BASIC CARBAPENEM ANALOGS: SYNTHESIS AND *IN VITRO* ACTIVITY OF 1β-METHYL-2-(PYRIDYLMETHYLTHIO)-CARBAPENEMS

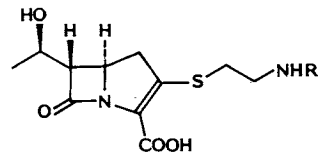
Sir:

Since the discovery of thienamycin (**1**),[1,2] the first broad spectrum carbapenem antibiotic, considerable effort has been directed toward the development of more stable and even more potent analogs.[3~6] Several problems were initially evident. Firstly, the chemical instability of **1** required attenuation. This feat was accomplished by derivatization of the primary amino group which led to the development of imipenem, the *N*-formimidoyl derivative (**2**).[7] Secondly, it was found that both thienamycin and imipenem were rapidly metabolized and rendered inactive by a mammalian dehydropeptidase, DHP-I.[8] The discovery reported from these laboratories that carbapenems bearing a methyl group in the 1-position possessed both enhanced chemical stability as well as significantly lowered DHP-I susceptibility,[9] left the objective of obtaining increased potency, especially against *Pseudomonas aeruginosa*.[10]

Observations on carbapenems that possess a basic moiety in the 2-position led one to expect an improvement in potency relative to less basic side chain analogs.[11] We focused our efforts on the synthesis of 2- and 4-aminopyridyl analogs since they are more basic than the unsubstituted[12,13] or the 3-amino isomers.[14~17] The investigation of the structure-activity relationship of 1β-methyl-2-[(2- and 4-aminopyridyl)methylthio]carbapenem analogs in relationship to their antibacterial spectrum and DHP-I susceptibility is the subject of this communication. A correlation will be made between the basicity of the side chain in the 2-position and potency against certain organisms.

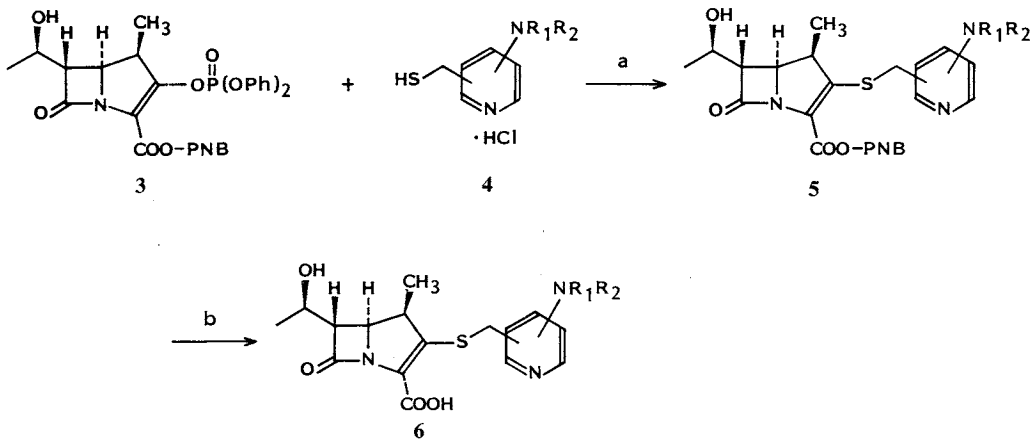
We envisioned the synthesis of the requisite carbapenems *via* the methodology developed in these laboratories[9,18,19] of addition of thiols **4a**~**4k** to *p*-nitrobenzyl (1*R*,5*R*,6*S*)-2-(diphenylphosphono)oxy-6-[1(*R*)-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**3**) in the presence of a hindered base. Subsequent hydrogenolysis of the *p*-nitrobenzyl ester protecting group of **5a**~**5k** would reveal the 3-carboxyl group of the carbapenem to complete the syntheses of **6a**~**6k** (Scheme 1). Compounds **6a** and **6c**~**6k** were prepared by this method, however, **6b** was prepared by a different route. The synthesis of **6b** is described first (Scheme 2).

