100. The Synthesis of *cis*- and *trans*-7-Phenylacetamido-*O*-2-isocephem[1])

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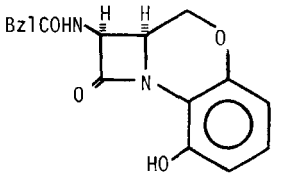
Summary

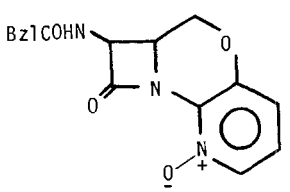
The synthesis of the title compounds is described.

Structure-activity relationship of non-classical β-lactam antibiotics has been extensively reviewed [1]. *Doyle et al.* [2], showed that the biological activity of some *O*-2-isocephems is better than, or comparable to the corresponding cephalosporins. The nuclear analogues of cephalosporin in which a phenolic group replaces the carboxylic function (*e.g.* **A**) have recently been described as weak anti-bacterial β-lactam antibiotics [3] [4].

In this paper we report the synthesis of the non-classical β-lactam **A** analogues **1**, which might have interesting antibacterial activity.



A



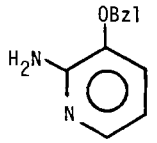
1a (*trans*)
1b (*cis*)

Bzl = Benzyl

Treatment of 2-amino-3-benzyloxypyridine **2** with methyl glyoxylate gave the corresponding *Schiff* base which upon reaction with either azidoacetyl chloride or bromoacetyl chloride gave the corresponding β-lactams **3a** and **4**, respectively (20% of the *trans*-product only) [5] [6]. Both β-lactams obtained were *trans*-fused, as was determined by ^{1}H-NMR (J = 2.5 Hz) of all derivatives in which the relevant protons did not overlap with other signals. The low yield of the *trans*-stereoisomers **3a** and **4** reflects a change in the mechanism of cycloaddition, proposed by *Doyle et al.* [5] [7] and supported by *Sullivan et al.* [8], where electron-rich *Schiff* bases give consistently high yield of *cis*-β-lactams. However, our findings were compatible with the report of *Just et al.* [9] that the electron-poor *Schiff* bases obtained from anilines with electron-withdrawing substituents [1] [9] afforded only a low yield of *trans*-isomer. Since one of the

[1]) *O*-2-Isocephems are alternatively called isooxacephems.

essential features of the classical β-lactam antibiotics is the presence of a *cis*-fused β-lactam [10] [11], the preparation of **3b** from **4** was achieved by means of NaN_3 in DMF [6]. The azide function in **3a** and **3b** was reduced (H_2S/NEt_3 [12]) and the resulting amines directly acylated to the phenylacetamido-β-lactams **5a–b**. $NaBH_4$ reduction of the methyl ester of **5a–b** in wet THF to the alcohols **6a–b** was followed by methanesulfonation to yield **7a–b** (overall 36% from **5**) [13]. Hydrogenolysis of the benzyloxy group of **7a–b** with Pd/C in AcOEt gave the corresponding phenols **8a–b** in good yield. Reaction of **8a–b** with exactly one equivalent of *t*-BuOK in THF at 5° afforded the tricyclic products **9a–b**. Compounds **9a–b** transformed to their respective *N*-oxide **1a–b** by means of *m*-chloroperbenzoic acid [14] (*ca.* 20% yield). All attempts to carry out the cyclization of type **8**→**10** failed, recovering instead the starting material or giving the compound **8**.



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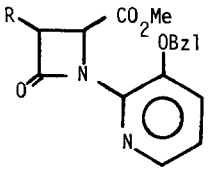
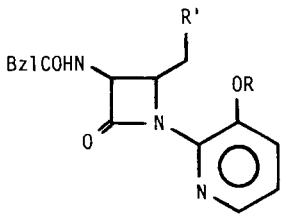
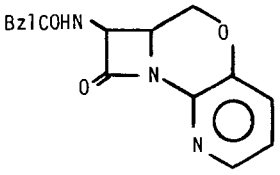


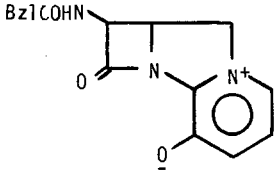
3a (*trans*) R = N_3
3b (*cis*) R = N_3
4 (*trans*) R = Br
5a (*trans*) R = NHCOBzl
5b (*cis*) R = NHCOBzl



6a (*trans*) R' = OH, R = Bzl
6b (*cis*) R' = OH, R = Bzl
7a (*trans*) R' = OMs, R = Bzl
7b (*cis*) R' = OMs, R = Bzl
8a (*trans*) R' = OMs, R = H
8b (*cis*) R' = OMs, R = H



9a (*trans*)
9b (*cis*)



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The *cis*-β-lactam **1b** exhibited very interesting anti-microbial activity while the *trans*-isomer **1a** was completely inactive. The results of biological screening and physical chemical studies of **1a–b** will be reported elsewhere.

