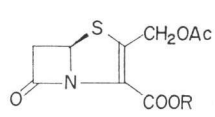
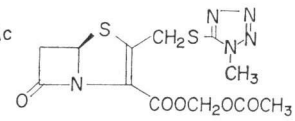
ANTIBACTERIAL ACTIVITY OF NOVEL BROAD-SPECTRUM "(5R)-PENEM" DERIVATIVES

Sir:

Recent investigations in the β-lactam field have been increasingly focused on the new "penem" family[1~3]. We wish to describe here the antibacterial activity of two novel structures which appear as new leads chemically derived from penicillins[4]. Optically active compounds **Ia, Ib** and **II** maintain the absolute configuration of natural β-lactam antibiotics and are in some way reminiscent of the cephalosporin functionality.



Ia: R=CH_2OCOCH_3
Ib: R=H



II

Antibacterial activities of **Ia** and **II** were tested *in vitro* by the agar dilution method after hydrolysis in fresh rat serum. The data reported in Table 1 indicate such compounds to display a remarkable and broad-spectrum antibiotic action. Since their hydrolysis rates were not determined before testing, we are presently unable to compare the intrinsic activity of the two derivatives and to establish their potency. However the latter can not certainly be lower than that expressed by the values found. The compounds, although ineffective on β-lactamase producing Gram-negative organisms, show high enough inhibitory activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Salmonella* strains to justify our interest in these structures.

Crude **Ib** was subsequently obtained[4] by hydrogenolysis of the corresponding *p*-nitrobenzyl-ester (see the Scheme) and characterised through its methyl ester (I.R., mass spectrum). The free acid was tested *in vitro* (MIC≤1 μg/ml against *S. aureus*) and proved to be also effective *in vivo* on the experimental infections (subcutaneous administration) of mice by *Shigella flexneri* $PD_{50}\leq$ 10 mg/kg, same order as cefazolin) and *Staphylococcus aureus*.

Scheme.

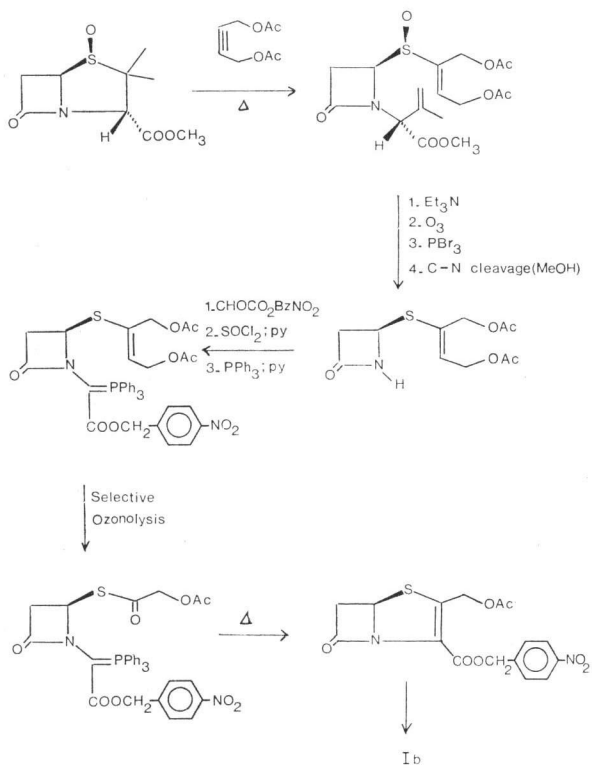


Table 1. Comparative *in vitro* activities of **Ia**, **II**, ampicillin and cefoxitin.

Strains	Minimum inhibitory concentration (μg/ml)			
	Ia	**II**	Ampicillin	Cefoxitin
Staphylococcus aureus FDA 209 P	0.39	0.39	≤0.19	0.78
〃 〃 153	1.56	0.78	1.56	0.78
〃 〃 PV 2	0.39	0.78	≤0.19	0.78
〃 〃 Smith ATCC 13709	≤0.19	0.39	≤0.19	0.78
Streptococcus pyogenes ATCC 12384	3.12	0.78	3.12	1.56
Escherichia coli B	1.56	0.78	0.39	1.56
〃 〃 B cef R	>100	—	>100	>100
〃 〃 V 14	1.56	0.78	1.56	3.12
〃 〃 V 23	3.12	0.78	3.12	12.5
Enterobacter cloacae 214	>100	—	>100	>100
〃 sp. V 19	12.5	>100	>100	12.5
Klebsiella pneumoniae ATCC 10031	—	3.12	50	0.78
〃 *aerogenes* 1082 E	>100	>100	>100	6.25
〃 sp. R 2	25	—	50	12.5
〃 〃 V 28	>100	>100	>100	12.5
〃 〃 V 29	>100	>100	>100	12.5
Proteus vulgaris V 15	3.12	6.25	1.56	0.78
〃 *mirabilis* V 15	0.39	0.78	≤0.19	0.78
〃 〃 525	3.12	0.78	0.39	1.56
Shigella flexneri	0.39	0.39	≤0.19	0.78
Pseudomonas aeruginosa	3.12	0.39	25	6.25
〃 〃 9229 B	>100	>100	>100	>100
Salmonella typhimurium	1.56	0.78	0.78	3.12
〃 *panamae* F 15	1.56	0.78	0.78	1.56
〃 *saint-paul* F 20	1.56	0.78	0.78	3.12
〃 *derby* F 14	3.12	0.78	0.78	3.12
〃 *montevideo* F 16	3.12	0.78	0.78	3.12

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