SEMISYNTHETIC PENICILLINS AND CEPHALOSPORINS CONTAINING THE SUBSTITUTED 6-VINYL-1,2-DIHYDRO-2-OXO- AND 1,4-DIHYDRO-4-OXO-3-PYRIDINECARBOXYLIC ACID SIDE CHAINS

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS

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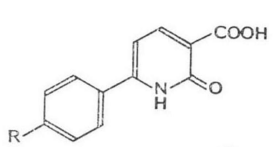
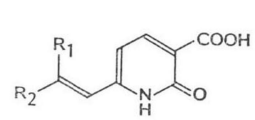
A series of penicillins and cephalosporins containing the substituted 6-vinyl-1,2-dihydro-2-oxo- and 1,4-dihydro-4-oxo-3-pyridinecarboxylic acid side chains has been prepared and compared to piperacillin and cefoperazone. The compounds show good activity when tested *in vitro* against an array of Gram-negative bacteria. *In vitro* activity was also demonstrated against several species of Gram-positive bacteria. Two compounds, **14** and **21**, show good *in vivo* activity when tested against *Klebsiella pneumoniae*, *Enterobacter cloacae*, and two strains of *Pseudomonas aeruginosa*.

A large number of penicillins and cephalosporins are currently available for therapy against bacterial infections, and research in this area continues unabated. The goal of our research effort was the synthesis of compounds having a broad spectrum activity against Gram-negative bacteria. We were particularly interested in combating the more serious infections encountered in hospitals and caused by *Klebsiella*, *Enterobacter*, and particularly *Pseudomonas* species. When we began our work the only penicillins showing anti-*Pseudomonas* activity were carbenicillin, piperacillin[1] and ticarcillin, all of which showed only moderate *in vivo* activity against this species. The leading new cephalosporins at that time were cefamandole and cefazolin, both of which had no significant anti-*Pseudomonas* activity, and cefoperazone,[2] which showed only moderate *in vivo* anti-*Pseudomonas* activity. Since that time several cephalosporins have been reported to have *Pseudomonas* activity, the most potent compound among them being ceftazidime[3].

Recent reports[4~8] from these laboratories have described the excellent broad-spectrum activity against Gram-negative bacteria, especially against *Pseudomonas* species, conferred on penicillins and cephalosporins by the 1,2-dihydro-2-oxo-6-(substituted)phenyl-3-pyridinecarboxylic acid moiety, **1**. In pursuing this lead, we decided to explore the effect on activity of inserting an ethylene spacer in the 6-position between the pyridone ring and the aryl group leading to compounds of type **2**. The effect on activity conferred by the isomeric 4-pyridone derivatives **3** was also explored.



