# EM5400, A FAMILY OF MONOBACTAM ANTIBIOTICS PRODUCED BY *AGROBACTERIUM RADIOBACTER*

## II. ISOLATION AND STRUCTURE DETERMINATION

WILLIAM L. PARKER and MARLENE L. RATHNUM

The Squibb Institute for Medical Research
P.O. Box 4000, Princeton, New Jersey 08540, U.S.A.

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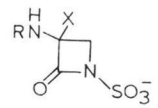
*Agrobacterium radiobacter* produces a mixture of monocyclic β-lactam antibiotics that belong to a recently discovered class called monobactams. Five components of this mixture have been isolated and structures **6**～**10** assigned.

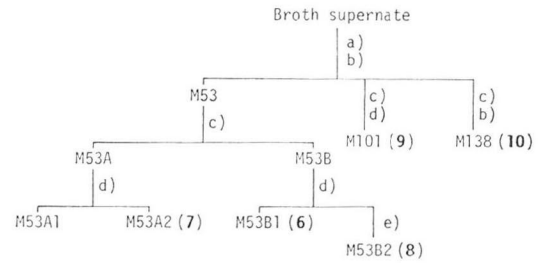
The monobactams are a new class of antibiotics that has recently been discovered independently by workers at Takeda Chemical Industries[1,2] and at the Squibb Institute for Medical Research.[3~5] This class consists of monocyclic β-lactam antibiotics that are *N*-acyl derivatives of (*S*)-3-aminomonobactamic acid (**1**) or (*R*)-3-amino-3-methoxymonobactamic acid (**2**). All monobactams discovered to date are produced by bacteria. The first members of this class to be reported are sulfazecin (**3**)[1,2], isosulfazecin (**4**)[1] and SQ 26,180 (**5**)[3~5]. We wish to report a group of monobactams, EM5400, produced by *Agrobacterium radiobacter* SC 11,742. A preliminary account of this work has been published[3]. The production and detection of EM5400, the biological properties of the individual components and the characterization of the producing organism are described in the accompanying publication[6].

EM5400 is resolved by electrophoresis at pH 7.0 and 1.9 into three zones (detected with *Bacillus licheniformis* SC 9262) having mobilities relative to vitamin $B_{12}$ (0) and nosylate anion (100) of 53, 101 and 138. The undiminished mobility at pH 1.9 indicates that the EM5400 components, like SQ 26,180, are all strongly acidic. Five components of EM5400 were isolated as shown in Fig. 1 and their structures determined. The designations for the components are based on the electrophoretic mobilities. Other related components were clearly present but quantities of pure material sufficient for characteri-



| | R | X |
|---|---|---|
| **1** | H | H |
| **2** | H | $CH_3O$ |
| **3** | γ-D-Glu-D-Ala | $CH_3O$ |
| **4** | γ-D-Glu-L-Ala | $CH_3O$ |
| **5** | $CH_3CO$ | $CH_3O$ |

Fig. 1. Isolation of EM5400 components.




a) Ion-pair extraction
b) Chromatography on Sephadex G-10
c) Chromatography on QAE Sephadex
d) Chromatography on CHP20P
e) Chromatography of $Bu_4N^+$ salts on silica gel

Table 1. $^1$H NMR data in $D_2O$.

