A Novel Synthetic Method for Penicillanic Acid Derivatives by Electroreduction

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Electroreductive dehalogenation of 6-halopenicillanic acid derivatives was conveniently carried out to give the corresponding penicillanic acid derivatives, key intermediates in syntheses of various β-lactamase inhibitors, in good yields.

Keywords—penicillanic acid; sulbactam; β-lactamase inhibitor; 6-halopenicillanic acid; electroreduction; dehalogenation; prodrg

Penicillanic acid (6a) and its esters (6b, c, e) are key intermediates in syntheses of β-lactamase inhibitors such as sulbactam (1a),1) YTR-830,2) etc. and their prodrugs, e.g., 1b.3) Penicillanic acid (6a) and its simple ester were prepared by the reductive dehalogenation of 6,6-dibromo (4a) or 6-bromopenicillanic acid (9a) and their esters, respectively.4) However, in our synthesis of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl penicillanate 1,1-dioxide (1b), a useful prodrug of sulbactam, the reduction of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 6,6-dibromopenicillanate (4b) by catalytic hydrogenation using palladium on calcium carbonate4b) was found to be impractical.5) Thus far, several reduction methods of 6-halopenicillanic acid 1,1-dioxide have been reported, including catalytic hydrogenation,5) and zinc-,6) magnesium-,7) cadmium-promoted8) reductions, but these methods gave unsatisfactory results in the reduction of 4b. Thus, a new reduction method, widely applicable to 6-halopenicillanic acid derivatives, has been required.

Electroreduction is generally considered to be more attractive than metal-promoted reduction involving electron transfer because of the following features: 1) it is applicable to a variety of compounds by changing the electrode potential; 2) it can be done under various conditions (acidic, basic, neutral); 3) it is a clean reaction, without the use of any reducing reagent, thus being suitable for large-scale preparation. Although extensive studies on electroreduction of simple alkyl of aromatic halides have been reported,9) there have been few
papers concerning electroreduction of \(\beta\)-lactam derivatives such as penicillin.\textsuperscript{10} Therefore, we wish to report herein our results on electroreduction of 6-halopenicillanic acid derivatives.

The electrolysis was in principle performed in methanol (MeOH) containing tetraethyl-

ammonium \(p\)-toluenesulfonate (Et\(_4\)NOTs) as a supporting electrolyte at 0—5 \(^\circ\)C using a beaker-type divided cell equipped with a ceramic cylinder as a diaphragm under the constant-
current conditions. At first, we tried the electroreduction of 6,6-dibromopenicillanic acid (4a). Electricity (6—7 F/mol) was passed through the system until 4a was consumed. After usual work-up, penicillanic acid (6a), the dehalogenated product, was obtained as a sole product (Table I, entry 1). Using a carbon rod as an anode, we then studied the effect of cathode material to find a suitable cathode for the electroreduction of 4a. A lead cathode gave the best yield as shown in Table I.

Next, electroreduction of 4a in water was examined, because water (having high
electroconductance) was considered to be superior in current efficiency, as well as being the
cheapest solvent. Further, an expensive electrolyte such as Et\(_4\)NOTs was not always needed in
electroreduction in water. The reduction of 4a was complete after passing 5 F/mol of
electricity, and penicillanic acid (6a) was obtained in 74\% yield. It is recognized\textsuperscript{11} that
electroreduction of halogeno compounds generally involves competitive reactions between
simple dehalogenation (halogen atoms are substituted by protons) and dimerization, and the
ratio of the products depends on reaction conditions such as electrode potential, character of
the solvent, cathode material, etc. In the electroreduction of 4a, however, the simple reduction
product, penicillanic acid (6a), was obtained in good yield, and the corresponding dimer was
not detected.

In order to improve the total yield of penicillanic acid (6a) from 6-aminopenicillanic acid
(6-APA), a one-pot-like electroreduction of 4a was carried out in water without isolation of 4a
prepared by two-phase diazotization/bromination of 6-APA. In this direct method, the
potassium salt of 6a was obtained from 6-APA in 66\% yield (average of five runs). When 4a
was isolated as an intermediate, the overall yield of 6a from 6-APA was 57\% (average of five
runs). In this manner, penicillanic acid (6a) could be obtained easily, and this direct method
has afforded an efficient preparation of penicillanic acid.