1 R = SO_2NR_2, $NHCR_1$ (O)



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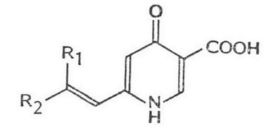
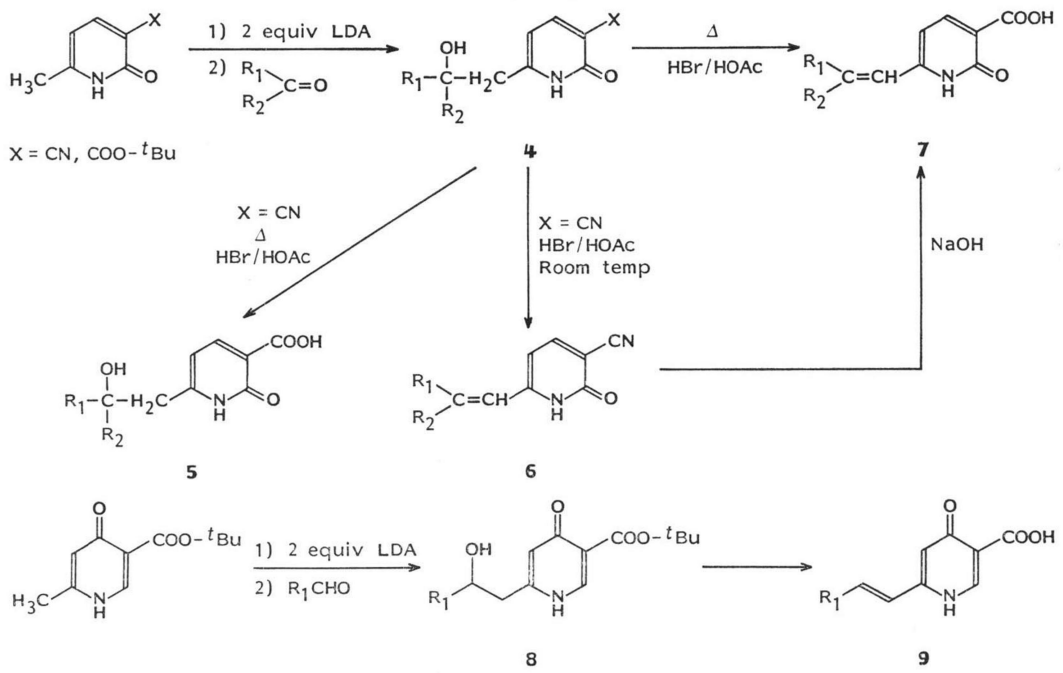


3

Scheme 1.



LDA: Lithium diisopropylamide.

Chemistry

The vinyl pyridone side chains were prepared according to Scheme 1.

A detailed description of this synthetic route, together with the physical properties of the vinyl pyridones used in this work has recently been published.[9] When the carbonyl compound which was added to the pyridone dianion was a pyridyl ketone (R_1, $R_2 \neq H$), the intermediate tertiary alcohol could not be dehydrated and compounds of type **5** resulted from acid hydrolysis.

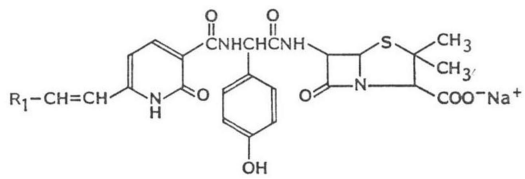
Oxidation of the (methylthio)phenyl pyridone derivative with excess hydrogen peroxide gave the corresponding sulfone (side chain for **21**). Bromination of the 2-pyridyl pyridone derivative resulted in bromination of the pyridone ring rather than the vinyl grouping to give the 5-bromo derivative (side chain for **25**).

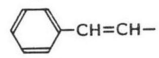
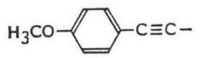
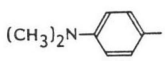
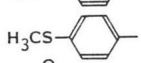
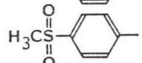
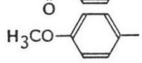
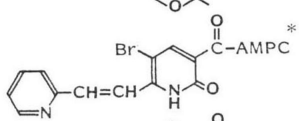
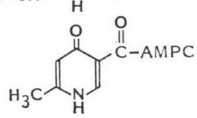
The pyridones were activated for coupling by preparing the imidazolides with 1,1′-carbonyldiimidazole. These were condensed with the appropriate β-lactams in *N,N*-dimethylacetamide. The products were isolated, suspended in water, and the pH adjusted to 6.5~7.5. Freeze-drying gave the β-lactam derivatives as the sodium salts.

Antimicrobial Activity

The *in vitro* antibacterial activities were determined by microtitration dilution[10] in Trypticase soy broth with an inoculum of 10^3 cfu (colony forming units) for Gram-negative bacilli. The tests for *Staphylococcus* and *Streptococcus* were run using an inoculum of 10^5 cfu. The minimum inhibitory concentrations (MIC) were determined after 16~18-hour incubation at 37°C on the basis of complete inhibition of visible growth. These results are listed in Tables 1, 2 and 3. The median protective dose (PD_{50}) is the cumulative result of at least two tests each employing eight mice per dose level. These tests were performed in groups of Charles River female mice weighing 18~22 g. The intraperitoneal challenge

Table 1. *In vitro* antibacterial activity (MIC, μg/ml).

