

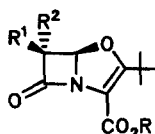
Are 6-Acylamino Oxapenems Stable Compounds ?

Hanno Wild

Bayer AG, Chemistry Science Laboratories Pharma,
 P.O.Box 101709, D-5600 Wuppertal 1, Germany

Summary: The 6-acylamino oxapenem **10** is no isolable compound, but rearranges to the isomeric oxazoline **9** under the conditions of its formation. However, 6-azido (**5**), 6-imino (**12**) as well as 6-carbamoyl oxapenems (**14**) were prepared for the first time.

The oxapenem class of β -lactams was first described in 1977¹. Although some derivatives showed interesting activity as β -lactamase inhibitors², the instability of the highly strained oxapenem ring system towards chemical hydrolysis precluded their use in biological systems. Recently, it was discovered³ that 2-*tert*-alkyloxapenems **1b,c** are much more stable than expected and it was even possible to prepare free

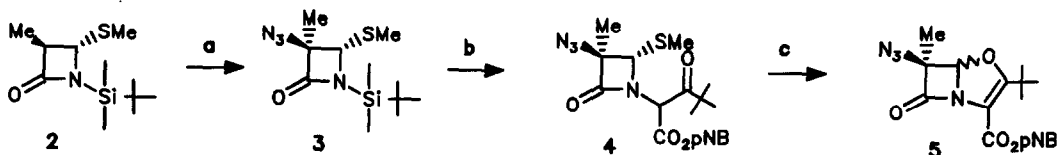


- a $R^1 = RCONH$, $R^2 = CH_3$
- b $R^1, R^2 = H, CH_3$
- c $R^1 = H$, $R^2 = CH_2OH$
- d $R^1, R^2 = R^3 \sim \sim \sim$

6-methylene oxapenems **1d** as their sodium salts⁴. So far a 6-acylamino group, a prerequisite for biological activity of penicillins and recently also used in penems⁵ and carbapenems⁶, has not been described for oxapenems. Therefore, the aim of this investigation was the preparation of racemic 6-acylamino oxapenems **1a** in order to study, if this activating group would be compatible with the labile oxapenem skeleton. For the stabilization of the bicyclic system we envisaged the 2-*tert*-butyl substituent and an additional 6-methyl group³.

Following standard β -lactam methodology an azido group was introduced into the 3-position of β -lactam **2** using 2,4,6-triisopropylbenzene sulfonylazide (Tris- N_3)⁷, followed by deprotection and build-up of the *N*-side chain (scheme 1)^{8,9}. Transformation of the 4-methylthio substituent of compound **4** into a chloride

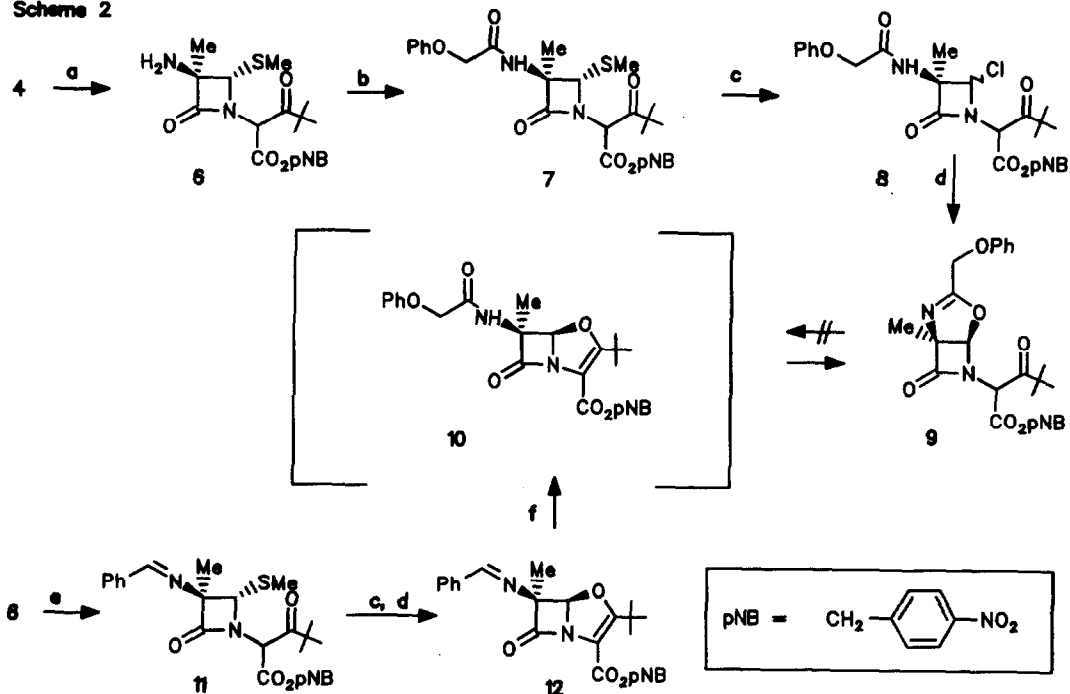
Scheme 1



(a) LDA, Tri-N_3 , -78°C ; Me_3SiCl , $-78^\circ\text{C} \longrightarrow \text{rt}$ (42 %); (b) Bu_4NF , AcOH , THF , rt (97 %);
 $t\text{-BuCOCH}_2\text{CO}_2\text{PNB}$, Ca_2CO_3 , CH_3CN , rt (88 %); (c) Cl_2 , CH_2Cl_2 , -78°C ; KOt-Bu , THF , 0°C (61 %).

