Notes

Effect of 6-α Substitution in Penicillins and 7-α Substitution in Cephalosporins upon β-Lactam Reactivity

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Strominger hypothesized that penicillins and cephalosporins may irreversibly acylate bacterial transpeptidase because they have a conformation similar to one possible for D-alanylalanine, the terminal fragment of the peptide with which this enzyme is believed to react.[1] Consequently, he proposed that 6-α-methylpenicillins and 7-α-methylcephalosporins might show increased antibacterial properties over the corresponding 6-α-H and 7-α-H compounds because of increased structural resemblance to the D-alanylalanine fragment. The discovery of naturally occurring 7-α-methoxycephalosporins, with their increased gram-negative activity, seemed to support this proposal.[2] As a result, many synthetic approaches to these and other 6-α and 7-α derivatives were developed.†

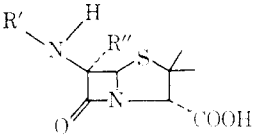
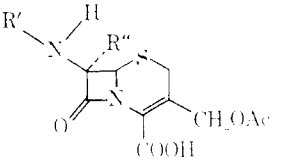
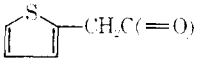
methoxy, or S-methyl group to a penicillin results in a reduction of both transpeptidase inhibition and antibacterial activity. In contrast, the addition of a 7-α-methoxy group to a cephalosporin results in compounds that are better transpeptidase enzyme inhibitors than their unsubstituted counterparts although they do not necessarily possess better antibacterial properties.

Our purpose in this study was to examine the effect of 6-α and 7-α substitution in penicillins and cephalosporins, respectively, upon the reactivity of the β-lactams to determine whether chemical reactivity parallels antibacterial activity.

The rates of base hydrolysis of a series of α-substituted and α-unsubstituted penicillins and cephalosporins are listed in Table I.

These results show that 6-α substitution in penicillins resulted in compounds with less reactive β-lactams than the parent compound. This effect must be steric rather than polar because polar substituent constants σ_I or σ^* would predict the rate of hydrolysis of the 6-α-methoxypenicillin to be faster and the 6-α-methylpenicillin to be slower than the unsubstituted parent penicillin.

Table I. Pseudo-First-Order Rates of Base Hydrolysis at pH 10, 35°

Side chain (R′)	6(7)-α substituent (R″)	$K_{obsd} \times 10^5$ sec^{-1}	$\frac{K_{obsd}\ (\alpha\text{-R}'')}{K_{obsd}\ (\alpha\text{-H})}$	Compd ref
				
$PhOCH_2C(=O)$	H	6.90 ± 0.48	1	*a*
	CH_3	0.77 ± 0.08	0.1	*b*
	OCH_3	2.35 ± 0.48	0.3	*b*
	SCH_3	0.77 ± 0.02	0.1	*b*
$PhCH_2C(=O)$	H	5.08 ± 0.15	1	*c*
	OCH_3	1.17 ± 0.22	0.2	*d*
	OC_2H_5	0.67 ± 0.13	0.1	*d*
				
$(NH_3)^+CH(COO^-)(CH_2)_3C(=O)$	H	10.4 ± 0.11	1	*e*
	OMe	13.2 ± 0.13	1.3	*f*
	H	9.70 ± 0.65	1	*g*
	OMe	12.40 ± 0.65	1.3	*h*

[a] O. K. Behrens, J. Corse, J. P. Edwards, L. Garrison, R. G. Jones, Q. F. Soper, F. R. Van Abeele, and C. W. Whitehead, *J. Biol. Chem.*, **175**, 793 (1948). [b] W. A. Spitzer, T. Goodson, *Tetrahedron Lett.*, 273 (1973). [c] Penicillin G. [d] R. A. Firestone, N. Schelochow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972). [e] G. G. F. Newton, and E. P Abraham, *Biochem. J.*, **62**, 651 (1956). [f] Reference 2. [g] R. R. Chauvette, E. H. Flynn, B. G. Jackson, E. R. Lavagnino, R. A. Morin, R. A. Mueller, R. P. Pioch, R. W. Roeske, C. W. Ryan, J. L. Spencer, and E. Van Heyningen, *J. Amer. Chem. Soc.*, **84**, 3401 (1962). [h] L. Cama, U. S. Leanza, T. R. Beattie, and B. G. Christensen, *ibid.*, **94**, 1408 (1972).

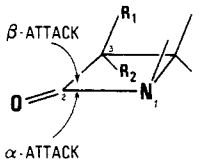
The antibacterial activities of the series of 6-α- and 7-α-substituted penicillins and cephalosporins discussed in this paper, together with their ability to inhibit extracellular transpeptidase, have been reported elsewhere.[3,4,‡] To summarize these results, the 6-α addition of a methyl,

In retrospect, these steric effects might have been predicted in view of published reports of the effect of substituents on isolated β-lactam reactivity. In principle, the carbonyl of any β-lactam may be attacked by a nucleophile at both faces (α and β faces of penicillins and ceph-

†See compound reference in Table I for synthetic approaches to 6-α- and 7-α-substituted penicillins and cephalosporins, respectively.