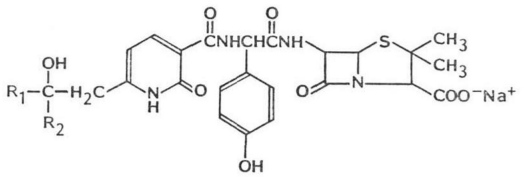


R_1	Compound	SAU[a]	SAS	SF	KP	SM	ECI	PA2	PAB	PAU	ECV	ECB	PV
	**10**	0.2	>50	0.8	12.5	3.1	3.1	1.6	3.1	3.1	6.3	1.6	1.6
CH_3–	**11**	0.2	>50	0.4	12.5	6.3	12.5	1.6	3.1	0.8	12.5	6.3	1.6
	**12**	0.1	>50	0.4	1.6	1.6	3.1	0.4	1.6	0.8	3.1	0.4	1.6
	**13**	0.2	>50	0.8	6.3	1.6	3.1	0.8	1.6	1.6	1.6	6.3	3.1
	**14**	0.2	>50	0.4	3.1	3.1	3.1	0.8	1.6	0.4	0.8	6.3	3.1
	**15**	0.2	>50	1.6	3.1	3.1	3.1	0.4	1.6	1.6	1.6	6.3	3.1
	**16**	0.1	>50	0.8	6.3	3.1	6.3	3.1	3.1	3.1	1.6	3.1	3.1
	**17**	0.2	>50	0.8	12.5	3.1	6.3	6.3	6.3	6.3	3.1	12.5	3.1
	**18**	0.1	25	0.4	3.1	0.8	3.1	1.6	1.6	1.6	0.8	1.6	1.6
	**19**	0.1	25	0.4	6.3	3.1	3.1	1.6	0.8	0.8	1.6	3.1	3.1
	**20**	0.4	50	0.8	6.3	3.1	6.3	6.3	6.3	6.3	1.6	6.3	6.3
	**21**	0.4	>50	0.8	3.1	3.1	6.3	1.6	1.6	0.8	0.4	3.1	1.6
	**22**	0.1	>50	0.4	12.5	6.3	12.5	3.1	6.3	3.1	3.1	6.3	6.3
	**23**	0.2	>50	1.6	12.5	3.1	6.3	6.3	6.3	6.3	3.1	6.3	3.1
	**24**	0.4	50	1.6	12.5	3.1	6.3	3.1	6.3	6.3	3.1	12.5	1.6
	**25**	0.2	>50	1.6	25	12.5	25	1.6	3.1	3.1	6.3	25	6.3
	**26**	0.8	>50	1.6	12.5	12.5	12.5	0.8	0.8	0.8	1.6	12.5	0.8
Piperacillin	**27**	0.8	>50	1.6	3.1	0.8	0.8	1.6	3.1	1.6	1.6	0.8	0.4

[a] SAU; *Staphylococcus aureus* UC-76, SAS; *S. aureus* S18713, SF; *Streptococcus faecalis* MGH-2, KP; *Klebsiella pneumoniae* MGH-2, SM; *Serratia marcescens* IMM11, ECI; *Enterobacter cloacae* IMM11, PA2; *Pseudomonas aeruginosa* 28, PAB; *P. aeruginosa* BRK-12-4-4, PAU; *P. aeruginosa* UI-18, ECV; *Escherichia coli* Vogel, ECB; *E. coli* Brig, PV; *Proteus vulgaris* 1810.

* AMPC; Amoxicillin.

