131. The Synthesis of Dibenzyl *trans*-{7-oxo-3-phenyl-6-phenylacetamido-1-azabicyclo[3.2.0]heptane}-2, 2-dicarboxylate (Carbapenam)

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Summary

The synthesis of the title compound is described.

The nuclear analogues of penicillin and cephalosporin in which the S-atom is replaced by C-atom have been reported [1] [2]. The S-atom may be replaced by O- or C-atoms without substantial loss of antimicrobial activity [3]. We now report a short synthesis of the carbapenam **8** using the (2-Hydroxy-2-phenylethyl)-azetidinone **5** as a key intermediate.

We chose readily available dibenzyl aminomalonate (**1**) as the starting material. It was treated with phenylpropargyl aldehyde and the corresponding *Schiff* base upon reaction with azidoacetyl chloride [4], using the methods described by *Doyle et al.* [5], gave a (4:1)-mixture of the dibenzyl oxoazetidinylmalonate **2a** and **2b** (25% from amino ester **1**). Using the major *trans*-product **2a**, we were hoping to achieve the synthesis of the carbapenam **8**. Thus, the azide function in **2a** was reduced (H_2S/triethylamine [6]) and the resulting amine directly acylated to the phenylacetamido-β-lactam **3**. Compound **3** was then transformed to the ketone **4** with mercuric trifluoroacetate/mercuric oxide [7] in ethyl acetate. Sodium borohydride reduction of **4** afforded (2-hydroxy-2-phenylethyl)azetidinone **5** as a mixture of two isomers which was treated with excess methanesulfonyl chloride/pyridine in methylene chloride. Instead of the expected methanesulfonate **6**, the (2-chloro-2-phenylethyl)-β-lactam **7** was isolated along with some styryl-β-lactam **9**. This suggested the S_N2 displacement of the methanesulfonate group in **6** by chloride ion from pyridinium hydrochloride.

Cyclization of compound **7** to the corresponding carbapenam **8** was achieved by means of triethylamine in methylene chloride at 25°. All attempts to split off the benzyl groups of **8** failed. The NMR. spectrum of **8** *(Figure)* showed the presence of a single epimer, the structure of which was consistent with that depicted. Decoupling experiments permitted assignment of the coupling constants.

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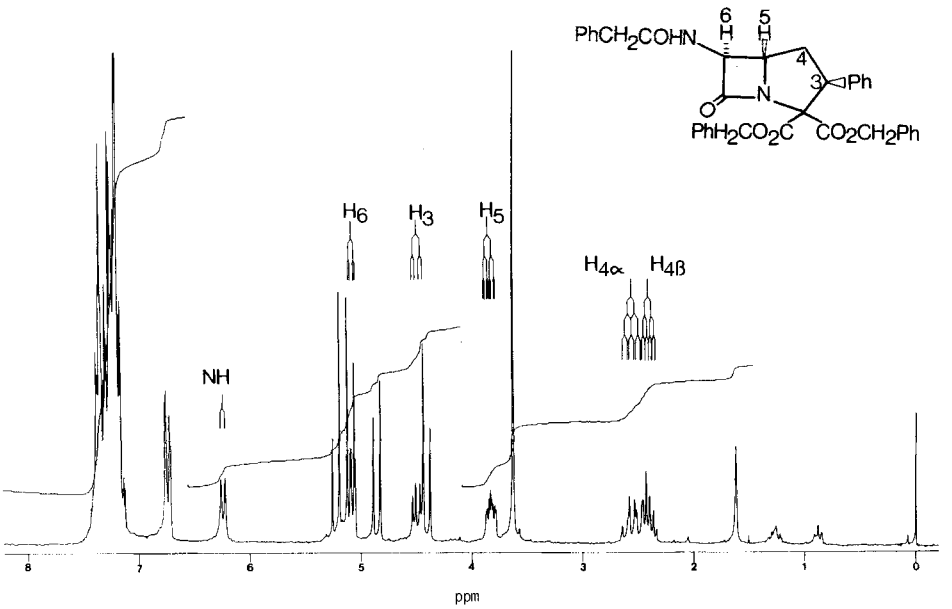


