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Are 6-Acylamino Oxapenems Stable Compounds ?

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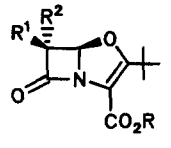
Summary: The 6-acylamino oxapenem **10** is no isolable compound, but rearranges to the isomeric oxazoline **9** under the conditions of its formation. However, 6-azido (**5**), 6-imino (**12**) as well as 6-carbamoyl oxapenems (**14**) were prepared for the first time.

The oxapenem class of ß-lactams was first described in 1977[1]. Although some derivatives showed interesting activity as ß-lactamase inhibitors[2], the instability of the highly strained oxapenem ring system towards chemical hydrolysis precluded their use in biological systems. Recently, it was discovered[3] that 2-*tert*-alkyloxapenems **1b,c** are much more stable than expected and it was even possible to prepare free



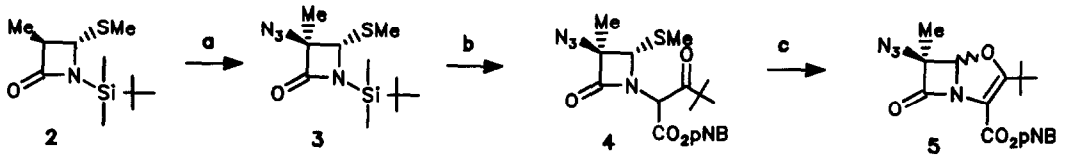
1

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^3N=

6-methylene oxapenems **1d** as their sodium salts[4]. So far a 6-acylamino group, a prerequisite for biological activity of penicillins and recently also used in penems[5] and carbapenems[6], 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 group[3].

Following standard ß-lactam methodology an azido group was introduced into the 3-position of ß-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

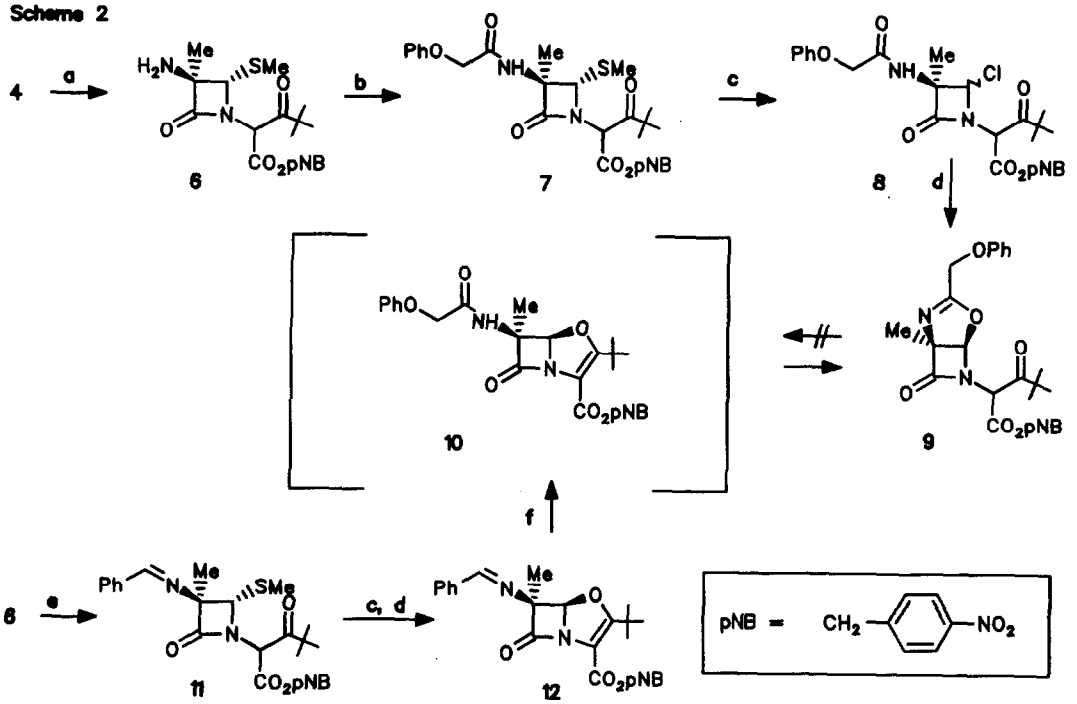
Scheme 1



(a) LDA, Tris–N_3, −78° C; Me_2SiCl, −78° C ⟶ rt (42 %); (b) Bu_4NF, AcOH, THF, rt (97 %); t–BuCOCHBrCO$_2$pNB, Ca_2CO_3, CH_3CN, rt (66 %); (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 ß-ketoester[3] gave oxapenem **5** after chromatography on silica gel at 0°C as a 6:1 mixture of *cis/trans*-stereoisomers[10]. However, further transformation of this oxapenem (deprotection, reduction of the azide) proved to be impossible due to the lability of the compound.

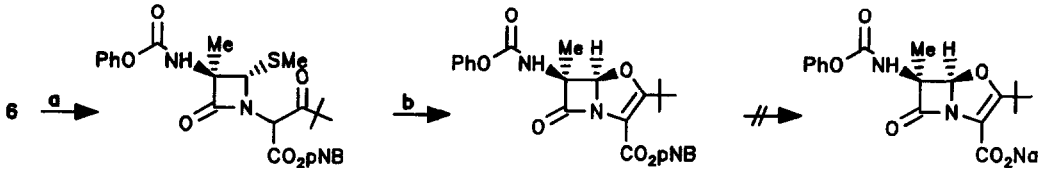
Scheme 2



(a) HS–$(CH_2)_3$–SH, NEt_3, i–PrOH, rt, then $CuSO_4$, H_2O (77 %); (b) $PhOCH_2COCl$, NEt_3, CH_2Cl_2, 0° C (76 %); (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_3, 110° C (75 %); (f) $PhOCH_2CO_2H$, EEDQ, H_2O, THF, rt or $PhOCH_2COOCOOEt$, 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 product[10] 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, H_2O, 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



13 14 15

(a) PhOCOCl, DMAP, CH_2Cl_2, −20° C ⟶ rt (80 %); (b) Cl_2, CH_2Cl_2, −78° C; NEt_3, 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 (H_2, Pd-C, EtOAc/aq. $NaHCO_3$, 0°C, 15 min) gave only rise to decomposition products other than ß-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.

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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 (^{1}H-NMR, IR, MS) in accord with their assigned structures. (b) Typical data for selected compounds: **5**: IR (KBr): 1805 cm^{-1}; ^{1}H-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}; ^{1}H-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}; ^{1}H-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^{5}H), 110.0 (C^3), 160.4 (C^2), 161.4 (CH=N), 175.3 (C^7=O), 180.2 (CO_2). **14**: IR (KBr): 1805 cm^{-1}; ^{1}H-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^{5}H), 110.6 (C^3), 153.3 (O-CO-N), 160.2 (C^2), 173.2 (C^7=O), 177.4 (CO_2).
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