# New 1β-Methylcarbapenems Having a Hydantoin Moiety

## Neue 1β-Methylcarbapeneme mit Hydantoin-Substitution

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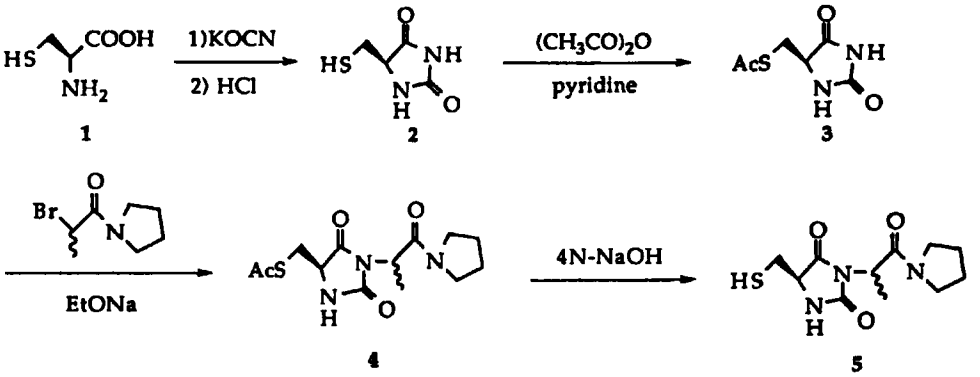
The mercaptans used in this work were prepared from cysteine. As shown in Scheme 1, cysteine-hydantoin **2** was synthesized by potassium cyanate cyclization from cysteine[1]. The thiol group of cysteine hydantoin was protected by acetic anhydride and pyridine. *N*-3-Alkylation of the cysteine hydantoin **3** was carried out with *N*-(α-bromopropionyl)pyrrolidine in the presence of sodium ethoxide and the compound **4** was readily hydrolyzed with 4N NaOH to produce the 5-mercaptomethyl hydantoin **5**.

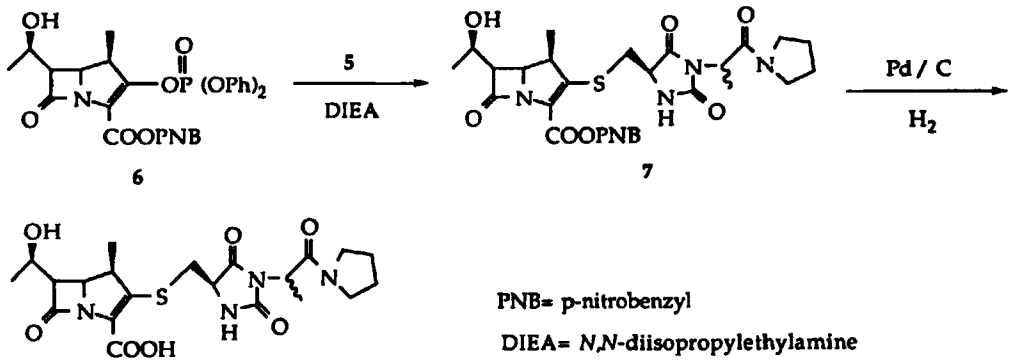
Preparation of the 2-(diphenylphosphoryloxy)carbapenem **6** has been reported[2]. As shown in Scheme 2, reaction of **6** with **5** in the presence of diisopropylethylamine provided the 2-substitued carbapenem **7**. Synthesis of the final compound **8** was completed by catalytic hydrogenolysis over 10% Pd/C in the presence of phosphate buffer (pH = 7).

### *Antibacterial Activity*

The minimum inhibitory concentrations (MICs) of the new carbapenem compounds **8–17** were determined by an agar dilution method using *Mueller-Hinton* agar (Table 1). The effect of the substituent on the hydantoin ring was investigated: the larger the substituent, the lower the activity against *Gram*-positive and *Gram*-negative bacteria. Compound **10** having a hydroxyl group was more active than compound **11** having a methyl group. Analogous substituent effects were already demonstrated by us[3,4,5].