Figure. *200 MHz ^{1}H-NMR. spectrum of* **8**, *in $CDCl_3$*

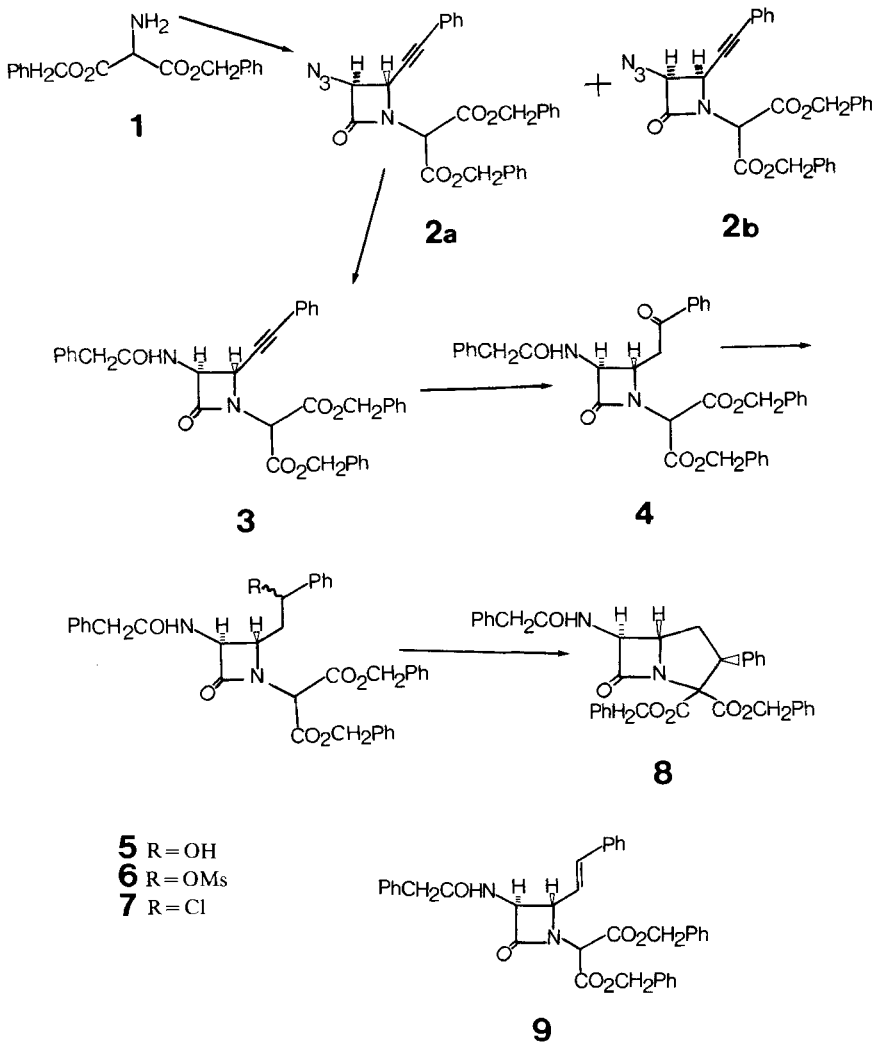
Experimental Part

General procedures: see [8].

Preparation of trans- *and* cis-*benzyl (3-azido-2-oxo-4-phenylethynyl-1-azetidinyl)malonate* (**2a** *resp.* **2b**). The procedure was identical to that previously described [9] for the conversion of dibenzyl aminomalonate to the corresponding *N*-substituted 3-azido-4-styryl-*cis*-β-lactam. β-Lactams **2a** and **2b** were separated by flash chromatography using AcOEt/petroleum ether 2:7. *trans*-β-Lactam **2a** was obtained in 20% yield. – IR. (film): 2220 (C≡C), 2110 (azide), 1785 (β-lactam), 1750 (ester). – NMR. (200 MHz, $CDCl_3$): 4.81 (*d*, J=2 Hz, 1H, H–C(4)); 4.89 (*d*, J=2 Hz, 1H, H–C(3)); 5.11 and 5.23 (2 *AB*-systems, 4H, 2 PhCH_2); 5.30 (*s*, 1H, CHCOO); 7.15–7.38 (*m*, 15H, 3 C_6H_5). *cis*-β-Lactam **2b** was obtained in 5% yield. – IR.: identical to that of **2a**. – NMR.: similar to that of **2a** except for the coupling constants of H–C(3) and H–C(4), J=5 Hz.