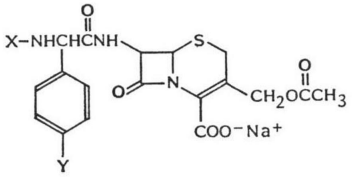
Table 2. *In vitro* antibacterial activity (MIC, μg/ml).

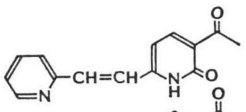
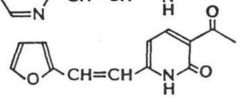
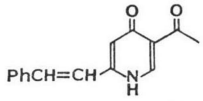
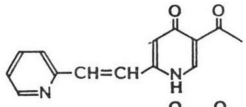
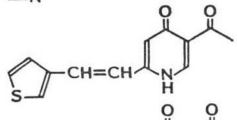
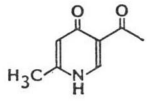


R_1	R_2	Compound	SAU[a]	SAS	SF	KP	SM	ECI	PA2	PAB	PAU	ECV	ECB	PV
	CH_3	**28**	0.4	50	1.6	50	25	25	12.5	25	12.5	6.3	25	6.3
	CH_3	**29**	0.8	>50	1.6	12.5	6.3	6.3	3.1	6.3	3.1	1.6	6.3	3.1
		**30**	1.6	>50	3.1	25	25	25	6.3	12.5	6.3	12.5	50	12.5

[a] See footnote of Table 1.

Table 3. *In vitro* antibacterial activity (MIC, μg/ml).



X	Y	Compound	SAU[a]	SAS	SF	KP	SM	ECI	PA2	PAB	PAU	ECV	ECB	PV
	H	**31**	0.4	3.1	12.5	6.3	25	6.3	3.1	6.3	3.1	1.6	12.5	12.5
	H	**32**	0.8	1.6	25	12.5	25	12.5	6.3	12.5	6.3	6.3	12.5	12.5
	OH	**33**	3.1	12.5	25	25	>50	50	12.5	25	25	6.3	50	25
	OH	**34**	0.4	1.6	6.3	1.6	50	12.5	0.8	1.6	1.6	1.6	25	3.1
	OH	**35**	0.8	0.8	6.3	3.1	50	12.5	0.8	0.8	1.6	3.1	>50	6.3
	OH	**36**	1.6	3.1	12.5	6.3	>50	25	1.6	1.6	1.6	3.1	50	6.3
Cefoperazone	—	**37**	0.8	1.6	25	0.05	0.2	0.05	1.6	1.6	1.6	0.05	0.1	0.05

[a] See footnote of Table 1.

Table 4. *In vivo* activity, PD_{50} (mg/kg, mice) (total of 2 doses).

Compound	PAU[a]	PAB	KP	ECI	LD_{50}[b] (mg/kg)
10	112	—	—	—	707
11	360	—	—	—	2,350
12	130	156	60	48	>2,000
13	20	30	34	29	1,100
14	24	64	32	44	>2,000
15	72	—	—	—	<1,000
16	214	—	—	—	<1,000
17	114	—	—	—	<1,000
18	106	—	—	—	<1,000
19	80	—	—	—	<1,000
20	176	—	—	—	1,100
21	32	44	18	24	>2,000
22	164	—	—	—	1,450
23	180	—	—	—	<1,000
24	110	—	—	—	<2,000
25	158	—	—	—	<1,000
26	24	22	90	64	>2,000
Piperacillin	150	100	38	20	>2,000

[a] See footnote of Table 1.
[b] Based on a single iv dose to groups of 5 mice.

consisted of approximately 100 median lethal doses (LD_{50} of the bacterium in question) and therapy was by a single subcutaneous dose at the time of challenge and a second dose two hours post challenge. These results are listed in Table 4.

