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ATTEMPTED SYNTHESIS OF QUINONEMETHINE DERIVATIVE OF NOCARDICIN A ANALOGUES

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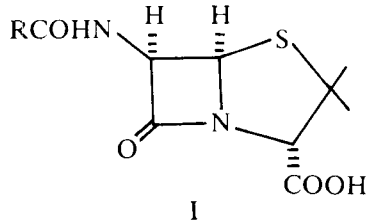
Abstract

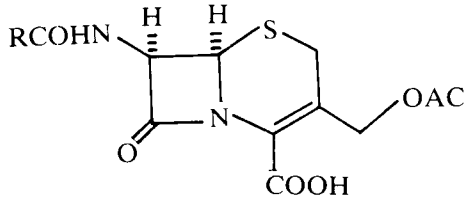
The synthesis of some ß-lactams is described. The electronic activation of monocyclic ß-lactams provided by a quinonemethine function was found to instabilize the ß-lactam ring toward nucleophilic attack by water.

The essential features of the classical ß-lactam antibiotics penicillin **I** and cephalosporin **II** are (*a*) a *cis*-fused ß- lactam ring; (*b*) an acylamino side chain which can be considerably varied; (*c*) an acidic function; (*d*) a five-membered ring or a six-membered ring containing a double bond conjugated with the ß- lactam nitrogen conferring enough ring strain so as to raise the ß-lactam frequency to $\geq 1765\ cm^{-1}$. It has been shown that the sulfur atom can be replaced by oxygen or carbon without substantial loss of antimicrobial activity [1].

The IR. absorption frequency of the carbonyl of a ß-lactam can also be considered as a measure of its reactivity towards nucleophilic attack [2], therefore higher frequency might indicate the potential for higher biological activity. The synthesis of several monocyclic nuclear analogues of ß-lactam antibiotics, in which the ring strain of fused ß-lactams was replaced by electronic activation has been reported [3,4].

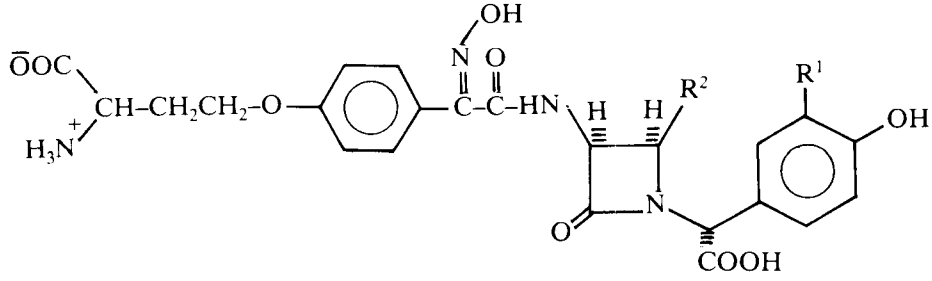


I



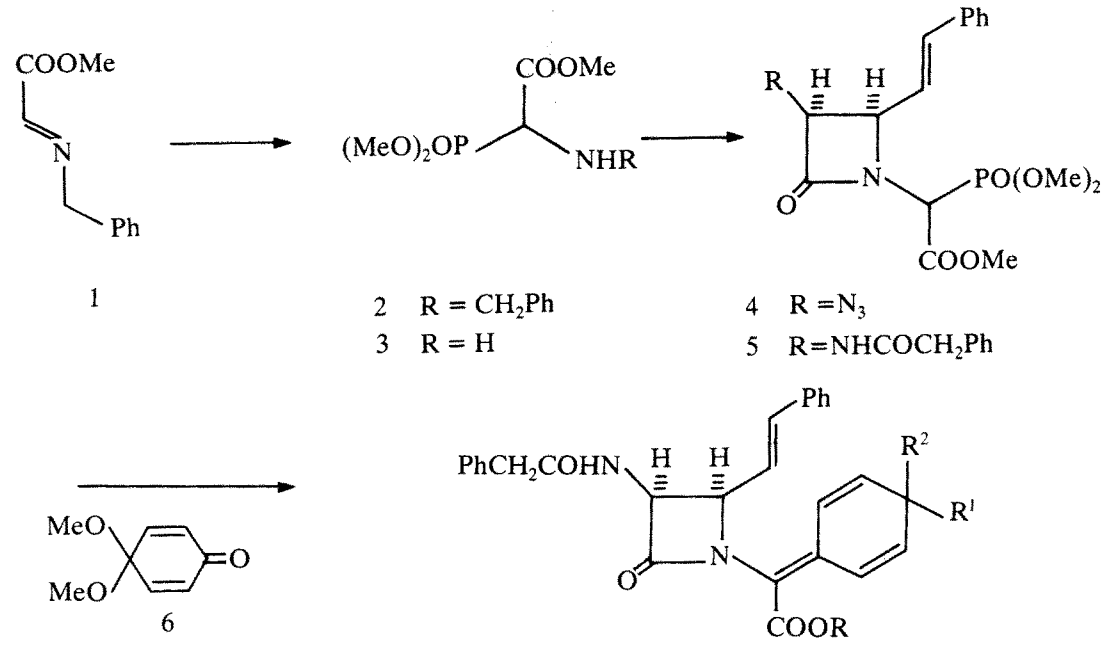
II

Nocardicin A [5] **III**, the first monocyclic ß-lactam antibiotic described, is remarkably active against Gram-negative organisms *in vivo* [6] although it



