A NEW SEMISYNTHETIC ANALOGUE OF NOCARDICIN

Sir:

As a result of the discovery of the nocardicin family (**1**)[1], there has been considerable interest in the synthesis of nocardicin analogues with new side chains on β-lactam nitrogen atom[2~4]. Only few synthetic compounds have exhibited some antibacterial activity. Recently, the isolation of chlorocardicin[5] and formadicins[6] has enlarged the family of nocardicin-type monocyclic β-lactam antibiotics.

In connection with our study on penicillin transformation products as dipolarophiles[7], a new type of nocardicin analogue with antibiotic properties has been recently obtained.

In earlier reports, we have described[7] the 1,3-cyclo-addition of 2,6-dichlorobenzonitrile *N*-oxide to the exo-methylene group of 1,2-seco-penicillins and we have reported[8] the formation of oxazoline-azetidinone derivative (**2**) and benzothiazole sulfide (**3**) from Fuji disulfide adducts. When a single diastereomer of oxazoline-azetidinone (**2**, sodium salt) was cleaved with H_2 on Pd-C in water, followed by acidic extraction and chromatographic purification on silica gel, a diastereomer of nocardicin analogue (**4**) was obtained in high yield. The same compound was produced by Raney nickel desulfurization of benzothiazole sulfide derivative (**3**, sodium salt) in boiling water after extraction and chromatography on silica gel.

Since the configuration of the isoxazoline assymmetric center of the diastereomers of the starting materials has been established previously[9] and the reactions appeared not to isomerize the compounds, the substrate configurations are proposed for the diastereomers of nocardicin analogue (**4**). In addition, steric compression shift analysis of the two diastereomers of **4** generally follows that observed previously[9] for pairs of diastereomers of other adducts. Therefore, the *R* configuration of the isoxazoline C-5 is assigned to the product diastereomer with the downfield methyl protons and the *S* configuration to the other diastereomer.

Nocardicin analogue *R*-**4**: 71% yield from **2**, 78% from **3**, foams, Rf (acetone - ethanol, 3 : 1) 0.24; IR $\tilde{\nu}_{co}$ (KBr) cm^{-1} 1735, 1721, 1675; ^1H NMR (100 MHz, DMSO-d_6) δ 1.92 (3H, s, CH_3), 3.15 (1H, dd, J=2 and 6 Hz, 4-H$_\beta$), 3.17 and 3.35 (2H, dd, AB, J=19 Hz, isoxazoline CH_2), 3.69 (2H, s, CH_2Ph), 3.81 (1H, dd, J=4.5 and 6 Hz, 4-H$_\alpha$), 4.71 (1H, s, CHCOO), 4.94 (1H, dd, J=2 and 4.5 Hz, 3-H$_\alpha$), 7.1~7.15 (5H, m, C_6H_5), 7.32~7.37 (3H, m, $C_6H_3Cl_2$); *Anal* calcd for $C_{23}H_{21}N_3O_5Cl_2$ (MW 490.37): C 56.33, H 4.33, N 8.57; found: C 56.30, H 4.36, N 8.48.

Nocardicin analogue *S*-**4**: 68% yield from **2**,

Scheme 1.