Results and Discussion

Table 1 shows the activities when these side chains are attached to the amino group of amoxicillin. All the penicillins thus formed show good activity against the broad array of Gram-negative bacteria that we use in our initial screen. Good activity was also demonstrated against the Gram-positive species *Staphylococcus aureus* UC-76 and *Streptococcus faecalis* MGH-2. None were active against *S. aureus* S18713, a β-lactamase producing antibiotic resistant strain. Certain of these compounds either matched or bettered the activity of piperacillin[1], except for activity *versus Enterobacter cloacae* and *Proteus vulgaris*.

In the broad area of Gram-negative bacteria, our particular interest was to find compounds active against *Pseudomonas* species. Several of these compounds, **12**, **13**, **14**, **15**, **18**, **19** and **21** showed excellent MIC values when tested against three different strains of *Pseudomonas aeruginosa*.

In Table 2, the compounds containing the tertiary alcohol in the side chain which could not be dehydrated showed a fall off in activity against all the Gram-negative species, although compound **29** still maintained respectable MIC values.

Table 3 contains the results of attaching several of these side chains to cephalosporins. It also contains compounds where the 6-vinyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety is appended. In general the overall activities were somewhat lower than the corresponding penicillins. Compounds **34** and **35** maintained excellent activity against all *Pseudomonas* strains. Noticeable departures of activity were particularly evident *versus Serratia marcescens* and *Escherichia coli*. The penicillinase pro-

Table 5. Physical constants of the penicillins and cephalosporins.

Compound	Iodometric assay (%)	$[\alpha]_D^{23}$ ° (solvent)	UV, λ_{max} ($E_{1cm}^{1\%}$) pH 7 buffer
10	87	+183 (MeOH)	380 (528), 279 (177)
11	97	+163 (MeOH)	356 (342)
12	98	−166 (pH 7)	375 (440), 273 (288)
13	89	−75.5 (pH 7)	377 (468), 273 (224)
14	94	+161 (pH 7)	378 (474), 265 (188)
15	87	+174 (pH 7)	380 (466), 266 (159)
16	84	−2,120 (pH 7)	398 (602), 279 (179)
17	91	−246 (pH 7)	396 (404), 273 (177)
18	85	+1,570 (pH 7)	385 (354), 230 (280)
19	76	+272 (DMSO)	422 (497)
20	77	+175 (pH 7)	395 (534), 228 (322)
21	85	+173 (MeOH)	382 (478), 282 (275)
22	83	−562 (pH 7)	393 (443), 273 (94)
23	83	−122 (pH 7)	382 (258)
24	68	−83 (pH 7)	—
25	83	+231 (pH 7)	392 (302), 294 (162), 269 (178), 228 (331)
26	99	+125 (MeOH)	275 (106)
28	86	+147 (pH 7)	326 (110), 260 (102), 229 (233)
29	86	+126 (MeOH)	330 (215), 230 (247)
30	90	+156 (pH 7)	372 (69), 331 (167), 267 (114), 261 (129)
31	91 (HPLC)	+103 (pH 7)	377 (394), 262 (264)
32	94 (HPLC)	—	—
33	83 (HPLC)	+15.3 (DMSO)	308 (312), 270 (249), 227 (386)
34	96 (HPLC)	−6.0 (DMSO)	309 (447), 259 (453)
35	90 (HPLC)	−19.2 (DMSO)	—

ducing *S. aureus* S18713 was susceptible to all the cephalosporins prepared.

Table 4 shows the *in vivo* activity of the penicillin derivatives. When high PD_{50} values *versus P. aeruginosa* UI-18 or LD_{50} values <2,000 mg/kg dampened our interest in a particular compound, *in vivo* evaluation *versus* the other Gram-negative species was not performed. Among the penicillins, compounds **13**, **14** and **21** exhibited good *in vivo* activity against *Klebsiella*, *Enterobacter* and two strains of *P. aeruginosa*. These activities compare quite favorably with **26**, a compound described by ISAKA *et al.*[11] and piperacillin (**27**)[1]. The LD_{50} of both **14** and **21** was >2,000 mg/kg. The tertiary alcohols **28**~**30** and cephalosporins **31**~**35** showed disappointing *in vivo* activity against *P. aeruginosa* UI-18 and consequently were not tested further. An exception was **34** which had a PD_{50} vs. *Klebsiella pneumoniae* MGH-2 of 24 mg/kg and vs. *P. aeruginosa* UI-18 of 40 mg/kg. The physical constants of the penicillins and cephalosporins that we have prepared are listed in Table 5.

