SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF A NOVEL BIPHENYL-UREIDO PENICILLIN

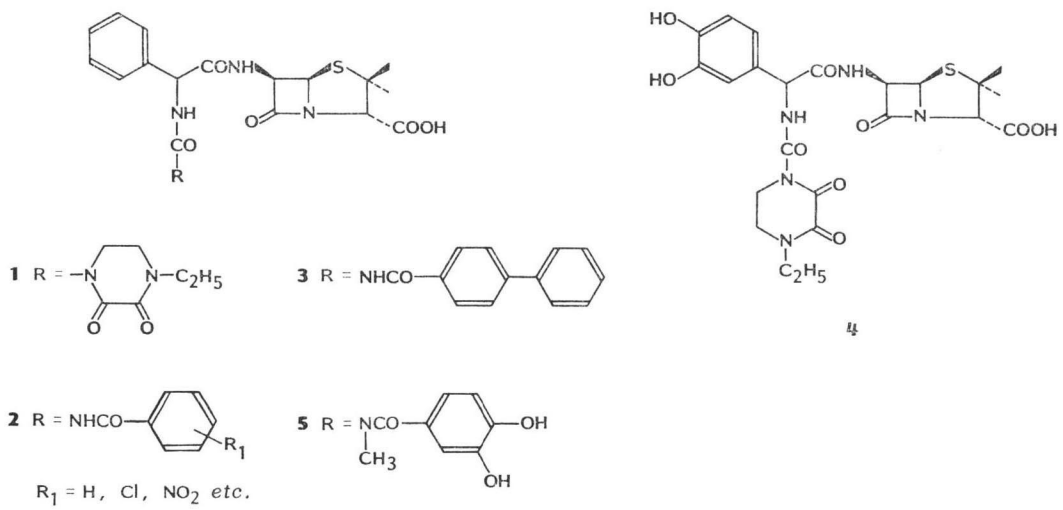
Sir:

Intensive research over many years on acylated ampicillin derivatives has led to the discovery of broad-spectrum antibacterial agents such as piperacillin (**1**)[1]. Ureido penicillins of type (**2**), although generally less potent, also possess broad-spectrum activity[2]. We found that in this series the biphenyl derivative (**3**) was particularly active against Gram-positive organisms. Recently penicillin derivatives possessing a 3,4-dihydroxyphenyl moiety, *e.g.* (**4**)[3] and (**5**)[4], have been shown to display enhanced activity against Gram-negative bacteria, especially against certain strains of *Escherichia coli* and *Pseudomonas aeruginosa*. We now report the synthesis of sodium 6β-*R*,2-[3′-(4-phenylphenylcarbonyl)-3′-methyl-1′-ureido]-2-(3,4-dihydroxyphenyl)acetamido penicillanate (**15**), a novel penicillin derivative containing both the 3,4-dihydroxyphenyl and biphenyl moieties. The *in vitro* activity of this compound is compared with that of piperacillin and related penicillins **12**~**14**.