| Position number | $\delta$ ($J$ Hz) | | | | | |
|---|---|---|---|---|---|---|
| | **5** | **6** | **7** | **8** | **9** | **10** |
| 2 | | *ca.* 4.85 (m) | | | | |
| 3 | 3.98 (s) | $\alpha$ 3.85 (5.8, 5.8)<br>$\beta$ 3.44 (2.9, 5.6) | 3.82 (6.7)<br>3.72 (6.7) | 3.80 (s) | 3.94 (s) | 3.94 (s) |
| 4 | 3.50 (s) | | 3.36 (s) | 3.35 (s) | 3.43 (s) | 3.42 (s) |
| 6 | 2.09 (s) | 4.46 (7.7, 7.7) | 4.51 (7.1, 8.5) | 4.44 (7, 7) | obscured | 4.83 (7.0) |
| 7 | | 2.97 (7.6) | 3.1 (m) | 2.97 (8.8) | 5.08 (6.8) | 5.57 (7.0) |
| 9 | | 7.12 (8.8) | | 7.12 (8.5) | 7.37*(9) | 7.38*(9.0) |
| 10 | | 6.85 (8.8) | 7.35 (s) | 6.85 (8.5) | 7.46*(9) | 7.51*(9.0) |
| 11 | | | | | | |
| 13 | | 1.98 (s) | 2.01 (s) | 2.00 (s) | 1.95 (s) | 1.94 (s) |

$\delta$: ppm down field from TSP (sodium 3-trimethylsilylpropionate-2,2,3,3-$d_4$) using HDO (4.73 ppm) or dioxane (3.76 ppm) as internal standards.
* Assignments may be interchanged.

Table 2. $^{13}$C NMR data.

| Position number | $\delta$ | | | | | |
|---|---|---|---|---|---|---|
| | **5**[a] | **6** | **7** | **8** | **9** | **10** |
| 1 | 160.5 (s) | 166.5 (s) | 162.3 | 162.4 | 162.8 (s) | 162.5 (s) |
| 2 | 89.5 (s) | 55.6 (d)* | 91.2 | 91.5 | 91.8 (s) | 91.7 (s) |
| 3 | 53.1 (t) | 48.5 (t) | 55.1* | 55.1* | 55.1* | 55.2 (t) |
| 4 | 51.8 (q) | | 53.7* | 53.8* | 54.0* | 54.0* |
| 5 | 170.5 (s) | 174.4 (s)# | 174.9 | 174.8 | 172.6 (s)# | 171.2 (s)# |
| 6 | 22.5 (q) | 56.2 (d)* | 56.3* | | | |
| 7 | | 37.1 (t) | 38.0 | | 73.3 (d) | 79.3 (d) |
| 8 | | 128.9 (s) | 136.6 | 128.4 | 131.4 | 134.4 (s) |
| 9 | | 131.4 (d) | 129.7# | | 128.8 (d) | 129.2 (d) |
| 10 | | 116.3 (d) | 130.0# | | 122.5 (d) | 122.4 (d) |
| 11 | | 155.4 (s) | 128.3 | | 152.1 (s) | 152.3 (s) |
| 12 | | 174.7 (s)# | 174.9 | | 174.6 (s)# | 174.4 (s)# |
| 13 | | 22.5 (q) | 22.4 | | 22.5 (q) | 22.5 (q) |

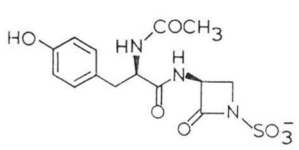
$\delta$: ppm down field from TMS, using dioxane (67.4 ppm) as an internal standard for spectra taken in $D_2O$ (**6**~**10**) and TMS (0.0 ppm) for the spectrum of **5** taken in DMSO-$d_6$.
*, #: Assignments may be interchanged.
[a] Reference 5.

zation were not obtained. The $^1$H and $^{13}$C NMR spectra of the EM5400 components and SQ 26,180 are listed in Tables 1 and 2 and other characterization data are listed in Table 3.