The preparation of 4-nitropyridylmethanol (**8**) was accomplished *via* the Katada reaction[20] of *N*-oxide **7**. Treatment of **8** with *p*-toluenesulfonyl chloride gave the pyridyl chloride which was reacted with trityl mercaptan to give sulfide **9**. The nitro group was displaced with lithium azide and removal

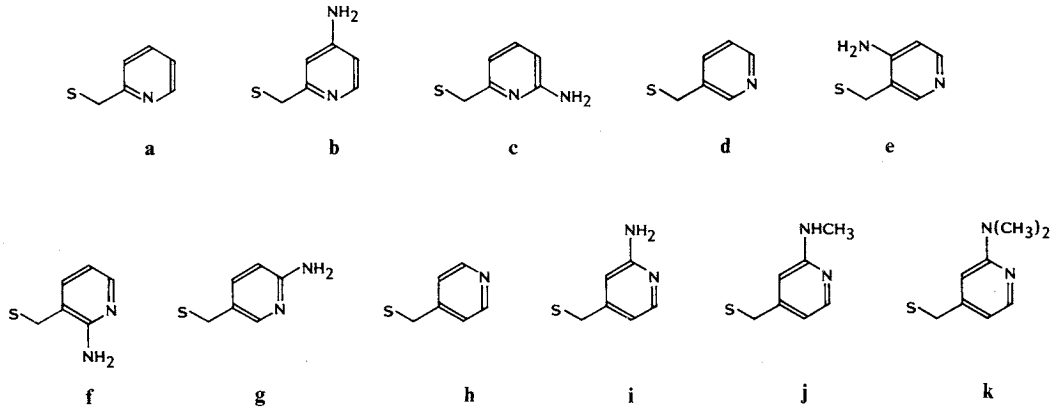


Thienamycin (**1**) R=H
Imipenem (**2**) R=HC=NH

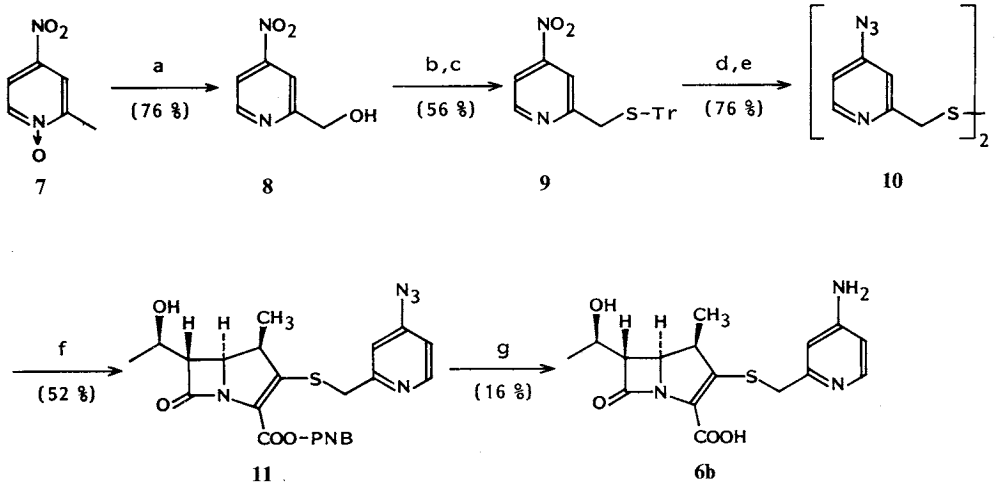
Scheme 1.



a) 2.1 equiv *iso*-Pr_2NEt, CH_3CN, 0°C, b) H_2, 10% Pd-C, THF, EtOH, H_2O ($NaHCO_3$).



Scheme 2.