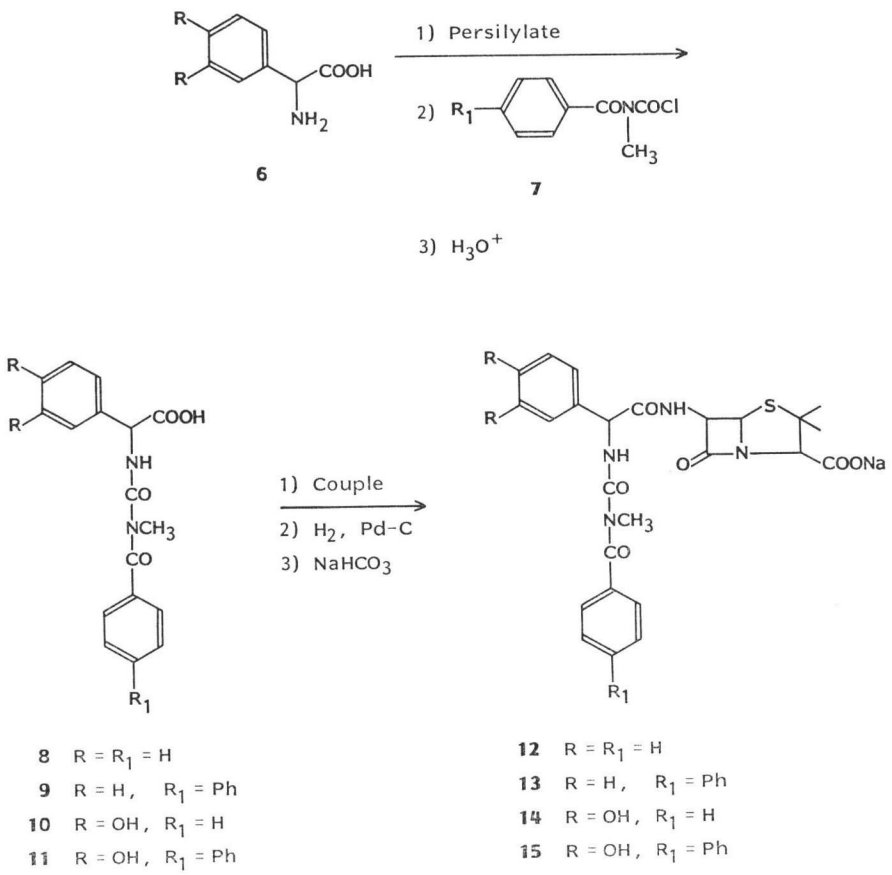
The penicillins **12**~**15** were synthesized (Scheme 1) by heating the appropriate D-amino acid (**6**, R=H or OH) with a mixture of hexamethyldisilazane and chlorotrimethylsilane and then reacting the resulting persilylated intermediate with the *N*-carbonylchloride (**7**, R_1=H or Ph). Hydrolytic work-up gave the free acids (**8**~**11**) which were coupled to benzyl 6β-aminopenicillanate using *N*,*N*′-dicyclohexylcarbodiimide (for R=H) or mixed anhydride activation (for R=OH). The resulting esters were deprotected (H_2, Pd-C) and converted to sodium salts (**12**~**15**) using sodium bicarbonate.

Table 1 shows the antibacterial activity of penicillins **12**~**15** compared with that of piperacillin. It can be seen that compound **12** displayed broad-spectrum activity but was generally from 2- to 5-fold less active than piperacillin. The biphenyl analogue (**13**), apart from modest activity against *Pseudomonas* compared favourably with piperacillin against other Gram-negative species and was considerably more active against Gram-positive organisms such as *Staphylococcus aureus* Oxford and *Enterococcus faecalis* I. The dihydroxyphenyl compound (**14**) had improved Gram-negative activity when compared with the unsubstituted phenyl analogue (**12**) and piperacillin, but showed reduced activity against Gram-positive organisms. In contrast the dihydroxyphenyl biphenyl derivative (**15**) combined the Gram-positive activity of compound **13** with the Gram-negative activity of **14** and was from 2- to 10-fold more active than piperacillin against most of the organisms tested. Plasmid-mediated β-lactamase-producing organisms proved generally less susceptible and, indeed, none of the compounds were active against R-TEM-producing *E. coli* JT4. Interestingly *E. coli* JT425, a chromosomally-mediated β-lactamase-producing strain, proved considerably more sensitive to **15** than to piperacillin.

The penicillin **15** proved to have considerably



Scheme 1.



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8 R = R_1 = H
9 R = H, R_1 = Ph
10 R = OH, R_1 = H
11 R = OH, R_1 = Ph

12 R = R_1 = H
13 R = H, R_1 = Ph
14 R = OH, R_1 = H
15 R = OH, R_1 = Ph

Table 1. Comparative antibacterial activity of ureido penicillins (**12**~**15**) and piperacillin.

Organism	MIC (μg/ml)[a]				
	12	**13**	**14**	**15**	Piperacillin
Escherichia coli NCTC 10418	2.5	0.25	≦0.06	≦0.06	1
E. coli JT 4 (R_{TEM})	>128	>128	>128	>128	>128
E. coli JT 425[b]	64	4	8	0.5	16
Pseudomonas aeruginosa NCTC 10662	32	16	2	1	4
Klebsiella pneumoniae A	16	8	1	0.25	4
Serratia marcescens US 32	4	0.25	1	0.25	1
Enterobacter cloacae N1	8	1	2	1	1
Morganella morganii I	4	0.25	≦0.06	≦0.06	1
Staphylococcus aureus Oxford	0.5	0.12	2	0.25	0.5
S. aureus Russell[b]	128	64	32	32	>128
Enterococcus faecalis I	2	1	8	2	4
Streptococcus pyogenes CN 10	<0.06	0.06	0.12	≦0.06	0.06

[a] Determined by serial dilution in Blood Agar Base (Oxoid) against an inoculum of 10^8 cfu.
[b] Ampicillin-resistant strain.

diminished activity when tested *in vivo* compared to its potency *in vitro*. This may be attributed to a very high level of serum binding (>95%).

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