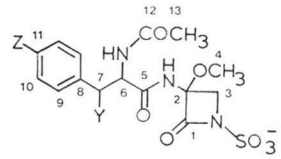
The component giving the most robust response with *B. licheniformis* was M53B1. The infrared spectrum of M53B1 has absorption characteristic of $\beta$-lactam carbonyl (1761 cm$^{-1}$), secondary amide (1654 cm$^{-1}$) and sulfamic acid groups (1238 and 1045 cm$^{-1}$). The UV spectrum in water (276 nm) and 0.1 N NaOH (294 nm) indicated the presence of a phenol. Hydrolysis in 6 N HCl at 117°C for 3 hours gave a mixture of amino acids that was separated by ion-exchange chromatography into D-tyrosine and L-diaminopropionic acid. The presence of an acetyl group was apparent from the NMR spectra and thus structure **6** was readily derived for M53B1. This assignment was supported by synthesis of M53B1

Table 3. Properties of EM5400 components.

| | **6** (M53B1) | | **7** (M53A2) | | **8** (M53B2) | | **9** (M101) | | **10** (M138) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Analysis (%) | Found. | Calcd. | Found. | Calcd. | Found. | Calcd. | Found. | Calcd. | Found. | Calcd. |
| C | 40.89 | 41.07 | 43.85 | 44.22 | 32.99 | 41.00 | 32.17 | 33.28 | 28.63 | 28.00 |
| H | 4.08 | 3.94 | 4.62 | 4.46 | 3.61 | 4.13 | 3.43 | 3.16 | 2.90 | 2.51 |
| N | 10.21 | 10.26 | 10.08 | 10.31 | 7.53 | 9.56 | 8.05 | 7.76 | 6.88 | 6.53 |
| S | 7.81 | 7.83 | 7.82 | 7.87 | ND | 7.29 | 11.88 | 11.84 | 14.97 | 14.95 |
| Na | — | — | 5.8 | 5.64 | — | — | 9.29 | 8.49 | 10.6 | 10.72 |
| K | 9.36 | 9.55 | — | — | 16.69 | 8.90 | — | — | — | — |
| Empirical formula | $C_{14}H_{16}N_3O_7SK$ | | $C_{15}H_{19}N_3O_7SNa$ | | $C_{15}H_{18}N_3O_8SK$ | | $C_{15}H_{17}N_3O_{12}S_2Na_2$ | | $C_{15}H_{16}N_3O_{15}S_3Na_3$ | |
| $[\alpha]_D^{21}$ ($H_2O$) | −15.9° (*c* 1) | | +12.3° (*c* 1) | | +12.1° (*c* 0.77) | | +5.5° (*c* 1) | | −17.8° (*c* 1) | |
| UV (nm) $H_2O$ ($E^{1\%}$) | 223 (249)<br>276 ( 33) | | 251 (sh, 11.8)<br>258 (10.9)<br>264 (9.3)<br>267 (sh, 8.3) | | 222 (sh, 171)<br>275 (22) | | 260 (sh, 7)<br>266 (sh, 6.4)<br>273 (sh, 4.3) | | 260 (sh, 7.8) | |
| dilute NaOH | 244 (270)<br>293 ( 54) | | | | 244 (175)<br>293 ( 36) | | decomposes | | | |
| IR ($cm^{-1}$) in KBr | 3350, 1761, 1654, 1515, 1238, 1045, 639 | | 3334, 1764, 1654, 1519, 1243, 1044, 634 | | 3320, 1771, 1655, 1515, 1245, 1047, 631 | | 3380, 1765, 1645, 1515, 1240, 1048, 866, 629 | | 3470, 1757, 1647, 1501, 1228, 1040, 837, 616, 578 | |
| TLC, silica gel, 2-BuOH - $H_2O$ - HOAc, 3:1:1, 37°C | Rf 0.35 | | Rf 0.41 | | Rf 0.50 | | Rf 0.25 | | Rf 0.17 | |



**6** (M53B1, SQ 26,700)

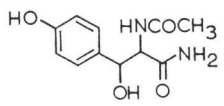


| | Y | Z | |
|---|---|---|---|
| **7** | H | H | (M53A2, SQ 26,823) |
| **8** | H | OH | (M53B2, SQ 26,875) |
| **9** | OH | $OSO_3^-$ | (M101, SQ 26,970) |
| **10** | $OSO_3^-$ | $OSO_3^-$ | (M138, SQ 26,812) |

from *N*-acetyl-D-tyrosine[7] and **1**[8], the synthetic and natural materials being indistinguishable from each other by chromatography, spectroscopy (IR, NMR, UV) and optical rotation. M53B1 is particularly noteworthy in that it is the only naturally-occurring monobactam known to date that lacks a methoxyl group in the 3 position.