leaving group followed by smooth cyclization of the potassium enolate of the β -ketoester³ gave oxapenem 5 after chromatography on silica gel at 0°C as a 6:1 mixture of *cis/trans*-stereoisomers¹⁰. However, further transformation of this oxapenem (deprotection, reduction of the azide) proved to be impossible due to the lability of the compound.

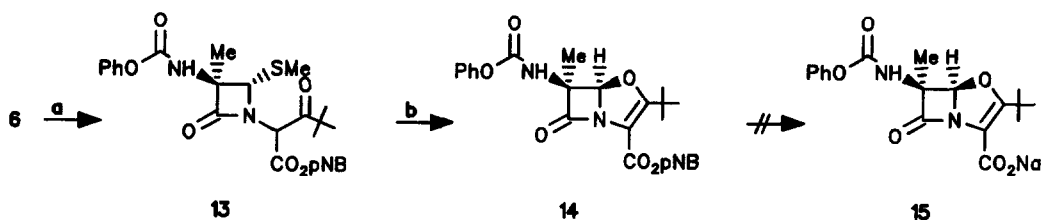
Scheme 2



(a) $\text{HS-(CH}_2)_3\text{-SH}$, NEt_3 , $i\text{-PrOH}$, rt , then CuSO_4 , H_2O (77 %); (b) $\text{PhOCH}_2\text{COCl}$, NEt_3 , CH_2Cl_2 , 0°C (78 %);
 (c) Cl_2 , CH_2Cl_2 , -78°C ; (d) KOt-Bu or NEt_3 , THF , 0°C (9 : 22.5 %, 12 : 42 %); (e) PhCHO , MgSO_4 ,
 Ph-CH_2 , 110°C (75 %); (f) $\text{PhOCH}_2\text{CO}_2\text{H}$, EEDQ , H_2O , THF , rt or $\text{PhOCH}_2\text{COOCOOEt}$, H_2O , THF , rt (50 %).

Therefore, the azide was reduced before closure of the second ring (scheme 2)¹¹. The amine **6** obtained was acylated with phenoxyacetylchloride and the amide **7** subsequently chlorinated to yield the cyclization precursor **8**. Treatment of **8** with base gave the oxazolinoazetidinone **9**¹² as the only isolable product¹⁰ and not oxapenem **10**. Neither under basic nor under acidic conditions **9** could be interconverted with **10**. In a different approach amine **6** was protected as its imine **11**, which after chlorination could be cyclized smoothly to oxapenem **12**¹⁰ (3.5:1 mixture of *cis/trans*-stereoisomers). The main diastereomer **12** was isolated in pure form after chromatography on silica gel at 0°C (stereochemistry tentative, cp. **14** below). Deprotective acylation even under almost neutral conditions (phenoxyacetate ethylcarboxylate mixed anhydride, H₂O, THF, rt)¹³ gave **9** as the only product. Under these conditions oxapenem **10** must have been formed as an intermediate, yet apparently it is not stable, but rearranges to the oxazolinoazetidinone **9** by a known S_N1-mechanism^{3c}. However, this is not a definite answer of the title question, because it cannot be excluded that the initial step of the rearrangement, the ring opening of oxapenem **10**, is catalyzed by the acylating agent or by traces of acid formed during the reaction.

Scheme 3



(a) PhOCOCl, DMAP, CH₂Cl₂, -20° C → rt (80 %); (b) Cl₂, CH₂Cl₂, -78° C; NEt₃, THF, 0° C (59 %).

On the other hand, carbamate **13** after chlorination could be cyclized to the oxapenem **14** without problems (scheme 3)¹⁰. Obviously, the less nucleophilic carbonyl group of the carbamate is not reactive under the conditions of oxapenem formation. **14** was obtained together with 9% of its *trans*-stereoisomer. The *cis*-relationship of the 6-methyl group and the hydrogen at 5-position in oxapenem **14** was proven by NOE-experiments. Deprotection of the carboxylic acid even under very mild conditions (H₂, Pd-C, EtOAc/aq. NaHCO₃, 0°C, 15 min) gave only rise to decomposition products other than β-lactams, probably due to the hydrolytic instability of the highly activated bicyclic system.

In summary, the preparation of three oxapenems with different nitrogen substituents at the 6-position is demonstrated for the first time: azide **5**, imine **11** and carbamate **14**. However, the 6-acylamino oxapenem **10** cannot be isolated, but rearranges to the thermodynamically more stable oxazolinoazetidinone **9** under the conditions of its formation.