III $R^1 = H, R^2 = H$

IV $R^1 = OH, R^2 = CH_2OH$



displays but little activity *in vitro* [7,8]. It differs from all hitherto described ß-lactam antibiotics, 1770-1780 cm^{-1}, in having a relatively unstrained (1725 cm^{-1}) ß-lactam ring, and therefore being quite stable towards nucleophilic attack. It occured to us that the *in vivo* activation may well be linked to an oxidation of nocardicin A to the corresponding quinonemethine, in which the ß-lactam frequency should be considerably augmented, thus leading to a chemically and therefore perhaps biologically reactive lactam. Due to the difficulties in preparing quinonemethines [9], we reported [10,11] nocardicin analogues bearing two orto-related hydroxyl groups in which an *in vivo* and/or an *in vitro* oxidation to an ortho-quinone may be more easily achieved. The prepared compound **IV** showed no significant antibacterial activity *in vitro*. However, this does not rule out the aforementioned *vivo* oxidation, of nocardicin A, presumption.

We now report an attempt for the synthesis of ß-lactam **8**, in which the electronic activaton is provided by an quinonemethine function. Schiff base **1** was prepared [12] in high yield from benzylamine and methyl glyoxylate [13]. A t-butanol solution of **1** was treated for 1 h with one equiv. of dimethylphosphite and one equiv. of potassium t-butoxide to afford benzylamine **2** (50%). Catalytic debenzylation of its hydrochloride salt provided methyl *a*-aminodimethylphosphonoacetate **3** (80%). Compound **3** was converted to its cinnamylidine Schiff base which upon treatment with azidoacetyl chloride [14] using the methods described by Doyle et al [15], gave ß-lactam **4** as a mixture of epimers at the carboxyl bearing carbon. The ß-lactam obtained by this method was *cis* fused, as could be determined by NMR. (J=5 Hz) of all derivatives in which the relevant protons did not overlap with other signals. The azide function in **4** was reduced with H_2S/NEt_3[16], and the resulting amine directly acylated with phenylacetyl chloride in the presence of pyridine to give amide **5** (70%). Reaction of **5** with **6** by means of NaH in tetrahydrofuran (THF) at -15° afforded ß-lactam **7** (~ 15%). Although compound **7** in methanol was unstable and the ß-lactam ring function was opened within 5 to 10 min., in water it was found to be more stable (T/2 5h).

All attempts to convert **7** to the corresponding quinonemethine **8** resulted in the destruction of the ß-lactam ring.

Experimental Section

General Procedure: See ref. 17.

Benzylaminophosphonate **2.** To a solution of methyl glyoxylate (0.88 g, 0.01 mol) in 50 ml dry CH_2Cl_2

was added benzyl amine (1.07 g, 0.01 mol) and $MgSO_4$. After stirring for 20 h, it was filtered and evaporated to yield Schiff base **1** quantitatively as an oil. NMR. ($CDCl_3$): δ 7.64 (m, lH, N=CH), 7.43 (s, 5H, Ph), 4.91 (d, 2H, CH_2, J=lHz), 4.10 (s, 3H, Me). IR. (CH_2Cl_2): 1735, 1711, 1643 cm^{-1}.

To a solution of **1** (1.77 g, 0.01 mol) and dimethyl phosphite (1.10g, 0.01 mol) in 30 ml t-butanol, t-BuOK (1.12 g, 0.0l mol) was added. After stirring for 2 h, it was evaporated to dryness and the residue was dissolved in ether, washed with water and dried ($MgSO_4$). Filtration and evaporation gave crude product **2**. Purification by column chromatography using Al_2O_3, and elution with $CHCl_3$ gave **2** in 50% yield. NMR. ($CDCl_3$): δ 7.35 (s, 5H, Ph), 3.85-4.50 (3s, 9H, 3Me), 3.79 (d, 2H, CH_2, J=2 Hz), 3.58 (d, 1H, CH, J=20 Hz), 2.37 (b, 1H, NH, exchangeable with D_20). IR. (CH_2Cl_2): 3230-3550, 1729 cm^{-1}. MS: 287 (M^+).

2.HCL was prepared by the addition of a saturated ethereal solution of HCL to an ethereal solution of compound **2.**

Methyl a-amino-a-dimethylphosphonoacetate (3). Compound 2. HCl (3.225 g, 0.01 mol) was dissolved in 60 ml oxygen free methanol. Pd/C (10%, 0.4 g) was added, and the mixture was hydrogenated at 25°C and 45 Psi for 3 h. The solution was then filtered and evaporated to afford a compound **3.HCl** (80%). NMR. ($CDCl_3$): δ 8.51-8.95 (b, 3H, $NH_3^+Cl^-$, exchanged with D_20), 5.05 (d, 1H, CH, J=20 Hz), 3.90-4.49 (3s, 9H, 3Me).