Structures **7**~**10** were derived for components M53A2, M53B2, M101 and M138 from their $^1H$ and $^{13}C$ NMR spectra in comparison to those of M53B1 and SQ 26,180. Acid hydrolysis of M53A2 and M53B2 (6 N HCl, 107°C, 19 hours) gave phenylalanine and tyrosine, respectively, identified by TLC of the dansyl derivatives[9]. M101 and M138 are derivatives of the unusual amino acid, β-hydroxytyrosine. This amino acid was of interest as a possible biogenetic precursor of norepinephrine and epinephrine and has been prepared synthetically[10]. To the best of our knowledge, it has been reported as a naturally-occurring substance only in the vancomycin group of antibiotics. Vigorous acid hydrolysis of M138 (6 N HCl, 105°C, 3 hours) resulted in destruction of the β-hydroxytyrosine moiety[11] but gave sulfate (as the Ba salt) in 93% yield based on the elemental analysis. Milder hydrolysis conditions

(0.1 N HCl, 100°C, 0.5 hour) gave a fragment identified as **11** by NMR and mass spectroscopy. The relative and absolute stereochemistry have not been determined.



**11**

EM5400 thus constitutes a group of monobactam antibiotics that are all closely related in structure. None of these antibiotics has a high level of antimicrobial activity and the most highly charged component, M138, is nearly devoid of activity although it is produced in relative abundance. The question of what role these weak antibiotics perform for the producing organism is certainly intriguing. EM5400 and the previously reported monobactams do, however, provide an intellectual starting point that has led to synthetic analogs with superb antimicrobial activity and great potential for clinical use[12].

## Experimental

NMR spectra were determined on Varian Associates model XL-100-15 and JEOL Ltd. model FX60Q spectrometers. Infrared spectra were recorded on a Perkin-Elmer model 621 spectrometer. Rotations were measured on a Perkin-Elmer model 141 polarimeter. Elemental analyses were performed on dried samples (50°~70°C for 1 hour *in vacuo*). Rotations and UV spectra were determined on samples equilibrated with atmospheric moisture (containing 5~12% water by weight) and no corrections were applied. Mass spectra were determined on an AEI MS-902 double-focusing mass spectrometer.

### Isolation of EM5400 Components

At harvest, a 250-liter tank fermentation of *Agrobacterium radiobacter* SC 11,742 was adjusted to pH 4 (HCl) and the cells separated by centrifugation. The supernatant (220 liters) was extracted with 40 liters of 0.05 M cetyldimethylbenzylammonium chloride in $CH_2Cl_2$ and the extract concentrated *in vacuo* to 5.5 liters. The concentrate was extracted at pH 4.35 ($H_3PO_4$) with 2 liters of 1 M aqueous NaSCN and two 500-ml portions of 0.7 M NaSCN. The combined aqueous extract was concentrated *in vacuo* and methanol-insoluble material removed and discarded.

The resulting solid (194 g) was chromatographed on a 2.1-liter column of Sephadex G-10 (Pharmacia Fine Chemicals), eluting with MeOH - $H_2O$, 2: 1 to give 3.37 g of crude M53 and 135 g of a mixture of M53, M101, M138 and NaSCN. The mixture was triturated at 0~5°C with 135 ml of MeOH and the soluble portion (58 g) chromatographed on a 2.1-liter column of Sephadex G-10 eluting with water. This gave partial separation of M138, M101, M53 and full separation of NaSCN. Cross-contaminated fractions were combined and rechromatographed as above, finally resulting in a total of 3.5 g of crude M53, 1.43 g of crude M101 and 5.76 g of crude M138.