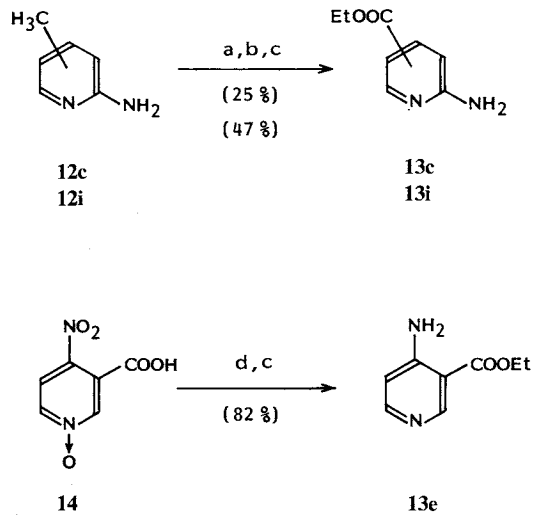
a) TFAA, CH_2Cl_2, b) TosCl, 4-dimethylaminopyridine, CH_3CN, c) TrSH, *n*-BuLi, THF, d) LiN_3, DMF, e) I_2, AgO_2CCF_3, f) **3**, TrSH, *iso*-Pr_2NEt, CH_3CN, $-10°C$, g) H_2 (3.5 kg/cm^2), 10% Pd-C, BuOH, EtOAc, pH 7 buffer.

of the trityl protecting group gave the azide disulfide **10**. The mercaptan of **10** was generated *in situ* by treatment with trityl mercaptan and trapped with enol phosphate **3**. Trityl mercaptan is too hindered to compete in the addition-elimination reaction. With protected carbapenem **11** in hand, simultaneous removal of the *p*-nitrobenzyl ester protecting group and reduction of the azido to the desired amino group was accomplished by hydrogenation on a Parr shaker. 2-[(4-Amino-2-pyridyl)methylthio]carbapenem (**6b**) was purified by reverse phase chromatography and isolated by lyophilization.

The synthesis of the remaining aminopyridylmethylmercaptans proceeded through the corresponding esters. 2-Amino-6-carboethoxypyridine (**13c**) and 2-amino-4-carboethoxypyridine (**13i**) were prepared in three steps from the corresponding aminopicolines **12c** and **12i** in 25% and 47% overall yields, respectively (Scheme 3). The synthesis of esters **13f** and **13g** was accomplished by Fischer esterification of the commercially available 2- and 6-aminonicotinic acids with concentrated H_2SO_4 in ethanol-benzene. The synthesis of ethyl 4-aminonicotinate **13e** was accomplished in 82% yield by catalytic reduction of 3-carboxy-4-nitropyridine *N*-oxide (**14**)[21] followed by Fischer esterification as described above (Scheme 3).

With the aminopyridine esters readily available, a method was sought for the transformation of an ester to a thiol. A four step sequence was developed as depicted in Scheme 4. The yields were generally good and are listed in Table 1. The synthesis resulted in the isolation of the pyridinium hydrochloride salt which avoided a problematic base-catalyzed

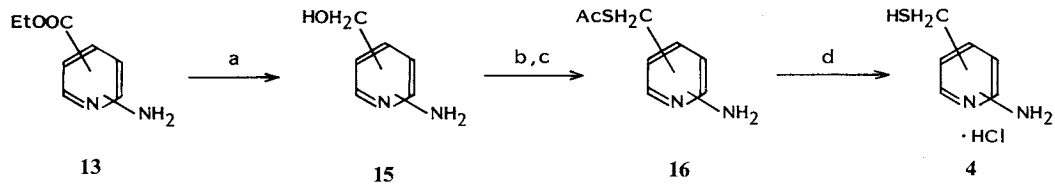
Scheme 3.



a) Ac_2O, $NaHCO_3$, THF, b) $KMnO_4$, H_2O, 90°C, c) EtOH, H_2SO_4, C_6H_6, reflux, d) H_2, 5% Pd-C, HOAc.