**Scheme 1**




**Scheme 2**

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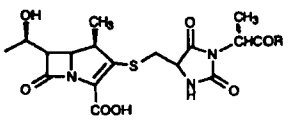
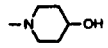
**Table 1.** Antibacterial activity of the carbapenem derivatives.



| compound | R | MIC(μg/ml) [a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | S.p[b] | S.a | E.c | P.a | K.o | En.C |
| 8 |  | <0.01 | 0.20 | 0.05 | 25 | 3.12 | 0.05 |
| 9 |  | <0.01 | 0.20 | 0.05 | 50 | 3.12 | 0.20 |
| 10 |  | <0.01 | 0.20 | 0.02 | 25 | 1.56 | 0.10 |
| 11 |  | 0.01 | 0.40 | 0.10 | 100 | 6.25 | 0.20 |
| 12 |  | 0.01 | 0.40 | 0.20 | 100 | 6.25 | 0.02 |
| 13 |  | <0.01 | 0.20 | 0.05 | 50 | 3.12 | 0.05 |
| 14 |  | 0.01 | 0.40 | 0.20 | >100 | 25 | 3.12 |
| 15 |  | 0.01 | 0.80 | 0.40 | >100 | 25 | 3.12 |
| 16 |  | <0.01 | 0.20 | 0.05 | 25 | 1.56 | 0.10 |
| 17 |  | 0.01 | 0.80 | 0.20 | 50 | 3.12 | 0.05 |
| | Imipenem | <0.01 | 0.01 | 0.10 | 1.56 | 0.40 | 0.20 |

[a] Agar dilution method.

[b] S.p.: *Streptococcus pyogenes* 77A, S.a.: *Staphylococcus aureus* 503, E.c.: *Escherichia coli* O55, P.a.: *Pseudomonas aeruginosa* 9027, K.o.: *Klebsiella oxytoca* 1082E, En.c.: *Enterobacter cloacae* 1321E.

## Experimental Part

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

*5-(S)-(Mercaptomethyl)hydantoin (2)*

To a solution of L-cysteine (**1**, 5.9 g, 0.049 mol) in water (50 ml) was added KOCN (8.8 g, 0.11 mol). The solution was heated on a steam-bath for 2 h. After cooling, this solution was refluxed for 2 h with 50 ml conc. HCl. The solid which crystallized when the solution was cooled was collected, yield 3.57 g (50%). m.p. 142–144 °C (from $H_2O$).– $[\alpha]^{25}$ = –6.76° (c = 0.02, $CH_3OH$).– $^1$H-NMR ([D6]DMSO): δ (ppm) = 2.21 (t, 1H, SH, J = 5.1Hz), 2.78 (m, 2H, $CH_2SH$), 4.31 (s, 1H, 5-H), 7.81 (s, 1H, $N_1$-H), 10.72 (s, 1H, $N_3$-H).

*5-(S)-(Acetylthiomethyl)hydantoin (3)*

Acetic anhydride (0.4 g, 3.9 mmol) was added dropwise to a solution of **2** (0.5 g, 3.4 mmol) in pyridine (3 ml) at 0 °C. After stirring for 1 h at room temp., the solution was diluted with ethyl acetate (10 ml) and ice water (10 ml). The pH was adjusted to 3 with 10% HCl. The org. layer was washed with water and brine, and dried over $Na_2SO_4$. Evaporation *in vacuo* gave a solid, yield 0.51 g (79%), m.p. 137–139 °C (from ethyl acetate).– $^1$H-NMR ($CDCl_3$): δ (ppm) = 2.35 (s, 3H, $CH_3COS$), 3.18 (m, 2H, $CH_2SH$), 4.31 (m, 1H, 5-H), 7.99 (s, 1H, $N_1$-H), 10.77 (s, 1H, $N_3$-H).

