SYNTHESIS OF PENEMS AND THEIR ANTIBACTERIAL ACTIVITIES

Sir:

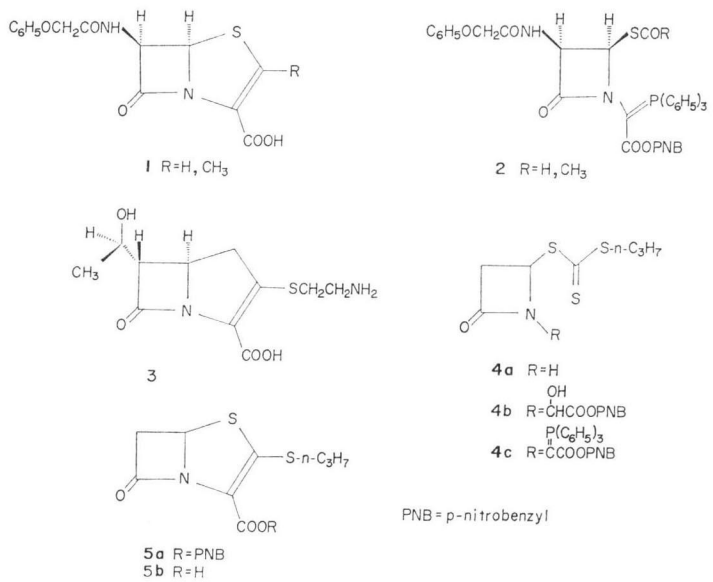
WOODWARD and his coworkers[1] were the first to synthesize penems (**1**) possessing thiazoline rings fused to β-lactams by using an intramolecular WITTIG reaction of 4-acylthioazetidinylphosphoranes (**2**) at the ring formation stage. Meanwhile, the structure of thienamycin, a β-lactam antibiotic of high antibacterial potency and a wide spectrum, has recently been disclosed as that of a 1-carbadethiapenem (**3**)[2], making the preparation of 2-(alkylthio)-penems even more attractive. Prompted by a recent report of a new synthetic approach to penems[3,4], we describe here the result of our studies on 2-alkylthio-substituted penems.

Sodium *n*-propyl trithiocarbonate, prepared by addition of carbon disulfide to a methanolic sodium *n*-propylmercaptide solution, was treated with a stoichiometric amount of 4-acetoxyazetidin-2-one[5] at room temperature to give the azetidinone trithiocarbonate* (**4a**) as fine yellow needles, mp 79~80°C (74% yield): IR (Nujol) 3210, 1759 cm^{-1}; NMR δ ($CDCl_3+D_2O$) 1.04 (3H, t, J=7 Hz), ~1.8 (2H, m), 3.05 (1H, dd, J=15.5, 2.5 Hz), 3.55 (1H, dd, J=15.5, 5 Hz), 3.42 (2H, t, J=7 Hz), 5.66 (1H, dd, J=5, 2.5 Hz). The azetidinone (**4a**) thus obtained was refluxed with *p*-nitrobenzyl glyoxylate in benzene to give the hemiaminal (**4b**) as a 1:1 epimeric mixture (75% yield) whose treatment with thionyl chloride in the presence of 2,6-lutidine followed by reaction with triphenylphosphine afforded the phosphorane (**4c**) as yellow prisms, mp 200~202°C (50% yield): IR (Nujol) 1759, 1657 cm^{-1}. Heating of the phosphorane (**4c**) in xylene at 130~135° for 14 hours gave 2-(propylthio)penem-3-carboxylate (**5a**) as fine needles, mp 150~151°C (57% yield): IR (Nujol) 1790, 1685 cm^{-1}; UV λ_{max}(ethanol) 262.2 nm (ϵ 16480), 339.5 nm (ϵ 11460); NMR δ ($CDCl_3$) 1.05 (3H, t, J=6.5 Hz), ~1.8 (2H, m), 2.98 (2H, t, J=7 Hz), 3.51 (1H, dd, J=16, 2Hz), 3.90 (1H, dd, J=16, 3.5 Hz), 5.26 (1H, d, J=14 Hz), 5.56 (1H, d, J=14 Hz), 5.77 (1H, dd, J=3.5, 2 Hz), 7.71 (2H, d), 8.32 (2H, d). The carboxylic acid (**5b**) was obtained as its sodium salt (powder) by shaking **5a** in hydrogen atmosphere over 10% palladium on charcoal in a buffer solution (pH 7) and was submitted to biological test.

Other 2-(alkylthio)penems as shown in Table 1 were also obtained from the corresponding mercaptans *via* analogous sequences. Penems possessing hydroxyl, amino or carboxylic acid groups in the side chain were obtained by starting from suitably protected mercaptans and by deprotection at a later stage of synthesis. Details will be reported in a forthcoming paper.

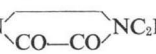
According to preliminary assays shown in Table 1, these 2-(alkylthio)penems have remarkable antibacterial activity against Gram-positive bacteria, resembling penicillins rather than cephalosporins. Further, these compounds are also active against some Gram-negative bacteria; however, they seem to show a weak activity against β-lactamase-producing bacteria. In general, introduction of hetero atoms in the side chain increased the activity of the penem molecule (No. 4, 5, 6, 8, 10, 11 and 16~19). Activity is also enhanced by the presence of more

Chart 1.



* All new compounds gave satisfactory elemental analyses.