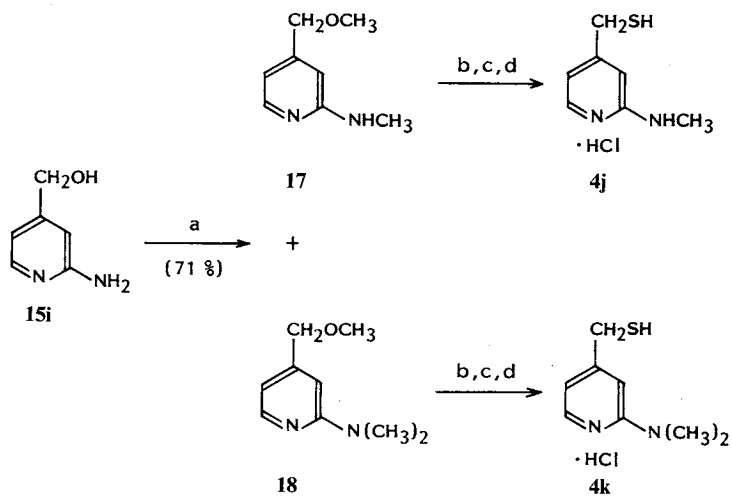
oxidative-dimerization to the disulfide. The ester **13** was reduced with lithium aluminum hydride (LAH) solution in THF to give the pyridylmethanol **15**. Solid LAH was inferior in these reductions giving little or no isolable alcohol. In the case of **13c**, neither LAH suspension nor solution gave any isolable product. This reduction was effectively carried out with lithium borohydride in THF in 96% yield. Heating the carbinol in 48% hydrobromic acid for several hours followed by removal of the excess HBr *in vacuo*, gave the pyridylmethylbromide hydrobromide salt. The crude product was immediately suspended in acetonitrile and treated with thiolacetic acid and sodium bicarbonate. The resultant thiol ester **16** was isolated and purified by silica gel chromatography. Removal of the acetyl group was effected by dissolution of **16** in methanol that contained hydrogen chloride. Evaporation of the solvent and trituration with ether gave the desired pyridylmethylmercaptan as a hydrochloride salt. A similar sequence could be applied to commercially available pyridylmethanols (**15d** and **15h**) to give

Scheme 4.



a) LAH ($LiBH_4$), THF, b) 48% HBr, 100°C, c) CH_3COSH, $NaHCO_3$, CH_3CN, d) HCl, MeOH.

Scheme 5.



a) MeI, NaH, *tert*-BuOH (cat), THF, b) 48% HBr, 90°C, c) CH_3COSH, $NaHCO_3$, CH_3CN, d) HCl, MeOH.

thiols **4d** and **4h**, respectively. Displacement of 2-picolyl chloride with thiolacetate and acidic removal of the acetate gave pyridylmethylmercaptan **4a** as a hydrochloride salt.

We wanted to prepare the monomethyl- and dimethylamino analogs (**6j** and **6k**) to evaluate the effect on potency of steric bulk placed next to the ring nitrogen. Thiols **4j** and **4k** were prepared starting with carbinol (**15i**). Alkylation of the dianion of **15i** with 3 equivalents of methyl iodide led to the isolation of methyl ethers **17** and **18** which were separable by silica gel chromatography (Scheme 5). Conditions for a controlled alkylation could not be found. Employment of the procedure described above for the alcohol to thiol transformation gave the desired compounds in good yield.

Coupling of the thiol hydrochlorides (**4a** and **4c**$\sim$**4k**) was accomplished by treatment of **4** and enol phosphate **3** with 2.1 equivalents of HUNIG's base in dry acetonitrile. The addition-elimination proceeded smoothly in most cases to give the 2-substituted carbapenem **5** after silica gel chromatography. Hydrogenolysis of the *p*-nitrobenzylcarboxylate with 10% Pd-C under one atmosphere of H_2 gave the desired carbapenems after purification by reverse phase chromatography. All of the final products except **6b** and **6e** were isolated as their sodium salts by performing the deblock in the presence of 1 equivalent of $NaHCO_3$. Compounds **6b** and **6e** were isolated as internal zwitterions. The yields for the sequence are listed in Table 1. All products gave satisfactory spectroscopic and/or analytical data.

The *in vitro* activity against a panel of Gram-positive and Gram-negative organisms determined by disc diffusion assay[22] using thienamycin or imipenem as an internal standard is summarized in Table 2. The zone sizes are converted to MIC's using the Humphrey-Lightbown equation.[23] The relative potency that is listed is the calculated ratio of the MIC's of **6** to thienamycin (**1**).[24] DHP-I susceptibility[8] is also listed in Table 2 and is the ratio of the susceptibility of substrate to that of thienamycin. Upon examination of the data, several conclusions can be drawn. First, 2-(pyridylmethylthio)carbapenems are potent antibiotics that possess better overall activity than thienamycin, especially against Gram-negative organisms, excluding *P. aeruginosa*. Secondly, as the basicity of the pyridine increases, a more balanced spectrum of activity is displayed. The more basic 4-aminopyridyl

Table 1. Yields (%) of carbapenems **6** and intermediates.