Experimental

General

Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WH-90 instrument modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported in δ values in ppm from internal tetramethylsilane. Rotations were recorded on a Perkin Elmer Model 141 automatic polarimeter. UV spectra were determined using a Varian Associates Cary 118.

Substituted 6-Vinyl-1,2-dihydro-2-oxo- and 1,4-Dihydro-4-oxo-3-pyridinecarboxylic Acids

The preparation of the requisite pyridones used for compounds **10**~**20**, **22**~**24** and **31**~**35** have

been described[9].

Tertiary Alcohols, **5**: Side Chains for Compounds **28**~**30**. General Procedure Illustrated with the Preparation of 1,2-Dihydro-6-[2-hydroxy-2-(3-pyridinyl)propyl]-2-oxo-3-pyridinecarboxylic Acid

A solution of 10.0 g (0.039 mol) of 1,2-dihydro-6-[2-hydroxy-2-(3-pyridinyl)propyl]-2-oxo-3-pyridinenitrile in 100 ml of acetic acid and 40 ml of 48% hydrobromic acid was heated at reflux overnight. The solvent was removed under reduced pressure and the residue taken up in a small amount of H_2O. On cooling the product precipitated and was collected and dried. There was obtained 10.5 g (75.5%) of the product as the hydrobromide salt, mp 252~253°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.6 (s, 3H, CH_3), 3.15 (d, J=3.5 Hz, 2H, CH_2), 6.3 (d, J=7 Hz, 1H, C5H), 7.95 (m, 1H, pyridine ring), 8.15 (d, J=7 Hz, 1H, C4H), 8.45 (d, J=9 Hz, 1H, pyridine ring), 8.8 (s, 2H, pyridine ring).

Anal Calcd for $C_{14}H_{14}N_2O_4 \cdot HBr$: C 47.34, H 4.26, N 7.89, Br 22.50.
Found: C 47.10, H 4.19, N 7.74, Br 22.90.

1,2-Dihydro-6-[2-[4-(methylsulfonyl)phenyl]ethenyl]-2-oxo-3-pyridinecarboxylic Acid. Side Chain for Compound **21**

A solution of 4.0 g (13.9 mmol) of 1,2-dihydro-6-[2-[4-(methylthio)phenyl]ethenyl]-2-oxo-3-pyridinecarboxylic acid in 120 ml of *N*,*N*-dimethylacetamide and 80 ml of 2.5% NaOH solution was treated in portions over a period of 3 days with 70 ml of 30% H_2O_2 solution. The suspension was treated with SO_2 gas, and the solid collected and washed with H_2O giving 2.26 g (50.8%) of the product, mp >300°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 3.3 (s, 3H, CH_3), 7.05 (d, J=8 Hz, 1H, C5H), 7.35 (d, J=16 Hz, 1H, vinyl), 7.95 (m, 5H, phenyl and vinyl), 8.42 (d, J=8 Hz, 1H, C4H).

Anal Calcd for $C_{15}H_{13}NO_5S$: C 56.41, H 4.10, N 4.39.
Found: C 56.00, H 4.23, N 4.60.