Conversion of **3.HCl** to aminophosphonate **3** was achieved by addition of an aq. solution of K_2HPO_4 (PH=9.3, 10ml) to 1.5 g **3.HCL**, followed by extraction with EtOAc. The organic layer was dried ($MgSO_4$), filtered and evaporated to give **3** (80%). NMR. ($CDCl_3$): δ 3.85 -4.35 (3s, 9H, 3Me), 4.01 (d, lH, CH, J=20 Hz), 2.25 (b, 2H, NH_2, exchanged with D_2O). IR. (CH_2Cl_2): 3350-3410, 1738 cm^{-1}. CI.-MS.: 198 (M^++1).

Preparation of methyl 2-(3-azido-2-Oxo-4-styryl-1-azetidinyl)- 2- dimethylphosphonatoacetate (4). To a solution of aminophosphonate (**3**, 1.97 g, 0.01 mol) in 40 ml dry CH_2Cl_2 was added cinnamaldehyde (1.6 g, 0.012 mol), and magnesium sulfate (10 g) After stirring at 25°C for 3 h the mixture was filtered. Triethylamine (1.01 g, 0.01 mol) was added, followed by the dropwise addition of azidoacetyl chloride (1.20g, 0.01 mol) at 25°C. After stirring for 1 h, the solution was washed with water, dried and evaporated to give the crude ß-lactam which was purified by column chromatography on silica gel. Elution with CH_2Cl_2 gave 3 g (80%) of the oily azido ß-lactam **4** as a mixture of two diastereoisomers. NMR. ($CDCl_3$): δ 7.35 (m, 5H, Ph), 6.12-6.98 (m, 2H, CH=CH), 4.91 (m, 2H, H-C (3,4)), 4.80 (d, J=22 Hz, 1H, CH), 3.58-4.21 (m, 9H, 3Me). IR (CH_2Cl_2): 2100 (N_3), 1765 (ß-lactam), 1745 (ester) cm^{-1}. CI.-MS.: 395 (M^++1).

Preparation of methyl 2-(2-Oxo- 3- Phenylacetamido-4- styryl-1-azetidinyl)-2-dimethylphosphonatoacetate (5). Triethylamine (0.6 g, 0.006 mol) was added to a solution of a diastereoisomeric mixture of **4** (1.97 g, 0.005 mol) in 50 ml of dry CH_2Cl_2 at O°C and H_2S was bubbled in for 35 min. The solution was allowed to stand for 2 h at 25°C. Nitrogen was bubbled in for 30 min. Then was added (1.3 g, 0.015 mol) pyridine, followed by the dropwise addition of 0.9 g (0.006 mol) phenylacetyl chloride in 20 ml CH_2Cl_2. The solution was stirred for 2 h at 25°C, then washed with 10% HCl, 10% of $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to give the impure amide **5** which was chromatographed on silica gel. CH_2Cl_2 eluted impurities, and $CHCl_3$/EtOAc (1:5) gave 2.31 g (90%) of ß-lactam **5**, a mixture of diastereoisomers, as an oil. NMR. ($CDCl)_3$): δ 7.81 (d, 1H, NH), 7.35 (s, 5H, Ph–C=C), 7.03 (s, 5H, Ph), 5.88-6.89 (m, 2H, CH=CH), 5.40-5.63 (m, lH, CHN), 4.63-5.35 (m, 2H, PCH and CH-C=C), 3.68-4.12 (m, 9H, 3Me), 3. 46 (s, 2H, CH_2Ph). IR. (CH_2 Cl_2): 3410 (NH), 1770 (ß-lactam), 1740 (ester), 1685 (amide) cm^{-1}. CI.–MS.: 458 (M^++1).

Preparation of ß-lactam 7. To a solution of **5** (4.57g, 0.01 mol) and **6** (1.54g, 0.01 mol) in 70 ml THF at -15°C was added NaH (0.01 mol). The solution was stirred for 2 h at the same temperature and then at 25°C for a further 4 h. The reaction mixture was quenched with aq. NH_4CL-solution and extracted with CH_2Cl_2. The crude product was purified with silica gel using CH_2Cl_2 as eluent to afford ß-lactam **7** in about 15% yield. NMR. ($CDCl_3$): δ 7.72 (d, lH, NH), 5.91-7.39 (m, l6H, 2Ph and 6 CH=C), 5.45 (d x d, J=5 and 10 Hz, lH, H-C (3)), 4.89 (br., lH, H-C(4)), 4.00-4.50 (3s, 9H, Me), 3.61 (s, 2H, CH_2Ph). IR. (CH_2CL_2): 3400 (NH), 1800 (ß- lactam), 1756 (ester), 1680(amide).

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