Synthesis and Antibacterial Activity of New 1β-Methyl carbapenem Having a Thiazolo[3,2-*a*]benzimidazole Moiety

Synthese und antimikrobielle Wirkung von neuen 1β-Methyl carbapenem mit Thiazolo[3,2-*a*]benzimidazol-Baustein

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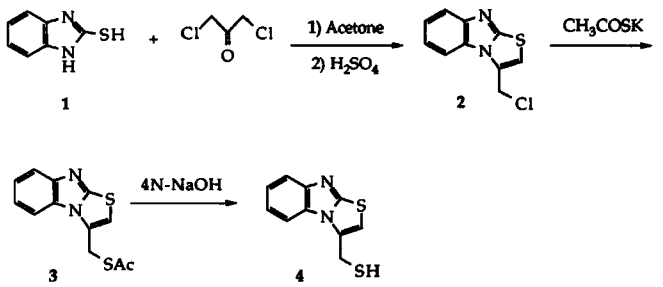
Received September 5, 1994

In the preceeding papers[1,2], we reported the synthesis and biological properties of carbapenems having various (substituted) pyrrolidin-3-ylthio groups at C-2. In this study a series of 1β-methyl carbapenems having a thiazolo[3,2-*a*] benzimidazole moiety at the C-2 position were synthesized and their *in vitro* antibacterial activities were tested.

Reaction of 2-mercaptobenzimidazole (**1**) with 1,3-dichloroacetone in acetone gave 1-(benzimidazolyl-2-thio)-3-chloro-2-propanon hydrochloride. Cyclization of this compound in sulfuric acid followed by basic work up provides compound **2** in moderate yield[3]. Treatment of **2** with potassium thioacetate in DMF and toluene gave 3-(acetylthiomethyl)-thiazolo[3,2-*a*]benzimidazole (**3**). Finally the acetylthio group of **3** was readily hydrolyzed with 4N-NaOH in methanol to give 3-(mercaptomethyl)-thiazolo[3,2-*a*]benzimidazole (**4**) (Scheme 1).

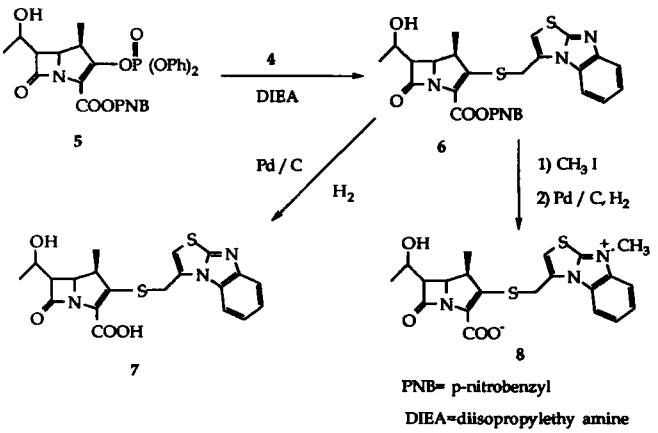


Scheme 1

Preparation of the 2-(diphenylphosphoryloxy)carbapenem compound **5** has been reported[4]. Reaction of **5** with **4** in the presence of diisopropylethylamine provided the 2-substituted carbapenem **6**. The corresponding quaternary ammonium salt was obtained by methyl iodide at room temp. The synthesis of the final compound **7**, **8** was completed by catalytic hydrogenolysis over 10% Pd/C in the presence of phosphate buffer (pH = 7). Compounds **9**-**14** were prepared analogously.

Antibacterial activity

The minimum inhibitory concentration (MIC) of the new carbapenem compounds **7**-**14** were determined by an agar dilution method using *Mueller-Hinton* agar (Table 1). The effect of the substituents on the thiazolobenzimidazole ring was investigated.



Scheme 2

Compound **11** having a nitro group exhibits inferior antibacterial activity compared to compound **7** against both *Gram*-positive and *Gram*-negative bacteria. In general, the basicity of the substituent was observed to affect the activity considerably[5]. Compounds having the quaternary ammonium salt moiety **8**, **10**, **12**, **14** possess an increased activity against *Escherichia coli* and *Enterobacter cloacae* as compared to compounds **7**, **9**, **11**, **13**.

Experimental Part

Melting points: Thomas Hoover apparatus, uncorrected.- UV-spectra: Hewlett-Packard 8451A UV-VIS spectrophotometer.- ^{1}H-NMR spectra: Varian Gemini 300 spectrometer, tetramethylsilane as internal standard.