Preparation of benzyl trans-*(2-oxo-3-phenylacetamido-4-phenylethynyl-1-azetidinyl)malonate* (**3**). H_2S was bubbled for 10 min into a solution of **2a** (0.946 g, 1.9 mmol) in CH_2Cl_2 (60 ml) and NEt_3 (0.193 g, 1.9 mmol) at 0°. The solution was allowed to warm, and after stirring for 1 h at r.t., N_2 was bubbled for 0.5 h. Pyridine (0.2 g, 2.5 mmol) was added at 0° followed by phenylacetyl chloride (0.386 g, 2.5 mmol) dropwise over 5 min. After stirring for 1 h at 25°, the solution was washed with water (3×40 ml) and brine (50 ml) then treated with $MgSO_4$ and charcoal. Filtration and evaporation followed by purification by flash chromatography with AcOEt/petroleum ether 3:7 gave 0.882 g (85%) of **3** as a foam. – IR. (film): 3300 (NH), 1785 (β-lactam), 1755 (ester), 1670 (amide). – NMR. (200 MHz, $CDCl_3$): 3.62 (*s*, 2H, PhCH_2CO); 4.87 (*d*, J=2.5 Hz, 1H, H–C(4)); 5.00 (*d*×*d*, J=2.5 and 8.0 Hz, 1H, H–C(3)); 5.09, 5.22 (2 *AB*-systems, 4H, 2 PhCH_2); 5.27 (*s*, 1H, CHCOO); 6.28 (*d*, J=8.0 Hz, 1H, NH); 7.15–7.45 (*m*, 20H, 4 C_6H_5).

Preparation of benzyl trans-*(2-oxo-3-phenylacetamido-4-phenacyl-1-azetidinyl)malonate* (**4**). A mixture of **3** (0.551 g, 0.94 mmol), HgO (0.406 g, 1.9 mmol) and $(CF_3COO)_2Hg$ (0.803 g, 1.9 mmol) in EtOAc (50 ml), containing water (0.4 ml), was stirred at 25° for 5 h. The mixture was then cooled to 0° and H_2S was bubbled through for 10 min. After stirring at 25° for 0.5 h HgS was removed by filtration and the solvent evaporated to give 0.362 g (64%) of **4**, after flash chromatography AcOEt/petroleum ether 3:7. – IR. (film): 3300 (NH), 1780 (β-lactam), 1750 (ester), 1680 (amide and phenyl ketone). – NMR. (200 MHz, $CDCl_3$): 3.60 (*d*, J=7.0 Hz, 2H, PhCOCH_2); 3.61 (*s*, 2H, PhCH_2); 4.36



5 R = OH
6 R = OMs
7 R = Cl

9

($d \times t$, J = 2.5 and 7.0 Hz, 1H, H_2C–C(4)); 4.69 ($d \times d$, J = 2.5 and 6.5 Hz, 1H, H–C(3)); 5.11, 5.24 (2 *AB*-system, 4H, 2 PhCH_2), 5.35 (*s*, 1H, CHCOO); 6.18 (*d*, J = 6.5 Hz, 1H, NH); 7.21–7.90 (*m*, 20H, 4 C_6H_5).

Preparation of benzyl trans-*[4-(2-hydroxy-2-phenylethyl)-2-oxo-3-phenylacetamido-1-azetidinyl]-malonate* (**5**). $NaBH_4$ (0.021 g, 0.56 mmol) was added to **4** (0.340 g, 0.56 mmol) in abs. ethanol (20 ml) at 0°. After stirring for 1 h at 0° and 20 min at 25°, pH 4.5 buffer solution (20 ml) was added and the solution extracted with CH_2Cl_2. Drying ($MgSO_4$) and evaporation of the solvent afforded a total of 0.232 g (68%) of alcohol **5**, as a mixture of 2 diastereoisomers which were separated by flash chromatography with AcOEt/petroleum ether 3:7; 0.178 g of less polar and 0.054 g of more polar materials were isolated).