Chromatography of crude M53 on a 270-ml column of QAE Sephadex A-25 ($NO_3^-$ form) eluting with 5 liters of a 0~0.25 M linear gradient of $NaNO_3$ gave M53A and M53B. These two fractions were partially desalted by trituration with methanol and then chromatographed on a 100-ml column of 75~150 $\mu$ CHP20P (Mitsubishi Chemical Industries) eluting with water. M53A gave 9.6 mg of impure M-53A1 (not further characterized) and 51.9 mg of M53A2, **7**, sodium 3-(2-acetamido-3-phenylpropionamido)-3-methoxy-2-oxoazetidine-1-sulfonate. The components of M53B were desalted but not well resolved from each other. The mixture (202 mg) was converted to the potassium salt on Dowex 50 ($K^+$ form) and rechromatographed on a 265-ml column of CHP20P. Elution with water gave 106 mg of M53B1, **6**, potassium (3*S*)-3-[(*R*)-2-acetamido-3-(4-hydroxyphenyl)propionamido]-2-oxoazetidine-1-sulfonate. Further elution with a gradient of methanol in water gave 86 mg of a mixture of M53B1 and M53B2. This mixture was dissolved in 84 ml of 0.5 M aqueous tetrabutylammonium sulfate and the solution was taken to dryness *in vacuo*. The residue was triturated with $CH_2Cl_2$ and the soluble portion (222 mg) chromatographed on a 120-ml column of silica gel (Mallinckrodt SilicAR CC-4), eluting with $CH_2Cl_2$ containing 0~40% MeOH. Fractions containing M53B2 (detected by TLC on silica gel eluting with $CH_2Cl_2$ - MeOH, 4: 1) were combined, giving 105 mg of the $Bu_4N^+$ salt. This was converted to the K salt with Dowex 50 ($K^+$ form), giving 53 mg of M53B2, **8**, potassium 3-[2-acetamido-3-(4-

hydroxyphenyl)propionamido]-3-methoxy-2-oxoazetidine-1-sulfonate. M53B2 was contaminated to the extent of *ca.* 20% with inorganic material, judging from the analysis and spectra. An additional 42 mg of M53B1 was also obtained.

Crude M101 was chromatographed on a 120-ml column of QAE Sephadex ($NO_3^-$ form), eluting with 2 liters of a 0~1 M linear gradient of $NaNO_3$. Fractions containing M101 were combined, partially desalted by trituration with methanol and then chromatographed on a 2.1-liter column of Sephadex G-10 eluting with water. The resulting material (364 mg) was further purified by chromatography on a 1.1-liter column of CHP20P, eluting with water, to give 135 mg of M101, **9**, dipotassium 3-[2-acetamido-3-hydroxy-3-(4-sulfooxyphenyl)propionamido]-3-methoxy-2-oxoazetidine-1-sulfonate. A small impure sample of a minor M101 component was also obtained but was not characterized.

Crude M138 was chromatographed on a 130-ml column of QAE Sephadex ($NO_3^-$ form) eluting with 4 liters of a 0~2 M linear gradient of $NaNO_3$. Fractions containing M138 were combined, concentrated and partially desalted by trituration with methanol. The methanol-soluble material was chromatographed on a 2-liter column of Sephadex G-10, eluting with water, to give 2.54 g of M138, **10**, trisodium 3-[2-acetamido-3-sulfooxy-3-(4-sulfooxyphenyl)propionamido]-3-methoxy-2-oxoazetidine-1-sulfonate.