3-(Chloromethyl)-thiazolo[3,2-a]benzimidazole (**2**)

To a solution of 2-mercaptobenzimidazole (**1**) (3.0 g, 20 mmol) in acetone (50 ml) at room temp. was added slowly 1,3-dichloroacetone (5.80 g, 45.7 mmol). After 10 min the reaction mixture was heated to 40°C for 2 h. The precipitate was washed with acetone and ethanol. The mixture of the above solid in 20 ml of conc. H_2SO_4 was stored at room temp. for 20 h,

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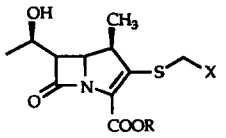
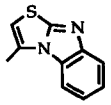
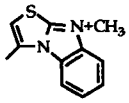
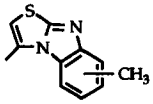
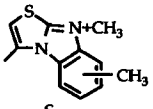
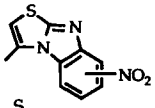
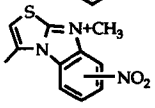
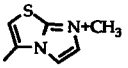


Table 1. Antibacterial activities of the carbapenem derivatives

compound	X	R	MIC(μg/ml) [a]					
			S.p[b]	S.a	E.c	P.a	K.o.	En.c
7		H	<0.01	0.02	12.5	25	1.56	12.5
8			<0.01	0.05	0.40	25	0.40	0.40
9		H	<0.01	0.04	12.5	50	6.25	12.5
10			<0.01	0.04	0.40	50	0.80	0.40
11		H	0.02	0.10	25	>100	25	50
12			0.04	0.10	0.80	100	1.56	1.56
13		H	<0.01	0.01	0.80	1.56	0.80	0.80
14			0.01	0.01	0.10	1.56	0.10	0.10

a. Agar dilution method

b. S.p.: *Streptococcus pyogenes 77A*; S.a.: *Staphylococcus aureus 503*; E.c.: *Escherichia coli 055*; P.a.: *Pseudomonas aeruginosa 9027*; K.o.: *Klebsiella oxytoca 1082E*; En.c.: *Enterobacter cloacae 1321E*

then poured on ice water and neutralized with $NaHCO_3$. The solid was filtered off and washed with water: m.p. 144-147°C, yield 2.61 g (51%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 5.35 (s, 2H, CH_2Cl), 7.30-7.41 (t, 2H, J = 6.5 Hz), 7.48 (s, 1H, 2-H), 7.69 (d, 1H, J = 7.2 Hz), 8.01 (d, 1H, J = 7.2 Hz).

3-(Acetylthiomethyl)-thiazolo[3,2-a]benzimidazole (**3**)

A mixture of **2** (1.0 g, 3.9 mmol) and potassium thioacetate (1.8 g, 15.4 mmol) in DMF (10 ml) and toluene (10 ml) was stirred at room temp. for 5 h under N_2. After cooling, the mixture was diluted with toluene (20 ml) and water (20 ml). The aqueous layer was re-extracted with toluene (20 ml). The combined org. layer was washed with brine and dried over Na_2SO_4. Removal of the solvent gave a crude residue, which was chromatographed on silica gel using ethyl acetate/n-hexane (1:2) to give a yellowish solid: m.p. 218-220°C, yield 0.89 g (78%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.35 (s, 3H, CH_3COS), 4.68 (s, 2H, CH_2S), 7.12 (s, 1H, 2-H), 7.25-7.41 (t, 2H, J = 6.4 Hz), 7.69 (s, 1H, J = 7.2 Hz), 7.85 (d, 1H, J = 7.2 Hz).

3-(Mercaptomethyl)-thiazolo[3,2-a]benzimidazole (**4**)

To a solution of **3** (1.0 g, 3.4 mmol) in CH_3OH (10 ml) were added 0.85 ml of 4N-NaOH in an ice bath. After stirring for 30 min 0.85 ml 4N-HCl were added and the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and distilled to remove the solvent in order to give **4**: m.p. 209-211°C (dec), yield 0.77 g (90%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.05 (s, 1H, SH), 3.98 (s, 2H, CH_2S), 6.65 (s, 1H, 2-H), 7.25-7.41 (t, 2H, J = 6.0 Hz), 7.63 (d, 1H, J = 6.8 Hz), 7.81 (d, 1H, J = 6.8 Hz).

p-Nitrobenzyl (1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(thiazolo[3,2-a]-benzimidazole-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylate (**6**)

A solution of *p*-nitrobenzyl-(1*R*,5*S*,6*S*)-3-(diphenylphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**5**, 1.20 g, 2.50 mmol) in CH_3CN (20 ml) was cooled to 0°C under N_2. To this solution was added diisopropyl-ethylamine (0.33 g, 2.50 mmol) and a solution of the mercapto compound **4** (0.64 g, 2.50 mmol) in CH_3CN (10 ml). After

stirring for 2 h, the mixture was diluted with ethyl acetate, washed with 10% $NaHCO_3$, brine, and dried over $MgSO_4$. Evaporation *in vacuo* gave a foam which was purified by silica gel CC to give **6** as a yellow powder: yield 0.93 g (60%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.15 (d, 3H, 1-CH_3, J = 7.2 Hz), 1.25 (d, 3H, C$\underline{H}_3$CHOH, J = 6.2 Hz), 2.75 (m, 1H, 1-H), 3.35 (m, 1H, 6-H), 4.05 (m, 1H, 5-H), 4.25-4.33 (bs, 3H), 5.25 (d, 1H, J = 12 Hz), 5.40 (d, 1H, J = 12 Hz), 6.58 (s, 1H, 2'-H), 7.29-7.42 (m, 2H), 7.73, 8.15 (d, 2H, J = 7.8 Hz), 7.70-7.88 (m, 2H).