REFERENCES AND NOTES

1. Eglington, A.J. *J. Chem. Soc., Chem. Commun.* **1977**, 720.
2. Cherry, P.C.; Newall, C.E.; Watson, N.S. *J. Chem. Soc., Chem. Commun.* **1978**, 469.
3. (a) Bayer AG, Eur. Patent 301394; *Chem. Abstr.* **1989**, 111, 39099. (b) Pfaendler, H.R.; Hendel, W.; Nagel, U. *Zeitschr. f. Naturforsch.* **1992**, 47b, 1037. (c) Pfaendler, H.R.; Neumann, Th.; Bartsch, R. *Synthesis* **1992**, in press.
4. Wild, H.; Hartwig, W. *Synthesis* **1992**, in press.
5. (a) Ernest, I.; Gosteli, J.; Greengrass, C.W.; Holick, W.; Jackman, D.E.; Pfaendler, H.R.; Woodward, R.B., *J. Am. Chem. Soc.* **1978**, 100, 8214. (b) Ghosez, L.; Marchand-Brynaert, J.; Vekemans, J.; Bogdan, S.; Cossement, E. *Tetrahedron* **1983**, 39, 2493. (c) Banville, J.; Lapointe, P.; Belleau, B.; Menard, M. *Can. J. Chem.* **1988**, 66, 1390.
6. Greenlee, M.L.; DiNinno, F.P.; Salzmann, T.N. *Heterocycles* **1989**, 28, 195.
7. Shibuya, M.; Jinbo, Y.; Kubota, S.; *Chem. Pharm. Bull.* **1984**, 32, 1303.
8. Gala, D.; Steinman, M.; Jaret, R.S. *J. Org. Chem.* **1986**, 51, 4488.
9. All compounds prepared are racemic mixtures of enantiomers. For convenience only one enantiomer is shown in the schemes.
10. (a) All new compounds exhibited spectroscopic properties (^1H -NMR, IR, MS) in accord with their assigned structures. (b) Typical data for selected compounds: **5**: IR (KBr): 1805 cm^{-1} ; ^1H -NMR (CDCl_3 , main diastereomer): δ = 1.35 (s, 9H), 1.62 (s, 3H), 5.23 (d, J = 14Hz, 1H), 5.45 (d, J = 14Hz, 1H), 5.64 (s, 1H, H^5), 7.65 (d, J = 9Hz, 2H), 8.25 (d, J = 9Hz, 2H). **9**: IR (CHCl_3): 1788 cm^{-1} ; ^1H -NMR (CDCl_3 , two diastereomers): δ = 1.17, 1.20 (2s, 9H), 4.63 (m, 2H), 5.15-5.35 (m, 3H), 5.57, 5.65 (2s, N-CH-CO), 5.80, 5.98 (2s, H^4), 6.85-7.03 (m, 2H), 7.25 (m, 3H), 7.45 (d, J = 8Hz, 2H), 8.23 (d, J = 8Hz, 2H). **12**: IR (CHCl_3): 1784 cm^{-1} ; ^1H -NMR (CDCl_3): δ = 1.37 (s, 9H), 1.62 (s, 3H), 5.21 (d, J = 13Hz, 1H), 5.47 (d, J = 13Hz, 1H), 5.90 (s, H^5), 7.45 (m, 3H), 7.63 (d, J = 8Hz, 2H), 7.77 (m, 2H), 8.22 (d, J = 8Hz, 2H), 8.55 (s, 1H); ^{13}C -NMR (CDCl_3): δ = 17.3 (Me), 28.0 (3C, t-Bu), 33.3 (1C, t-Bu), 65.0 (CH_2O), 85.5 (C^6), 96.7 (C^5H), 110.0 (C^3), 160.4 (C^2), 161.4 ($\text{CH}=\text{N}$), 175.3 ($\text{C}^7=\text{O}$), 180.2 (CO_2). **14**: IR (KBr): 1805 cm^{-1} ; ^1H -NMR (CDCl_3): δ = 1.30 (s, 9H), 1.57 (s, 3H), 5.18 (d, J = 14Hz, 1H), 5.45 (d, J = 14Hz, 1H), 6.14 (s, H^5), 7.05-7.37 (m, 5H), 7.63 (d, J = 9Hz, 2H), 8.20 (d, J = 9Hz, 2H); ^{13}C -NMR (CDCl_3): δ = 15.1 (Me), 27.4 (3C, t-Bu), 34.0 (1C, t-Bu), 64.7 (CH_2O), 73.4 (C^6), 96.0 (C^5H), 110.6 (C^3), 153.3 (O-CO-N), 160.2 (C^2), 173.2 ($\text{C}^7=\text{O}$), 177.4 (CO_2).
11. Bayley, H.; Standring, D.N.; Knowles, J.R. *Tetrahedron Lett.* **1978**, 3633.
12. Hoppe, D.; Kloft, M. *Liebigs Ann. Chem.* **1980**, 1527.
13. Bristol-Myers Squibb Co. Eur. Patent 372582; *Chem. Abstr.* **1991**, 114, 61831.

(Received in Germany 3 August 1992)