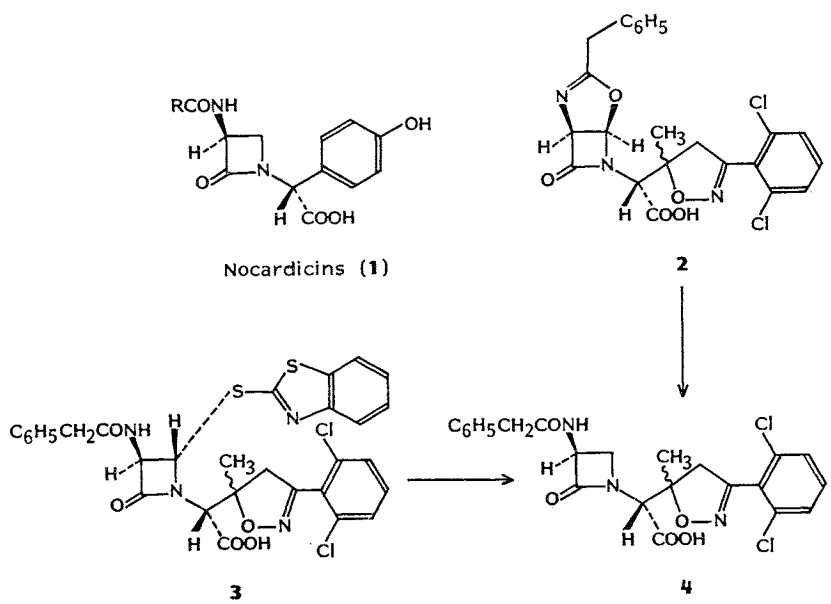

Table 1. Antibacterial activity of nocardicin analogue *R*-4.

Test organisms	MIC (μg/ml)	
	Ampicillin	*R*-4
Staphylococcus aureus 5664		8
S. aureus 548		31
S. aureus 50	62.5	125
S. aureus 56	62.5	125
Bacillus subtilis 9524	0.025	3.12
B. cereus 19637		500
Proteus vulgaris 8067		8
Alcaligenes faecalis 8750		31
Proteus mirabilis 123/76		62.5
Klebsiella pneumoniae 602	100	100
Escherichia coli 10536		125
E. coli 308/52		500
Streptococcus faecalis 6782	1.56	>100
Pseudomonas aeruginosa 37	>100	>100
Brucella bronchiseptica 8344		>500
Serratia marcescens 89		>500
Enterobacter cloacae 169/83	125	>500
Candida albicans 102		>500

Test was conducted in Müller-Hinton agar, pH 8.0.

80% from **3**, foams, Rf (acetone - ethanol, 3 : 1) 0.26; IR $\tilde{\nu}_{co}$ (KBr) cm^{-1} 1733, 1720, 1674; ^1H NMR (100 MHz, DMSO-d_6) δ 1.89 (3H, s, CH_3), 3.1~3.9 (4H, m, 4-CH_2 and isoxazoline CH_2), 3.71 (2H, s, CH_2Ph), 4.7~4.9 (m, CHCOO, 3-H_α and moisture), 7.1~7.15 (5H, m, C_6H_5), 7.3~7.4 (3H, m, $C_6H_3Cl_2$); *Anal* calcd for $C_{23}H_{21}N_3O_5Cl_2$ (MW 490.37): C 56.33, H 4.33, N 8.57; found: C 56.21, H 4.40, N 8.58.

The nocardicin analogue with the *R* configuration at the isoxazoline assymmetric center *R*-4 exhibited some activity against Gram-positive and Gram-negative bacteria as shown in Table 1; in addition, when mixed 1 : 1 with ampicillin, this compound decreased the MICs of ampicillin by a factor of 2 against ampicillin-resistant strains of *Staphylococcus aureus* 50 and 56, as well as *Enterobacter cloacae* 169/83. The *S* diastereomer of nocardicin analogue *S*-4 showed the same β-lactamases inhibition against *S. aureus* 50 and *E. cloacae* 169/83 but, in contrast to its *R* counterpart, *S*-4 was devoided of antibacterial activity.

In spite of relatively high MICs values, which may be due to the conditions of their determination[10] or to the nature of the amide side chain, transformations of secopenicillins and nitrile *N*-oxides or other 1,3-dipolar adducts may be a valuable method for preparation of nocardicin analogues of a new type. The ability of the secopenicillin exo-methylene group to form 1,3-dipolar cycloaddition products, bearing two chiral centers of proper configuration in relation to nocardicins, makes penicillin a convenient source of the monocyclic β-lactam antibiotics nucleus.

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