Experimental Part

General: [15] [16].

trans-*3-Azido*-N-*(2-benzyloxy-6-pyridyl)-4-methoxycarbonyl-2-azetidinone* (**3a**). To a solution of 2-amino-3-benzyloxypyridine (**1**, 2 g, 0.01 mol) in 40 ml dry CH_2Cl_2 was added methyl glyoxylate (0.9 g, 0.01 mol), and $MgSO_4$ (15 g). After stirring at r.t. for 24 h the mixture was filtered. Et_3N (1.01 g, 0.01 mol) was added, followed by dropwise addition of azidoacetyl chloride (1.20 g, 0.01 mol) at 25°. After stirring for 12 h, the

solution was washed with H_2O, dried and evaporated to afford the crude β-lactam which was purified by column chromatography on silica gel. Elution with CH_2Cl_2 gave 0.9 g (25%) of **2a** as a foam. IR: 2100 (N_3), 1779 (β-lactam), 1745 (ester). ^{1}H-NMR ($CDCl_3$): 3.81 (*s*, 3H, CH_3); 4.38 (*d*, J = 2.5, 1H, H–C(3)); 4.81 (*d*, J = 2.5, 1H, H–C(4)); 5.01 (*s*, 2H, CH_2); 6.81–7.45 (*m*, 8H, arom. H). Anal. calc. for $C_{17}H_{15}N_5O_4$ (353.03): C 57.79, H 4.25, N 19.83; found: C 57.70, H 4.14, N 19.63.

β-Lactam **4** was prepared in an identical manner, using bromoacetyl chloride instead of azidoacetyl chloride. Its spectra were compatible with the proposed structure.

cis-*3-Azido*-N-*(2'-benzyloxy-6'-pyridyl)-4-methoxycarbonyl-2-azetidinone* (**3b**). Sodium azide (1.95 g, 0.03 mol) was added to **4** (3.91 g, 0.01 mol) in 40 ml dry DMF, and the solution stirred at r.t. for 24 h. The solution was then partitioned between Et_2O (100 ml) and H_2O (200 ml). The org. layer was washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel. Impurities were eluted with CCl_4 and **3b** was eluted with CH_2Cl_2 (70%). IR was identical to that of **3a**. ^{1}H-NMR: similar to that of **3a** except for the coupling constants of H–C(3) and H–C(4), J = 5. Anal. calc. for $C_{17}H_{15}N_5O_4$ (353.12): C 57.79, H 4.25, N 19.83; found: C 57.67, H 4.01, N 19.71.

N-*(2-Benzyloxy-6-pyridyl)-4-methoxycarbonyl-3-phenylacetamido-2-azetidinone* (**5a,b**). β-Lactams **5a–b** obtained from **3a–b** [17] in approximately 80% yield. Their spectra were similar except for the values corresponding to the stereochemical variations of the β-lactam ring junction. **5a**: IR (CH_2Cl_2): 3450 (NH), 1780 (β-lactam), 1740 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.42 (*s*, 2H, CH_2CO); 3.91 (*s*, 3H, CH_3); 4.71–4.93 (*m*, 2H, H–C(3) and H–C(4)); 5.05 (*s*, 2H, CH_2); 6.81 (br., 1H, NH); 6.88–7.51 (*m*, 13H, arom. H). Anal. calc. for $C_{25}H_{23}N_3O_5$ (445.23): C 67.42, H 5.17, N 9.44; found: C 67.21, H 6.01, N 9.34.

N-*(2-Benzyloxy-6-pyridyl)-4-hydroxymethyl-3-phenylacetamido-2-azetidinone* (**6a,b**). β-Lactams **6a–b** obtained from **5a–b** in about 45% yield as described in [13] [18]. Their spectra were similar except for the values corresponding to the stereochemical variations of the β-lactam ring junction. IR (CH_2Cl_2): 3300–3400 (NH, OH), 1775 (β-lactam), 1650 (amide). ^{1}H-NMR ($CDCl_3$): 3.21–3.40 (*m*, 3H, CH_2OH); 3.41 (*s*, 2H, CH_2CO); 3.91–4.19 (*m*, 1H, H–C(4)); 5.01 (*s*, 2H, CH_2); 5.25 (*dd*, J = 2.5 and 7, 1H, H–C(3)); 6.85 (br., 1H, NH); 6.99–7.75 (*m*, 13H, arom. H). Anal. calc. for $C_{24}H_{23}N_3O_4$ (417.31): C 69.06, H 5.51, N 10.07; found: C 69.17, H 5.42, N 10.11.

N-*(2-Benzyloxy-6-pyridyl)-4-mesyloxymethyl-3-phenylacetamido-2-azetidinone* (**7a,b**). Alcohols **6a–b** were converted to the corresponding methanesulfonates **7a–b** in about 80% yield according to [19]. Their spectra were similar except for variations due to the β-lactams ring junction. **7a**: IR (CH_2Cl_2): 3410 (NH), 1785 (β-lactam), 1681 (amide). ^{1}H-NMR ($CDCl_3$): 2.81 (*s*, 3H, OSO_2CH_3); 3.51 (*s*, 2H, CH_2CO); 3.62 (br., 2H, CH_2OMs); 4.00–4.22 (*m*, 1H, H–C(4)); 4.99 (*dd*, J = 2.5 and 7, 1H, H–C(3)); 5.15 (*s*, 2H, CH_2); 6.83 (br., 1H, NH); 6.81–7.81 (*m*, 13H, arom. H). Anal. calc. for $C_{25}H_{25}N_3O_6S$ (495.31): C 60.61, H 5.05, N 8.48; found: C 60.50, H 5.21, N 8.53.