Less polar fraction. – IR. (film): 3400 (OH), 3300 (NH), 1775 (β-lactam), 1750 (ester), 1665 (amide). – NMR. (200 MHz, $CDCl_3$): 1.95 ($d \times d \times d$, J = 3.3, 9.0 and 14.5 Hz, 1H, one *H* of H_2C–C(4)); 2.26 ($d \times d \times d$, J = 4.5, 9.5 and 14.5 Hz, 1H, the other *H* of H_2C–C(4)); 3.13 (*d*, J = 5.2 Hz, 1H, OH); 3.55 (*s*, 2H, PhCH_2CO); 4.05 ($d \times d \times d$, J = 2.2, 4.5 and 9.0 Hz, 1H, H–C(3)); 4.68 ($d \times d$, J = 2.2 and

6.5 Hz, 1H, H–C(4)); 4.92 (*d*×*d*×*d*, *J* = 3.3, 5.2 and 9.5 Hz, 1H, PhC*H*OH); 5.14, 5.16 (2 *AB*-system, 4H, 2 PhCH_2O); 5.22 (*s*, 1H, C*H*COO); 6.35 (*d*, *J* = 6.5 Hz, 1H, NH); 7.20–7.37 (*m*, 20H, 4 C_6H_5).

More polar fraction. – IR. (film): 3350 (OH), 3300 (NH), 1775 (β-lactam), 1750 (ester), 1660 (amide). – NMR. (200 MHz, $CDCl_3$): 1.92 (*d*×*d*×*d*, *J* = 10.0, 10.0 and 14.0 Hz, 1H, one H of H_2C–C(4)); 2.20 (*d*×*d*×*d*, *J* = 3.0, 4.0 and 14.0 Hz, 1H, the other H of H_2C–C(4)); 3.60 (*s*, 2H, PhCH_2CO); 4.00 (*d*×*d*×*d*, *J* = 2.2, 4.0 and 10.0 Hz, 1H, H–C(3)); 4.40 (*d*, *J* = 4.4 Hz, 1H, OH); 4.68 (*m*, 1H, *H*C(OH)Ph); 4.71 (*d*×*d*, *J* = 2.2 and 6.0 Hz, 1H, H–C(4)); 5.12 (*s*, 2H, PhCH_2O); 5.18 (*AB*-system, 2H, PhCH_2O); 5.26 (*s*, 1H, C*H*COO); 6.35 (*d*, *J* = 6.0 Hz, 1H, NH); 7.20–7.38 (*m*, 20H, 4 C_6H_5).

Preparation of benzyl [4-(2-chloro-2-phenylethyl)-2-oxo-3-phenylacetamido-1-azetidinyl]malonate (**7**) *and benzyl [2-oxo-3-phenylacetamido-4-styryl-1-azetidinyl]malonate* (**9**). Methanesulfonyl chloride (0.07 g, 0.6 mmol) was added at 25° to the alcohol **5** (0.121 g, 0.2 mmol) in CH_2Cl_2 (2 ml) containing pyridine (0.048 g, 0.6 mmol). After stirring for 20 h, CH_2Cl_2 (20 ml) was added and the solution washed with water (3×5 ml), dried ($MgSO_4$) and evaporated to give 0.076 g (61%) of **7** and 0.025 g (21%) of **9**, after flash chromatography with AcOEt/petroleum ether 1:4.

