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The Synthesis of 7α-Amidocarbacephems

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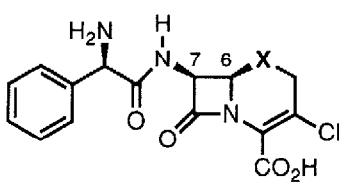
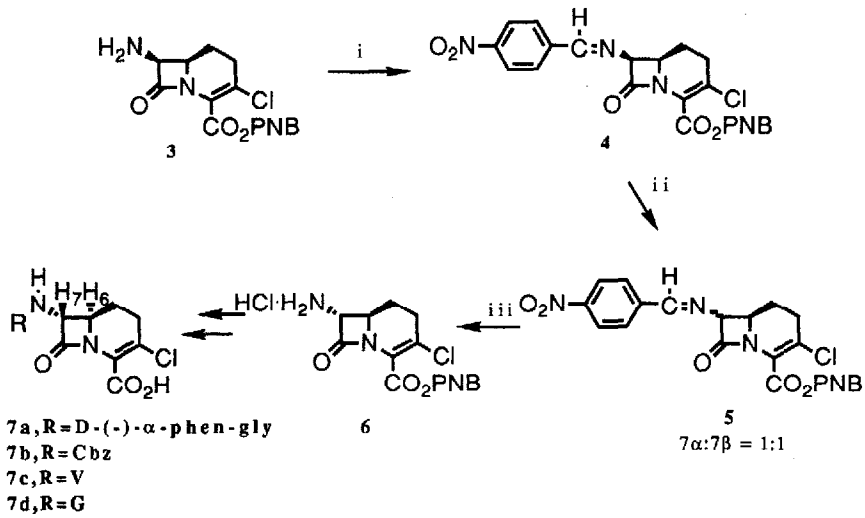
Key words: carbacephalosporin antibiotics; 7α-amidocarbacephalosporin; epimeric carbacephalosporins; carbacephems, epimerization

Abstract: Study of compounds related to the first clinically-investigated 7β-amidocarbacephem, loracarbef (**1**), led to the preparation of key 7α-amidocarbacephem derivatives. The synthesis, characterization, and biological properties of these compounds are reported.

Carbacephems have been shown to be effective antibiotic substances displaying antimicrobial activity comparable to that of their cephalosporin analogs.[1] One of these derivatives, loracarbef,[2] (**1**: LY163892/KT3777), the 1-carbadethia analog of cefaclor (**2**),[3] has been shown to be a useful clinical candidate, displaying activity against a broad spectrum of microbiological pathogens. During the course of our research, we became interested in the investigation of the heretofore unreported 7α-epimers of this class of important compounds. Although the 7α-amino cephalosporins,[4] -penicillins,[4a,5] and even -monobactams,[6] have been synthesized and their biological activity reported, such a study has not been carried out in the carbacephalosporin series. Herein we wish to report the results of our study to synthesize, characterize and test this new class of β-lactam compounds.



1 X = CH_2, loracarbef
2 X = S, cefaclor



Reagents and Conditions: i. p-Nitrobenzaldehyde, 4A Molecular Sieves, CH_2Cl_2, RT, 16 Hrs. ii. Diisopropyl Ethylamine, $CHCl_3$, RT, 12 Hrs. iii. HCl, 20/1 THF/H_2O, filtration, evaporation, Et_2O, EtOAc. PNB=p-nitrobenzyl; phen-gly=D-(-)-α-phenylglycine; Cbz=carbobenzoxy; V=phenoxy acetyl; G=phenylacetyl.

Scheme 1

Scheme 1 outlines the synthesis of the key epimeric 7α-aminocarbacephem (**6**). The amine (**3**) was prepared as previously described,[7] and condensed with p-nitrobenzaldehyde in methylene chloride in the presence of molecular sieves, to give the imine (**4**) in 87% overall yield, after recrystallization from chloroform/ethyl acetate (1:1). The imine (**4**) could be epimerized with triethylamine in dimethyl formamide, in analogy with previous work in the cephalosporin series.[4] However, these conditions resulted in significant decomposition of the substrate. Study of this reaction revealed that the use of tertiary amine bases in chloroform gave the highest yielding reactions, while performing the reactions in acetonitrile at reflux afforded a 10:1 ratio of the 7α:7β compounds, but in low overall yield. Treatment of (**4**) with diisopropyl ethylamine in chloroform gave a nearly quantitative yield of a 1:1 mixture of the epimeric imines (**5**), which were precipitated by treating the chloroform solution with 8 volumes of hexanes. The free amines could be liberated by treating (**5**) with 2,4-dinitrophenylhydrazine,[4] hydrazine, hydroxylamine or a variety of acids. The epimeric amines were separated by column chromatography (R_f 7β = 0.43; R_f 7α = 0.34) on silica using 2:1 toluene/acetone.