‡A preliminary report of the chemical reactivity of these compounds is also presented in these papers.

alosporins). Washkuhn and Robinson found that the reactivity of 3-monosubstituted β-lactams I correlates with the polar σ* values of the 3 substituents.[5] However, Holley and Holley found that disubstitution in isolated β-lactams (3,3-dimethyl) resulted in a 25-fold decrease in β-lactam reactivity relative to the monosubstituted (3-methyl) analog.[6] Thus, when both faces of a β-lactam are unhindered, monosubstitution affects reactivity in a manner predictable from linear free energy substituent values. In contrast, when one face of a β-lactam is already hindered, the introduction of a substituent on the unhindered face results in a β-lactam that is hindered on both faces to nucleophilic attack, and steric effects override polar effects. Penicillins are sterically similar to the case of the isolated β-lactam which has one face hindered. At the β face a penicillin β-lactam carbonyl is at an interatomic distance of only 2.79 Å from the C-3 proton (in the crystalline phase) and therefore is severely hindered to nucleophilic attack.[7] Thus, the addition of any α substituent results in a β-lactam hindered at both faces and lowers overall reactivity.§



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In contrast, 7-α-methoxy substitution in cephalosporins has no pronounced effect upon the β-lactam reactivity (Table I). We believe that the difference in response to 7-α substitution in cephalosporins compared with the response to 6-α substitution in penicillins is the result of the availability of the β face of the cephalosporin to nucleophilic attack.‡ Cephalosporins are sterically similar to isolated β-lactams where *both* faces of the ring are unhindered. The addition of the 7-α-methoxy substituent therefore does not totally hinder the β-lactam and the polar substituent effect on the overall reactivity can be observed.

Thus, we have shown that the differences in antibacterial activity as a result of 6-α and 7-α substitution in penicillins and cephalosporins, respectively, are paralleled by differences in chemical reactivity of their corresponding β-lactams. We attribute these differences in chemical reactivity to steric factors resulting from α substitution.

Experimental Section

β-Lactams. The penicillins and cephalosporins used in this study were synthesized by colleagues at Lilly Research Laboratories. Synthetic procedures for all these compounds are referenced in Table I.

Kinetic Methods. The hydrolysis rates of the penicillins and cephalosporins were measured by constant pH titration and uv methods, respectively, as described in the accompanying paper; see ref 7. The pseudo-first-order rates of β-lactam hydrolysis at pH 10.0, 35°, are listed in Table I.

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§In apparent contradiction to this argument the hydrolysis of 6-α-acetyl-6-phenoxyacetamidopenicillanic acid methyl ester has been found to be 2.4 times as reactive as phenoxyacetamidopenicillanic acid methyl ester in aqueous glyme.[8]

‡ Reports of intramolecular nucleophilic attack of the α-amino moiety on the β-lactam of cephradine,[9] cephalexin esters, and cephaloglycin lactone (ref 7) demonstrate the availability of the β face of cephalosporins to nucleophilic attack.

References

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Derivatives of 3,4-Dihydrocarbostyril as β-Adrenergic Blocking Agents

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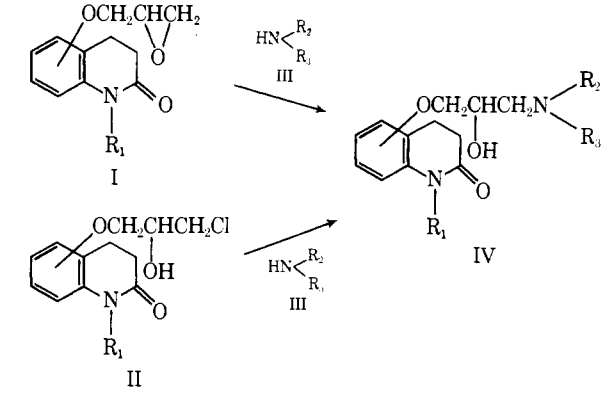
In the last decade, numerous compounds have been synthesized in an effort to find a drug possessing more specific adrenergic β-receptor blocking potency or more significant activity without cardiac contraction. Such a compound is expected to have an aromatic or heterocyclic nucleus attached to a 1-hydroxy-2-substituted aminoethyl or 2-hydroxy-3-substituted aminopropoxy substituent.[1] The present paper deals with the effects of using 3,4-dihydrocarbostyril as nucleus and 2-hydroxy-3-substituted aminopropoxy as substituent.

Chemistry. The compounds were prepared by reaction of derivatives of 5-, 6-, 7-, and 8-(2,3-epoxy)propoxy-3,4-dihydrocarbostyril (I) or 5-, 6-, 7-, and 8-(3-chloro-2-hydroxy)propoxy-3,4-dihydrocarbostyril (II) with the appropriate amine III in the usual manner (Scheme I). Formulas and physical properties of compounds IV are shown in Table I.

Scheme I



Pharmacology. Adrenergic β-receptor blocking activity was evaluated by inhibition of the depressor and the positive chronotropic responses to isoproterenol. It was gener-