Data of **7**. – IR. (film): 3300 (NH), 1775 (β-lactam), 1750 (ester), 1670 (amide). – NMR. (200 MHz, $CDCl_3$): 2.35 (*d*×*d*×*d*, *J* = 7.6, 9.5 and 14.2 Hz, 1H, one H of H_2C–C(4)); 2.63 (*d*×*d*×*d*, *J* = 4.0, 7.6 and 14.2 Hz, 1H, the other H of H_2C–C(4)); 3.55 (*s*, 2H, PhCH_2CO); 3.78 (*d*×*d*×*d*, *J* = 2.5, 4.0 and 9.5 Hz, 1H, H–C(3)); 4.64 (*d*×*d*, *J* = 2.5 and 7.8 Hz, 1H, H–C(4)); 4.98 (*d*×*d*, *J* = 7.6 and 7.6 Hz, 1H, PhC*H*Cl); 5.11–5.18 (*m*, 4H, 2 PhCH_2O); 5.30 (*s*, 1H, C*H*COO); 6.10 (*d*, *J* = 7.8 Hz, 1H, NH); 7.20–7.37 (*m*, 20H, 4 C_6H_5). – MS. (20 eV, 97°) (‰): 624 and 626 (0.6 and 0.4, M^+), 588 (1, $M^+ - HCl$), 454 (6, $M^+ - Cl^- - CO_2CH_2Ph^·$), 91 (1000, $PhCH_2^+$).

Data of **9**. – IR. (film): 3300 (NH), 1775 (β-lactam), 1750 (ester), 1670 (amide). – NMR. (200 MHz, $CDCl_3$): 3.65 (*s*, 2H, PhCH_2CO); 4.57 (*d*×*d*, *J* = 2.5 and 9.0 Hz, 1H, H–C(3)); 4.84 (*d*×*d*, *J* = 2.5 and 8.0 Hz, 1H, H–C(4)); 5.08, 5.24 (2 *s*, 4H, 2 PhCH_2O); 5.28 (*s*, 1H, C*H*COO); 6.20 (*d*, *J* = 8.0 Hz, 1H, NH); 6.22 (*d*×*d*, *J* = 9.0 and 16.0 Hz, 1H, PhCH=C*H*); 6.60 (*d*, *J* = 16 Hz, 1H, PhC*H*=CH); 7.25–7.45 (*m*, 20H, 4 C_6H_5).

Preparation of 3-bis(benzyloxycarbonyl)-2-phenyl-6-phenylacetamido-carbapenam (**8**). A solution of chloride **7** (0.063 g, 0.1 mmol) in CH_2Cl_2 (0.5 ml) containing NEt_3 (0.05 g, 0.5 mmol) was stirred for 48 h at r.t. Then CH_2Cl_2 (25 ml) was added and the solution was washed with pH 4.5 buffer (2×10 ml) and brine (10 ml), dried ($MgSO_4$) and evaporated to give 0.049 g (83%) of **8** after flash chromatography (AcOEt/petroleum ether 1:4). – IR. (film): 3300 (NH), 1785 (β-lactam), 1750 (ester), 1670 (amide). – NMR. (200 MHz, $CDCl_3$): 2.40 (*d*×*d*×*d*, *J* = 5.5, 6.0 and 13.0 Hz, 1H, one H of H_2C–C(4)); 2.56 (*d*×*d*×*d*, *J* = 9.5, 13.5 and 13.0 Hz, 1H, the other H of H_2C–C(4)); 3.63 (*s*, 2H, PhCH_2CO); 3.83 (*d*×*d*×*d*, *J* = 2.3, 5.5 and 9.5 Hz, 1H, H–C(3)); 4.44, 4.86 (*AB*-system, *J* = 12.0 Hz, 2H, PhCH_2O); 4.49 (*d*×*d*, *J* = 6.0 and 13.5 Hz, 1H, PhC*H*CH_2); 5.08 (*d*×*d*, *J* = 2.3 and 7.3 Hz, 1H, H–C(3)); 5.10, 5.23 (*AB*-system, *J* = 12.5 Hz, 2H, PhCH_2O); 6.24 (*d*, *J* = 7.3 Hz, 1H, NH); 6.70–6.80, 7.10–7.40 (*m*, 20H, 4 C_6H_5). – MS. (20 eV, 96°) (‰): 588 (9, M^+), 453 (118, $M^+ - CO_2CH_2Ph^·$), 413 (79, $M^+ - PhCH_2CONHCH{=}C{=}O$), 322 (130, $M^+ - PhCH_2CONHCH{=}C{=}O - CH_2Ph^·$), 278 (336, $M^+ - PhCH_2CONHCH{=}C{=}O - CO_2CH_2Ph^·$), 187.1 ($M^*$, 413 → 278).

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