Table 1. Minimum inhibitory concentrations of 2-(alkylthio)penem-3-carboxylic acids.

No.	2-Substituent	*S.a*(S)[a]	*S.a* (R)[b]	*E.c* (S)[c]	*E.c* (R)[d]	*S.f*[e]	*P.a*[f]	*K.p*[g]	*K.i*[h]	*P.v*[i]	*S.e*[j]
1	$-SCH_3$	0.4	0.4	3.1	50	3.1	>200	3.1	3.1	12.5	3.1
2	$-SCH_2CH_2CH_3$	0.4	1.5	1.5	>100	1.5	>100	6.2	6.2	12.5	1.5
3	$-SCH_2C_6H_5$	≤0.1	0.2	12.5	>200	3.1	>200	25	25	6.2	6.2
4	$-SCH_2CH_2OH$	0.4	1.5	0.8	100	0.8	>100	0.8	0.8	6.2	0.8
5	$-SCH_2CH_2CH_2OH$	0.2	0.8	0.8	100	0.8	>100	1.5	1.5	6.2	0.8
6	$-SCH_2CH_2OCOCH_3$	≤0.1	0.8	0.8	>50	0.8	>50	3.1	3.1	6.2	0.4
7	$-SCH_2CH_2CH_2OCOCH_3$	0.2	1.5	3.1	>100	1.5	>100	12.5	25	25	1.5
8	$-SCH_2CH_2OSO_2CH_3$	0.1	0.4	0.4	>200	0.8	>200	3.1	3.1	25	0.8
9	$-SCH_2CH_2OCOCOOCH_3$	0.4	1.5	0.4	>200	0.4	>200	1.5	0.8	6.2	0.4
10	$-SCH_2CH_2OCH_2CH_3$	0.2	0.8	0.4	200	0.4	>200	1.5	6.2	6.2	0.4
11	$-SCH_2CH_2SCH_3$	0.2	0.8	0.4	200	0.4	>200	1.5	3.1	12.5	0.4
12	$-SCH_2CH_2SCSN$	0.05	0.4	>100	>100	100	>100	>100	100	25	100
13	$-SCH_2CH_2SCSNH_2$	0.1	0.4	3.1	>50	1.5	>50	6.2	25	25	1.5
14	$-SCH_2CH_2COOH$	6.2	6.2	0.8	>100	1.5	>100	3.1	1.5	25	1.5
15	$-SCH_2CH_2COOC_2H_5$	≤0.1	0.4	6.2	>200	1.5	>200	6.2	12.5	25	1.5
16	$-SCH_2CH_2N_3$	≤0.1	0.8	0.4	100	0.4	>100	1.5	3.1	6.2	0.4
17	$-SCH_2CH_2NH_2$	0.2	0.8	1.5	50	1.5	100	3.1	3.1	6.2	1.5
18	$-SCH_2CH_2CH_2NH_2$	0.1	0.8	1.5	50	1.5	50	3.1	3.1	12.5	1.5
19	$-SCH_2CH_2NHCOCH_3$	0.8	3.1	0.8	>100	1.5	>100	3.1	1.5	25	1.5
20	$-SCH_2CH_2CH_2NHCOCH_3$	0.8	3.1	1.5	>100	1.5	>100	6.2	6.2	25	3.1
21	$-SCH_2CH_2NHCOCH_2C_6H_5$	0.4	1.5	1.5	>100	0.8	>100	6.2	50	6.2	1.5
22	$-SCH_2CH_2NHCOCHC_6H_4$-*p*-OH NH_2	0.8	3.1	1.5	>100	1.5	>100	3.1	12.5	25	3.1
23	$-SCH_2CH_2NHCON$  NC_2H_5	1.5	6.2	6.2	>100	6.2	>100	25	100	50	12.5
24	$-SCH_2CH_2NHCOC(=NOCH_3)CH_3$	0.8	3.1	6.2	>100	6.2	>100	25	50	50	12.5
	Ampicillin	≤0.1	1.5	3.1	>200	1.5	>200	50	6.2	1.5	0.4
	Cephalexin	0.8	3.1	6.2	6.2	12.5	>200	6.2	200	12.5	3.1

M.I.C. values are in mcg/ml, and were determined in heart infusion agar.

a) *Staphylococcus aureus* FDA 209P JC. b) *Staphylococcus aureus* 56 (PCase$^+$). c) *Escherichia coli* NIHJ JC-2. d) *Escherichia coli* 609 (CSase$^+$).

e) *Shigella flexneri* IID 642. f) *Pseudomonas aeruginosa* 1001. g) *Klebsiella pneumoniae* 806. h) *Klebsiella* sp. 846. i) *Proteus vulgaris* 1430.

j) *Salmonella enteritidis* G.

polar functions; for instance, the hydroxy group (No. 4 and 5) as compared to the acetoxy group (No. 6 and 7). Although most of these penems show no anti-*Pseudomonas* activity, penems possessing the amino function (No. 17 and 18) exhibit significant activity against *Pseudomonas aeruginosa*, suggesting a correlation between the cysteaminyl side chain of the thienamycin (**3**) and its excellent anti-*Pseudomonas* activity. Introduction of a bulky alkyl or acylamino groups or an ester function reduces activity against some Gram-negative bacteria (No. 3, 12, 15 and 21~24).

These penems were found to be unstable under long storage and their bioavailability seemed rather low considering that the urinary recovery of the penem No. 10 parenterally administrated to mice was only 5.8%.

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