Hydrolysis of M53B1 (**6**)

A solution of 18.9 mg of M53B in 1 ml of 6 N HCl was heated at 117°C for 3 hours and then concentrated *in vacuo*. The residue was chromatographed on a 1.1×26-cm column of BioRad AG 50W-X2 resin (100~200 mesh, pyridinium form) eluting with a linear gradient prepared from 5% HOAc and 2 M pyridinium acetate, giving 5.8 mg of tyrosine, $[\alpha]_D^{21}+9.5°$ (*c* 0.5, 88% $HCO_2H$) and 10.1 mg of diaminopropionic acid isolated as the dihydrochloride, $[\alpha]_D^{22}+6.0°$ (*c* 0.88, 1 N HCl). The rotations of authentic L-tyrosine and L-diaminopropionic acid dihydrochloride under these conditions are −12.9° and +20.5°, respectively. The NMR spectra of the hydrolysis products were identical to those of authentic material. The diaminopropionic acid is clearly not very pure although the NMR spectrum shows no proton-containing impurities.

Synthesis of M53B1 (**6**)

Tetrabutylammonium (3*S*)-benzyloxycarbonylamino-2-oxoazetidine-1-sulfonate[8] (124 mg, 0.25 mmole) in 5 ml of DMF was hydrogenated in the presence of 40 mg of 10% Pd on charcoal. The catalyst was removed and the resulting solution treated with 56 mg (0.25 mmole) of *N*-acetyl-D-tyrosine[7], 52 mg (0.38 mmole) of 1-hydroxybenzotriazole and 52 mg (0.25 mmole) of dicyclohexylcarbodiimide. After 22 hours at 20°C, the solvent was removed *in vacuo* and the residue triturated with 4 ml of acetone. The resulting solution was treated with 85 mg (0.25 mmole) of perfluorobutanesulfonic acid potassium salt dissolved in 1 ml of acetone and diluted with 5 ml of ether. The resulting precipitate (94 mg) was dissolved in water and chromatographed on a 100-ml column of CHP20P. Elution with water gave 29.0 mg of **6**, $[\alpha]_D^{23}-16.0°$ (*c* 1, $H_2O$), indistinguishable from the natural material by IR, NMR, and UV spectroscopy and by TLC and electrophoresis. Both the synthetic and natural **6** were found to crystallize (with some difficulty) from methanol. Crystallization of 24 mg of synthetic **6** from methanol gave 6 mg of crystals.

*Anal.* Calcd. for $C_{14}H_{16}N_3O_7SK \cdot \frac{1}{2}H_2O$: C 40.18, H 4.10, N 10.04
Found. C 39.99, H 4.26, N 9.94

Hydrolysis of M138 (**10**)

A solution of 101 mg of M138 in 5 ml of 0.1 N HCl was heated at 100°C for 0.5 hour. The resulting solution was passed through a 2-g column of Dowex 50W-X2 ($H^+$ form), washing with water. The effluent was concentrated to 5 ml and passed through a 2-g column of BioRad AG 1-X2 ($Cl^-$ form), washing with water and 0.1 N HCl in MeOH - $H_2O$, 1: 1. The effluent was concentrated and the residue, 29.6 mg, purified by preparative TLC, eluting with $CHCl_3$ - MeOH, 4: 1. A fluorescence-quenching band, Rf 0.28~0.41, was collected, giving 8.3 mg of amorphous solid **11**: NMR ($CD_3CO_2D$) $\delta$ 1.92 (s, impurity), 2.03 (s), 4.87 (d, $J$=4.4 Hz), 4.91 (s, impurity), 5.23 (d, $J$=4.4 Hz), 6.81 (d, $J$=8.7 Hz) and 7.23 ppm (d, $J$=8.7 Hz); IR (KBr) 3290, 1657, 1611 and 1514 $cm^{-1}$; low resolution mass spectrum, *m/z* (relative intensity): 220 (1, $M^+-H_2O$), 202 (39), 178 (20), 133 (68), 122 (81), 121 (100), 107 (32), 93 (32), 73 (64), 65 (37), 43 (87); high resolution mass spectrum of the tetrakis(trimethylsilyl) derivative:

calculated for $C_{22}H_{43}N_2O_4Si_4$ ($M^+-CH_3$), 511.2300; found, 511.2244.

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