*3-(2-Propionylpyrrolidin-1-yl)-5-(S)-(acetylthiomethyl)hydantoin (4)*

**3** (0.91 g, 4.8 mmol) was added to a stirred solution of Na (0.11 g, 4.8 mmol) in EtOH (10 ml). After refluxing for 1 h, *N*-(α-bromopropionyl)pyrrolidine (1.0 g, 4.8 mmol) was added to the suspension and reflux was continued for 3 h. The resulting solution was evaporated and the residue was extracted with ethyl acetate (50 ml). The org. layer was washed with water and brine, and dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave an oily residue, yield 0.62 g (42%).– $^1$H-NMR ($CDCl_3$): δ (ppm) = 1.32 (d, 3H, $CH_3CH$, J = 5.8Hz), 1.68–1.95 (m, 4H), 2.33 (s, 3H, $CH_3COS$), 3.28 (m, 2H, $SCH_2$), 3.35–3.53 (m, 4H), 4.33 (m, 1H, 5-H), 4.79 (q, 1H, $CHCH_3$, J = 5.8Hz), 7.55 (s, 1H, $N_1$-H).

*3-(2-Propionylpyrrolidin-1-yl)-5-(S)-(mercaptomethyl)hydantoin (5)*

To a solution of **4** (0.3 g, 0.9 mmol) in methanol (5 ml) were added 0.28 ml of 4N NaOH at 0 °C. After stirring for 20 min, 0.28 ml of 4N HCl were added, and the mixture was diluted with ethyl acetate, washed with water and brine, dried [$Na_2SO_4$], and then distilled to give the oily mercapto compound **5**, yield 0.22 g (92%).– $^1$H-NMR ($CDCl_3$): δ (ppm) = 1.35 (d, 3H, $CH_3CH$, J = 6.2Hz), 1.69–1.98 (m, 4H), 3.28 (m, 2H, $SCH_2$), 3.37–3.55 (m, 4H), 4.34 (m, 1H, 5-H), 4.75 (q, 1H, $CHCH_3$, J = 6.2Hz), 7.59 (s, 1H, $N_1$-H).

*p-Nitrobenzyl(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3-((R/S)-2-propionylpyrrolidin-1-yl)-5-(S)-hydantoin-5-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylate (7)*

A solution of *p*-nitrobenzyl-(1*R*,5*S*,6*S*)-3-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-1-methyl-carbapen-2-em-3-carboxylate[2] (**6**, 1.20 g, 2.50 mmol) in $CH_3CN$ (20 ml) was cooled to 0 °C under $N_2$. To this solution was added *N,N*-diisopropylethylamine (0.33 g, 2.50 mmol) and a solution of 0.78 g (2.50 mmol) of the mercapto compound **5** (0.78 g, 2.50 mmol) in $CH_3CN$ (10 ml). After stirring for 2 h, the mixture was diluted with ethyl acetate, washed with 10% $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation *in vacuo* gave a foam which was purified by silica gel-cc to give **7** as a yellow gum, yield 0.96g (61%).– $^1$H-NMR ($CDCl_3$): δ (ppm) = 1.17 (d, 3H, 1-$CH_3$, J = 6.8Hz), 1.26 (d, 3H, $CH_3CHOH$, J = 6.0Hz), 1.39 (d, 3H, $CH_3CH$, J = 6.0Hz), 1.71–2.02 (m, 4H), 2.77 (m, 1H, 1-H), 3.25–3.60 (m, 7H), 4.05 (m, 1H, 5-H), 4.15–4.33 (bs, 3H), 5.25 (d, 1 H, J = 11.5Hz), 5.40 (d, 1H, J = 11.5Hz), 7.68, 8.15 (2d, 2H each, J = 8.8Hz).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3-((R/S)-2-propionyl pyrrolidin-1-yl)-5-(S)-hydantoin-5-yl)methyl]thio-1-methylcarbapen-2-em-3-carboxylic acid (8)*

Compound **7** (1.01 g, 2.30 mmol) and 1.0 g of 10% Pd/C were suspended in THF/phosphate buffer (pH = 7) (1:1, 20 ml each) and hydrogenated at 3 atm for 1 h. This solution was filtered through celite and washed with water (2x20 ml). The combined filtrate was washed with ether (2x20 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 the title compound **8** as a white powder, yield 0.21 g (19%); m.p. 68–171 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.44 (d, 3H, $CH_3CH$, J = 7.2Hz), 1.79–2.11 (m, 4H), 3.17 (m, 1H, 1-H), 3.25–3.55 (m, 4H), 3.60–3.81 (m, 3H), 4.11–4.29 (bs, 4H).

