evaporated under reduced pressure to afford after column chromatography (elution with AcOEt) the isomeric chlorides (1 g, 61% based on **3**), Rf = 0.29 (AcOEt). – IR.: 2.92, 5.61, 5.71, 5.97, 6.58, 7.41, 7.61 and 9.35. These chlorides (1 g) and triphenylphosphine (1.064 g, 2 mol-equiv.) were dissolved in 2 ml of dry THF and the reaction mixture was allowed to stand at RT. for 24 h. The reaction mixture was then diluted with 30 ml of precooled CH_2Cl_2 and washed with aqueous hydrogencarbonate solution. The organic phase was dried, evaporated and the residue chromatographed on silica gel (elution with AcOEt). The obtained phosphorane **6** ($R=(CH_2)_2NHCOCH_3$) was recrystallized from CH_2Cl_2 to give 0.597 g (41%) of pure **6** ($R=(CH_2)_2NHCOCH_3$), m.p. 208–210°, Rf = 0.16 (AcOEt). – IR. (KBr): 3.08, 5.68, 6.0, 6.25, 6.66, 6.94, 7.41, 7.87, 8.06, 9.09, 9.26, 9.43 and 12.65.

$C_{35}H_{32}N_3O_6PS_3$	Calc.	C 58.57	H 4.49	N 5.85	S 13.40%
(717.81)	Found	„ 58.64	„ 4.68	„ 5.69	„ 13.11%

p-*Nitrobenzyl 2-alkylthiopenem carboxylates* (**7**). – *General procedure.* The phosphoranes **6** were heated in *o*-xylene to 145° under N_2 in presence of a catalytic amount of hydroquinone. The reaction solutions were evaporated under reduced pressure and the products 7 isolated by column chromatography (SiO_2, separation from triphenylphosphinesulfide).

Preparation of **7** ($R=C_2H_5$). The reaction time was 10 h. Elution from silica gel with toluene/ethyl acetate 19:1 gave triphenylphosphinesulfide and 9:1 elution afforded product **7**, yield 64.7%, m.p. 133–134° (CH_2Cl_2/ether). – UV.: 337 (10,287), 261 (14,735). – IR.: 5.57, 5.9, 6.22, 6.55, 6.65, 7.42, 7.55, 8.37, 9.0, 9.7. – ^{1}H-NMR.: 8.2 (*m*, 2 H); 7.6 (*m*, 2 H); 5.7 (*d*×*d*, 1 H); 5.32 (*m*, 2 H); 3.9–3.4 (*m*, 2 H); 2.95 (*m*, 2 H); 1.4 (*t*, 3 H).

$C_{15}H_{14}N_2O_5S_2$	Calc.	C 49.17	H 3.85	N 7.64	O 21.83	S 17.50%
(366.40)	Found	„ 49.26	„ 3.94	„ 7.75	„ 21,82	„ 17.25%

Preparation of **7** ($R=(CH_2)_2NHCOCH_3$). The reaction time was 7 h. The product was eluted from silica gel with ethyl acetate; yield 65%, m.p. 159–160° (CH_2Cl_2/ether). – UV.: 335 (11,441), 259 (17,087). – IR.: 2.92, 5.59, 5.97, 6.58, 7.44, 7.55, 8.37, 9.01. – ^{1}H-NMR.: 8.23 (*m*, 2 H); 7.65 (*m*, 2 H); 6.04 (br., 1 H); 5.75 (*d*×*d*, *J* = 2 and 4, 1 H); 5.35 (*m*, 2 H); 4.0–3.1 (*m*, 6 H); 2.00 (*s*, 3 H).

$C_{17}H_{17}N_3O_6S_2$	Calc.	C 48.22	H 4.05	N 9.92	S 15.14%
(423.46)	Found	„ 48.04	„ 4.20	„ 9.72	„ 14.63%

2-Ethylthiopenem carboxylic acid (**8**) ($R=C_2H_5$). The corresponding ester **7** ($R=C_2H_5$); 1 g (2.73 mmol) was dissolved in 70 ml of ethyl acetate. To this solution 40 ml of an 0.2M aqueous $NaHCO_3$ and 2 g of

Pd/C 10%) were added. The mixture was stirred vigorously for 50 min under N_2 and the catalyst removed by filtration over *Hyflo*. The filter aid was washed once with hydrogencarbonate solution and three times with ethyl acetate. Washings and filtrate were combined, the phases were separated and the aqueous one was washed with methylene chloride and acidified with 5% aqueous citric acid solution. Extractions with methylene chloride (3×) yielded after drying (Na_2SO_4) and evaporation i.V. 258 mg of pure crystalline **8** (R = C_2H_5): yield 44.4%, m.p. 143–145°. – UV.: 325 (7373), 253 (5890). – IR. (KBr): 3.6–3.3, 5.6, 6.0, 6.75, 6.97, 7.5, 7.9, 8.15 and 8.8. – ^{1}H-NMR. (DMSO-d_6): 5.75 (*d*×*d*, *J* = 2,4, 1 H); 3.95–3.4 (*m*, 2 H); 2.95 (*m*, 2 H); 1.3 (*t*, 3 H). – MS.: 231 (*M*), 214, 189.

$C_8H_9NO_3S_2$ (231.28) Calc. C 41.55 H 3.93 N 6.06% Found C 41.20 H 3.95 N 5.96%

2-(N-Acetyl-β-aminoethylthio)penem carboxylic acid (**8**) (R = $(CH_2)_2NHCOCH_3$) (sodium salt). The corresponding ester **7** (R = $(CH_2)_2NHCOCH_3$) (0.1 g, 0.24 mmol) was dissolved in 30 ml of dioxane. To this solution was added 20 mg (1 mol-equiv.) of sodium hydrogencarbonate in 13.5 ml of water. After dilution with 16.5 ml of water and 6 ml of ethanol and addition of 200 mg of Pd/C (10%) the reaction mixture was stirred 1 h under H_2. Removal of the catalyst by filtration on *Hyflo* and washing of the filtrate with ethyl acetate (3.75 ml) afforded after lyophilization of the aqueous phase the crude sodium salt of **8**. Prep. TLC. on *Antec-gel*, OPTI-UP C_{12} (supplier: *Antec Ltd.*, 4431 Bennwil, Switzerland) with water/acetonitrile 9:1 gave 44 mg (60%) of the sodium salt corresponding to **8** (R = $(CH_2)_2NHCOCH_3$). – UV.: 328 (7118), 254 (5829). – IR. (KBr): 3.08, 5.68, 6.13, 6.39, 7.14 and 7.72. – ^{1}H-NMR. (DMSO-d_6): 8.16 (br., NH); 5.65 (*d*×*d*, 1 H); 4.0–3.05 (mc, 4 H, partially obscured by strong water peak); 3.0–2.8 (*m*, 2 H); 1.76 (*s*, 3 H).

$C_{10}H_{11}N_2NaO_4S_2 \cdot H_2O$	Calc.	C 36.59	H 3.99	N 8.53	S 19.53%
(328.2)	Found	„ 36.84	„ 4.01	„ 8.52	„ 18.10%

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