N-*(2-Hydroxy-6-pyridyl)-4-mesyloxymethyl-3-phenylacetamido-2-azetidinone* (**8a,b**). Both β-lactams **6a–b** were prepared in an identical manner. Their spectra were similar except for the stereochemical variations due to the β-lactams ring junction.

Compound **7a** (495 mg, 1 mmol) in 30 ml AcOEt with Pd/C (60 mg) was hydrogenated at r.t. at 40 psi for 6 h. The mixture was then filtered and evaporated to give the crude product as a foam. Purification on silica gel and elution with AcOEt gave **8a** (50%). IR (CH_2Cl_2): 3300–3500 (OH, NH), 1779 (β-lactam), 1670 (amide). ^{1}H-NMR (CDCl): 2.82 (*s*, 3H, OSO_2CH_3); 3.50 (*s*, 2H, CH_2CO); 3.59 (br., 2H, CH_2OMs); 4.01–4.20 (br., 1H, H–C(4)); 4.90 (*dd*, J = 2.5 and 7, 1H, H–C(3)); 6.72 (br., 1H, NH); 6.80–7.85 (*m*, 8H, arom. H); 8.27 (br., 1H, OH). Anal. calc. for $C_{18}H_{19}N_3O_6S$ (405.03): C 53.33, H 4.69, N 10.37; found: C 53.41, H 4.70, N 10.28.

7-Phenylacetamido-O-*2-isocephem* (**9a,b**). Compounds **9a** and **9b** were prepared in an identical manner and obtained in 20 and 60% yield, respectively. Their spectra were similar except for the variations due to the β-lactams ring junction. Their MS showed $M^+ - C_5H_4N$ or, in the case of **7b**, M^+. The following is a representative procedure.

To a solution of **8a** (405 mg, 1 mmol) in 10 ml dry THF was added *t*-BuOK (112 mg, 1 mmol) at 5° under N_2. The mixture was stirred for 10 h at the same temperature and 20 h at r.t. H_2O (20 ml) was added and the aq. solution was extracted with AcOEt. The org. layer was dried (Na_2SO_4), filtered and evaporated to afford crude **9a**. Iso-oxacepham **9a** was purified by column chromatography on silica gel. Elution with CH_2Cl_2 and $CHCl_3$ removed impurities and **9a** eluted with AcOEt (20%). IR (CH_2Cl_2): 3410 (NH), 1783 (β-lactam), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 3.61 (*s*, 2H, CH_2CO); 5.12 (*dd*, J = 2.5 and 8, 1H, H–C(7)); 3.71–4.50 (*m*, 3H, $CHCH_2O$); 6.82 (br. *d*, J = 8, 1H, NH); 7.00–7.81 (*m*, 8H, arom. H). Anal. calc. for $C_{17}H_{15}N_3O_3$ (309.05): C 66.02, H 4.85, N 13.59; found: C 66.13, H 4.86, N 13.61.

7-Phenylacetamido-O-2-isocephem N-*oxide* (**1a,b**). Both *N*-oxides **1a–b** were prepared identically and obtained in approximately 20% yield. Their spectra were similar except for the variations due to the β-lactam ring junction. Their microanalyses were compatible with the proposed structures.

To a stirred solution containing (**9a**, 309 mg, 1 mmol) and $CHCl_3$ (20 ml), was added *m*-chloroperbenzoic acid (259 mg, 1.5 mmol) at 25°. Stirring was continued for 15 h. The disappearance of the starting material was confirmed by TLC using AcOEt. Then to the solution was added portionwise 10 ml of 3% $NaHCO_3$ over a period of 15 min at −5° with stirring. The $CHCl_3$-layer was separated, washed with H_2O and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave the crude product which was recrystallized from Et_2O to afford **1a** (20%); m.p. 180–184° (dec.). IR (CH_2Cl_2): 3400 (NH), 1797 (β-lactam), 1666 (amide), 1576 (*N*-oxide). ^{1}H-NMR ($CDCl_3$/DMSO): 3.57 (*s*, 2H, CH_2CO); 5.21 (*dd*, $J = 2.5$ and 8, 1H, H–C(7)); 3.73-4.62 (*m*, 3H, $CHCH_2O$); 6.81 (br., 1H, NH); 7.15–8.03 (*m*, 8H, arom. H). Anal. calc. for $C_{17}H_{15}N_3O_4$ (325.03): C 62.76, H 4.61, N 12.92; found: C 62.50, H 4.37, N 12.65.

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