5-Bromo-1,2-dihydro-2-oxo-6-[2-(2-pyridinyl)ethenyl]-3-pyridinecarboxylic Acid. Side Chain for Compound **25**

A suspension of 5.0 g (20.6 mmol) of 1,2-dihydro-2-oxo-6-[2-(2-pyridinyl)ethenyl]-3-pyridinecarboxylic acid in 150 ml of DMF was warmed to 110°C to effect solution. The warm solution was then treated dropwise with 1.15 ml (20.6 mmol) of bromine and allowed to cool to room temp over 1 hour. The solution was diluted with H_2O and the product collected. Recrystallization from *N*,*N*-dimethylacetamide - H_2O gave 4.7 g (70.7%) of the product, mp 267~268°C. ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.5 (m, 2H, vinyl and pyridine), 7.8 (m, 3H, vinyl and pyridine), 8.35 (s, 1H, C4H), 8.68 (br s, 1H, pyridine).

1-[[1,2-Dihydro-2-oxo-6-[2-(2-pyridinyl)ethenyl]-3-pyridinyl]carbonyl]-1*H*-imidazole. A Representative Procedure for Imidazolide Formation

A suspension of 10.0 g (41.3 mmol) of 1,2-dihydro-2-oxo-6-[2-(2-pyridinyl)ethenyl]-3-pyridinecarboxylic acid in 100 ml of DMF was treated with 9.38 g (57.8 mmol; a 40% excess) of 1,1′-carbonyldiimidazole and heated at 60°C for 1 hour. Solution occurred in about 5 minutes, and another solid started to form immediately. The suspension was diluted with a 1 : 3 mixture of CH_2Cl_2 - Et_2O and the product collected. There was obtained 10.44 g (86.5%) of the product which was used directly in the subsequent coupling step.

Amoxicillin - DMSO Complex

50 g of amoxicillin·$3H_2O$ was added in portions with stirring to 375 ml of DMSO. The mixture was stirred at room temp for 2 hours, then diluted with 75 ml of CH_2Cl_2. After cooling in ice, the product was collected by filtration and washed with CH_2Cl_2. Analysis showed 3 mol of DMSO and 0.5 mol of H_2O for each mol of amoxicillin. The effective formula weight was 609.

Sodium 6-[D-α-[[1,2-Dihydro-2-oxo-6-[2-(2-pyridinyl)ethenyl]-3-pyridinyl]carbonylamino]-(4-hydroxyphenyl)acetamido]penicillinate. A Representative Coupling Procedure

A solution of 22.8 g (37.6 mmol) of amoxicillin-DMSO complex in 150 ml of *N*,*N*-dimethylacetamide was cooled in ice and treated with 10.0 g (34.2 mmol) of 1-[[1,2-dihydro-2-oxo-6-[2-(2-pyridinyl)-

ethenyl]-3-pyridinyl]carbonyl]-1*H*-imidazole and 4.8 ml (34.2 mmol) of triethylamine. The reaction mixture was stirred at 0°C for 1 hour, and then at room temp for 2 hours. Solution occurred in about 40 minutes. The solution was poured into 800 ml of ice water and the pH brought to 2.9 with dilute HCl. The solid was collected and resuspended twice in cold water. The solid was then suspended in 200 ml of cold water and the pH brought to 7.5 with 1 N NaOH. A few particles were filtered off and the filtrate freeze-dried to give 19.4 g (93%) of product. ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.4 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 3.84 (s, 1H, C3H), 5.3 (m, 2H, C5H, C6H), 5.74 (d, 1H, CH of hydroxyphenylglycine moiety), 6.65, 7.15 (pair of doublets, AB pattern, J=8 Hz, 4H, hydroxyphenyl group), 6.85, 8.22 (pair of doublets, AB pattern, J=8 Hz, 2H, C4H, C5H of pyridone ring), 7.44, 7.72 (pair of doublets, AB pattern, J=17 Hz, 2H, vinyl), 7.5 (m, 3H, pyridine), 8.56 (d, J=4 Hz, 1H, pyridine), 8.95 (d, J=8 Hz, 1H, NH), 10.55 (d, J=8 Hz, 1H, NH).

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