(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(thiazolo[3,2-a]benzimidazole-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (**7**)

Compound **6** (1.41 g, 2.30 mmol) and 1.4 g of Pd/C 10% were suspended in THF/phosphate buffer (pH = 7) (1:1, 20 ml each). The mixture was hydrogenated at 3 atm for 1 h. The solution was filtered through celite and washed with water (2 x 10 ml). The combined filtrate was washed with ether (2 x 20 ml) and lyophilized to give a yellow powder which was purified on a Diaion HP-20 column, eluting with 2% THF in water. Fractions having a UV absorption at 298 nm were collected and lyophilized again to give compound **7** as a white powder: m.p. 184-187°C (dec), yield 0.21 g (19%).- ^{1}H-NMR (D_2O): δ (ppm) = 1.13 (d, 3H, 1-CH_3, J = 7.2 Hz), 1.25 (d, 3H, C$\underline{H}_3$CHOH, J = 6.2 Hz), 2.76 (m, 1H, 1-H), 3.33 (m, 1H, 6-H), 4.05 (m, 1H, 5-H), 4.25-4.35 (bs, 3H), 7.10 (s, 1H, 2'-H), 7.12-7.37 (m, 2H), 7.67, 7.95 (d, 2H, J = 8.0 Hz).

(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(N-methyl-thiazolo[3,2-a]benzimidazolium-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (**8**)

To a solution of 0.86 g (1.39 mmol) **6** in acetone (10 ml) was added 4 ml of methyl iodide. The reaction mixture was stirred for 3 days at room temp. The precipitate was collected and washed with acetone (10 ml) to give the quaternized compound as a slightly yellow solid. Deblocking and purification by CC to **8** was carried out as described for **7**: m.p. 160-163°C (dec), yield 0.10 g (15%).- ^{1}H-NMR (D_2O): δ (ppm) = 1.13 (d, 3H, 1-CH_3, J = 7.2 Hz), 1.25 (d, 3H, C$\underline{H}_3$CHOH, J = 6.2 Hz), 2.76 (m, 1H, 1-H), 3.33 (m, 1H, 6-H), 4.08 (m, 1H, 5-H), 4.12 (s, 3H, N^+-CH_3), 4.25-4.33 (bs, 3H), 7.55 (s, 1H, 2'-H), 7.62-7.79 (m, 2H), 7.97, 8.25 (d, 2H, J = 8.2 Hz).

(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(thiazolo[3,2-a]-7-methylbenzimidazole-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (**9**)

Comp. **9** was synthesized from 2-mercapto-5-methylbenzimidazole as described for the preparation of **7**: m.p. 188-189°C (dec).- ^{1}H-NMR (D_2O): δ (ppm) = 1.15 (d, 3H, 1-CH_3, J = 6.8 Hz), 1.23 (d, 3H, C$\underline{H}_3$CHOH, J = 6.2 Hz), 2.79 (m, 1H, 1-H), 3.33 (m, 1H, 6-H), 4.15 (m, 1H, 5-H), 4.25-4.35 (bs, 3H), 7.05 (s, 1H, 2'-H), 7.15, 7.55, 7.84 (d, 1H, J = 8.2 Hz).

(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(thiazolo[3,2-a]-7-nitrobenzimidazole-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (**11**)

Comp. **11** was synthesized from 2-mercapto-5-nitrobenzimidazole as described for **7**: m.p. 237-240°C (dec).- ^{1}H-NMR (D_2O): δ (ppm) = 1.15 (d, 3H, 1-CH_3, J = 7.1 Hz), 1.25 (d, 3H, C$\underline{H}_3$CHOH, J = 6.4 Hz), 2.88 (m, 1H, 1-H), 3.48 (m, 1H, 6-H), 4.04 (m, 1H, 5-H), 4.22-4.37 (bs, 3H), 6.95 (s, 1H, 2'-H), 7.80, 8.20, 8.45 (d, 1H, J = 8.5 Hz).

(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(thiazoloimidazole-3-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (**13**)

Comp. **13** was synthesized from 2-mercaptoimidazole as described for **7**: m.p. 175-177°C (dec).- ^{1}H-NMR (D_2O): δ (ppm) = 1.13 (d, 3H, 1-CH_3, J = 7.2 Hz), 1.25 (d, 3H, C$\underline{H}_3$CHOH, J = 6.0 Hz), 2.74 (m, 1H, 1-H), 3.35 (m, 1H, 6-H), 4.05 (m, 1H, 5-H), 4.23-4.38 (bs, 3H), 7.10 (s, 1H, 2'-H), 7.15 (s, 2H).

The quaternized compounds **10**, **12**, and **14** were prepared as described for the preparation of **8**.

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[KPh639]