Compounds **9–17** were prepared as described for **8**.

**9**: m.p. 174–178 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.18 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.25 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.45 (d, 3H, $CH_3CH$, J = 7.2Hz), 1.81–2.05 (m, 4H), 3.07 (m, 1H, 1-H), 3.35–3.58 (m, 6H), 3.60–3.81 (m, 3H), 4.06–4.39 (bs, 4H).

**10**: m.p. 188–191 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.25 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.40 (d, 3H, $CH_3CH$, J = 7.2Hz), 1.89–2.21 (m, 4H), 3.18 (m, 1H, 1-H), 3.35–3.55 (m, 4H), 3.61–3.84 (m, 4H), 4.06 (m, 1H, 5-H), 4.15–4.35 (bs, 3H).

**11**: m.p. 168–171 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 0.95 (d, 3H, $CH_3$, J = 7.0Hz), 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.44 (d, 3H, $CH_3CH$, J = 7.2Hz), 1.79–2.11 (m, 5H), 3.17 (m, 1H, 1-H), 3.25–3.55 (m, 4H), 3.60–3.81 (m, 3H), 4.11–4.43 (bs, 4H).

**12**: m.p. 180–184 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.38 (d, 3H, $CH_3CH$, J = 7.2Hz), 3.10 (m, 1H, 1-H), 3.35–3.65 (m, 8H), 3.70–3.85 (m, 3H), 4.01–4.34 (bs, 4H).

**13**: m.p. 178–183 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.19 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.30 (d, 3H, $CH_3CHOH$, J = 6.8Hz), 1.54 (d, 3H, $CH_3CH$, J = 7.2Hz), 2.57-2.71 (bs, 4H), 3.05 (m, 1H, 1-H), 3.20 (m, 1H, 6-H), 3.45–3.55 (m, 2H), 3.60–3.81 (m, 4H), 4.01–4.33 (bs, 4H).

**14**: m.p. 168–172 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, C*H*$_3$CHOH, J = 6.8Hz), 1.40 (d, 3H, $CH_3$CH, J = 7.2Hz), 1.69–2.01 (bs, 8H), 3.11 (m, 1H, 1-H), 3.45–3.65 (m, 4H), 3.70–3.81 (m, 3H), 4.05–4.33 (bs, 4H).

**15**: m.p. 178–182 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, C*H*$_3$CHOH, J = 6.8Hz), 1.44 (d, 3H, $CH_3$CH, J = 7.2Hz), 1.67–2.01 (bs, 10H), 3.05 (m, 1H, 1-H), 3.45–3.58 (m, 4H), 3.64–3.81 (m, 3H), 4.05–4.30 (bs, 4H).

**16**: m.p. 192–196 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.17 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.25 (d, 3H, C*H*$_3$CHOH, J = 6.8Hz), 1.50 (d, 3H, C*H*$_3$CH, J = 7.2Hz), 1.59–1.78 (bs, 2H), 3.27 (m, 1H, 1-H), 3.43–3.58 (bs, 4H), 3.60–3.81 (m, 3H), 4.11–4.40 (bs, 4H), 5.80–5.95 (m, 2H, CH=CH).

**17**: m.p. 199–204 °C (dec.).– $^1$H-NMR ($D_2O$): δ (ppm) = 1.15 (d, 3H, 1-$CH_3$, J = 7.2Hz), 1.23 (d, 3H, C*H*$_3$CHOH, J = 6.8Hz), 1.42 (d, 3H, C*H*$_3$CH, J = 7.2Hz), 3.08 (s, 6H, $N(CH_3)_2$), 3.23 (m, 1H, 1-H), 3.55 (m, 1H, 6-H), 3.60–3.81 (m, 2H), 4.11–4.43 (bs, 4H).

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