A much more convenient synthesis was realized when the mixture of imines (**5**) was treated with hydrochloric acid in a 20:1 mixture of tetrahydrofuran/water. In this case, the amine hydrochloride salt of (**3**) crystallized from the mixture quantitatively, so that imine cleavage was accompanied by resolution. The mother

liquor containing (**6**) was evaporated, and the residue triturated with diethyl ether to remove p-nitrobenzaldehyde. The remaining solid was suspended in ethyl acetate, which induced crystallization of (**6**). Thus, the amine hydrochloride (**6**) was obtained in nearly 40% overall yield from the imine (**4**) in >95% d.e. by this procedure.[8] The amine hydrochloride was then elaborated by usual methods to give the epimeric 7α-amidocarbacephem derivatives, (**7a-d**).

The newly reported 7α-aminocarbacephem derivatives, with substituents at C-6 and C-7 *trans* to each other, were readily distinguished from the earlier reported 7β series, where these substituents are *cis*. As predicted by the Karplus equation[9] and the observed dihedral angles in each case, $J_{6,7}$ for the *trans* compounds were 1.0 - 1.5 Hz, while $J_{6,7}$ for the *cis* compounds were 5.0 - 6.0 Hz. Table 1 summarizes ^{1}H-NMR data for key compounds prepared in the study.

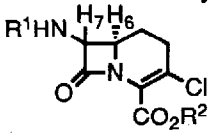


Table 1. ^{1}H-NMR data comparing $J_{6,7}$ for 7α- and 7β-substituted carbacephems.[a]

R^1	R^2	7β-(*cis*)	7α-(*trans*)
H[b]	PNB	5.0	1.5
V[b]	PNB	6.0	1.0
H[c]	H	5.0	1.0
D-(-)-α-phen-gly[d]	PNB	5.0	1.0

[a] J reported in Hz; [b]solvent=$CDCl_3$; [c]solvent=DCl/D_2O/dioxane; [d]solvent=D_6-DMSO

The antibiotic activity of compounds (**7a-d**) was investigated in a wide variety of gram positive and gram negative bacterial screens. Compound (**7a**), the 7-epimer of loracarbef (**1**), demonstrated diminished activity against bacteria normally responsive to (**1**). Generally, compound (**7b**) had diminished activity when compared to the corresponding *cis* compound, except against gram negative strains of *E. Coli* TEM, *Klebsiella*, *H. Influ.* C. L. and *H. Influ. res.* 76. Compounds (**7c**) and (**7d**) demonstrated no antibiotic activity. Compounds (**7b-d**) were tested and found inactive in antifungal screens using *Candida albicans*, *Trichophyton mentagraphytes* and *Asperfillus fumigatus*.[10]

The synthesis and testing of the 7α-amidocarbacephems has demonstrated the critical importance of the *cis* arrangement of the substituents on the β-lactam ring to achieve strong biological activity.

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analytical and spectral data; Mr. Thomas Butler, Ms. Helen Michael and Mr. Doug Zeckner for bioactivity test results. We also thank Drs. John Burks, Lowell Hatfield, Billy Jackson, Wayne Luke and Fred Perry for helpful discussions.

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8. All compounds reported in this Letter were fully characterized and their structure assignments supported by ^{1}H-NMR, ^{13}C-NMR, IR, MS and elemental analysis. Analytical data for the key intermediate amine hydrochloride (**5**): ^{1}H NMR (D_2O): d = 1.95 (1H, mult, CH_2); 2.65 (1H, mult, CH_2); 2.92 ppm (2H, mult, CH_2); 4.04 (1H, d of d of d, J = 9, 6, 1.5 Hz, β-lactam); 4.45 (1H, d, J = 1.5 Hz, β-lactam); 5.45 (ab pattern, 2H, benzyl); 7.65 (2H, d, J = 8 Hz, pNB); 8.25 (2H, d, J = 8 Hz, pNB). ^{13}C NMR (D_6-DMSO): d = 23.6, 30.7, 51.4, 59.4, 65.7, 122.9, 123.3, 126.8, 128.7, 142.5, 147.0, 158.8, and 159.4 ppm. IR (KBr): 3240, 3200, 3100, 3020, 1785, 1720, 1630, 1525, 1515, 1480, 1320 1310, 1270, 1245 cm^{-1}. Analysis calculated for $C_{15}H_{15}Cl_2N_3O_5 \cdot H_2O$: C, 44.30; H, 4.21; H, 10.35. Found: C, 43.90, H3.81, N, 10.51.
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