Analog	15	16	4	5	6
a	NA	—	49[a]	86	83
c	96	74	96	56	56
d	NA	71	100	90	59
e	61	71	100	25	48
f	99	68	100	67	53
g	99	57	100	54	72
h	NA	50	100	81	64
i	98	86	99	63	19
j	NA	74	97	34	44
k	NA	62	100	87	52

[a] Prepared starting with 2-picolyl chloride.
NA: Not applicable.
—: Not isolated.

Table 2. Antibiotic activity (relative potency) and DHP-I susceptibility of carbapenems **6**.[a]

Species[b]	a	b	c	d	e	f	g	h	i	j	k	1[c]
SA (4)	0.5	3.8	1.2	0.8	3.6	0.6	0.6	0.5	1.0	0.5	0.6	1 (0.04)
Ent (3)	0.9	2.4	1.5	0.9	3.2	2.0	1.4	1.0	1.8	1.6	1.3	1 (5)
EC (5)	2.1	3.0	3.8	5.8	4.3	5.0	4.8	2.3	8.2	3.7	1.3	1 (0.3)
Etb (6)	1.9	5.5	2.5	2.3	3.3	1.7	4.5	3.5	5.6	1.7	0.7	1 (1.4)
Klb (5)	0.8	4.5	2.1	2.1	3.9	2.3	3.9	1.4	6.8	2.1	0.6	1 (1.3)
Ser (2)	1.2	7.0	6.0	6.0	18	7.3	24	2.6	6.7	1.9	0.8	1 (2.5)
Pro (6)	11	4.4	13	10	6.3	17	22	7.5	21	6.4	2.0	1 (7.5)
PA (5)	0.03	0.4	0.05	0.04	0.2	0.04	0.04	0.03	0.04	0.03	0.03	1 (5.8)
DHP-I[c]	0.84	0.09	1.1	0.49	0.06	0.20	0.38	0.25	0.12	0.12	0.27	1
p*Ka*[d]	6.0	9.4	7.4	5.6	9.4	7.2	7.2	6.0	7.5	—	—	—

[a] See refs 8, 22$\sim$24.
[b] Number of strains given in parentheses. *SA*: *Staphylococcus aureus*, *Ent*: *Enterococcus* sp., *EC*: *Escherichia coli*, *Etb*: *Enterobacter* sp., *Klb*: *Klebsiella* sp., *Ser*: *Serratia* sp., *Pro*: *Proteus* sp., *PA*: *Pseudomonas aeruginosa*.
[c] DHP-I susceptibility is given relative to thienamycin = 1.0.
[d] p*Ka*'s of the conjugate acids of the corresponding picolines. See refs 14$\sim$17.
[e] The average MIC_{90}'s (μg/ml) for thienamycin are given in parentheses.

analogs (**6b** and **6e**) clearly show an increase in potency against *S. aureus* and *P. aeruginosa* compared to the 2-amino analogs and the unsubstituted pyridines. Thirdly, there is an inverse relationship between the basicity of the aminopyridine and the DHP-I susceptibility. Generally, as the basicity increases, the DHP-I susceptibility decreases (**6c** is an exception). Finally, increasing the bulk near the ring nitrogen as in compounds **6j** and **6k**, lowers the efficacy of these compounds as antibacterial agents. The utility of the 1β-methyl-2-[(aminopyridyl)methylthio]carbapenems warrants further investigation.

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JAMES M. BALKOVEC
MICHAEL J. SZYMONIFKA
JAMES V. HECK
RONALD W. RATCLIFFE

Department of Synthetic Chemical Research,
Merck Sharp and Dohme Research Laboratories,
Rahway, New Jersey 07065, U.S.A.

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