Next we tried the electroreduction of 4b, which has a labile ester residue, the (5-methyl-
2-oxo-1,3-dioxol-4-yl)methoxycarbonyl group. Electrolyses were performed in \(N, N\)-di-
methylformamide (DMF) containing Et\(_4\)NOTs as a supporting electrolyte at 0—5 \(^\circ\)C in a
similar manner. At first a lead plate was used as the cathode, and a carbon rod as the anode.
After 8.0 F/mol of electricity had been passed through the system, the reaction mixture was
analyzed by thin layer chromatography (TLC). A small amount of penicillanic acid (6a) was
found on TLC, but the desired penicillanate (6b) could not be obtained, and mostly the
decomposition of 6,6-dibromopenicillanate (4b) took place. These facts suggested that the
initially generated radical and/or carbamion intermediates\textsuperscript{12} might decompose because of an
insufficient amount of proton source and that formation of a small amount of 6a was due to
base-catalyzed hydrolysis of 6b in the neighborhood of the cathode. Therefore, acetic acid
(AcOH) was added to the solvent as a proton donor and a buffer agent in order to prevent
cleavage of the ester bond. In the presence of AcOH the electroreduction of 4b under the same
conditions was carried out successfully to give penicillanate (6b) in 40\% yield without
formation of penicillanic acid (6a) (Table I, entry 7). Furthermore, addition of methanol
(MeOH) to the solvent raised the yield of the penicillanate (6b) to 55\% (Table I, entry 8).
From further investigations, optimum reaction conditions were revealed to be as follows; a
copper plate as the cathode, and a mixture of DMF, AcOH and MeOH as the solvent (Table
I, entries 10, 11).

This electroreduction was also applied to the dehalogenation of other 6-halopenicillanic
acid derivatives including sulfoxide and sulfone to find its scope and limitations. The results are
summarized in Tables I, II and III. It seems noteworthy that electroreduction of 6-halopenicillanic acid derivatives (2—4, 7—11) to the corresponding penicillanic acid derivatives (1, 5, 6) occurred easily in good yield irrespective of the oxidation level of the 1-sulfur atom. Both 6-chloropenicillanic acid (11a) and its ester (11b) were easily reduced to 6a and 6b, respectively, in good yields similarly to 6-chloropenicillanate 1,1-dioxide (10b), as shown in Table III. In addition it is interesting that sulfone and sulfoxide groups at the 1-position are inert under these electroreduction conditions. On the other hand, by the use of catalytic hydrogenation or zinc-promoted reduction, sulfone derivatives (2, 7 and 10) are reduced more easily than sulfoxide (3 and 8) and sulfide (4, 9 and 11) derivatives, and the reduction of sulfide

**Table I. Electroreduction of 6,6-Dibromopenicillanic Acid Derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>n</th>
<th>Conditiona</th>
<th>Cathode</th>
<th>Amount of current (F/mol)</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>A</td>
<td>Pt</td>
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<td>6a</td>
<td>73</td>
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<td>—</td>
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<td>1b</td>
<td>64</td>
</tr>
</tbody>
</table>

a) A. MeOH-Et$_3$NOTTs; B. H$_2$O-K$_2$HPO$_4$; C. DMF-Et$_3$NOTTs; D. DMF/MeOH-Et$_3$NOTTs; E. DMF/MeOH/MeOH-Et$_3$NOTTs.

**Table II. Electroreduction of 6-Bromopenicillanic Acid Derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>n</th>
<th>Conditiona</th>
<th>Cathode</th>
<th>Amount of current (F/mol)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>B</td>
<td>Pb</td>
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<td>1a</td>
<td>75</td>
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<td>7b</td>
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<td>E</td>
<td>Cu</td>
<td>5.7</td>
<td>1b</td>
<td>73</td>
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<td>3</td>
<td>7e</td>
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<td>E</td>
<td>Pb</td>
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<td>1e</td>
<td>67</td>
</tr>
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<td>4</td>
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<td>Cu</td>
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<td>6b</td>
<td>55</td>
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</table>

a) B. H$_2$O-K$_2$HPO$_4$; E. DMF/MeOH-MeOH-Et$_3$NOTTs.
TABLE III. Electroreduction of 6-Chloropenicillanic Acid Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
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<th>Condition</th>
<th>Cathode</th>
<th>Amount of current (F/mol)</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
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<td>11b</td>
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<td>E</td>
<td>Pb</td>
<td>7</td>
<td>6b</td>
<td>53</td>
</tr>
</tbody>
</table>

a) B, H₂O-K₂HPO₄; E, DMF/AcOH/MeOH-Et₄NOTs.

derivatives (4, 9 and 11) is most difficult.¹³,¹⁴ In particular, 6-chloropenicillanic acid derivatives (11) could hardly be reduced to the corresponding penicillanic acid derivatives by catalytic hydrogenation.⁴⁶ These facts clearly show that electroreduction is superior to catalytic hydrogenation or metal-promoted reduction in its applicability to a wide range of compounds.

Ease of electroreduction of alkyl halides decreases in the following order; dibromomethane > monobromomethane > monochloromethane.⁹¹ This tendency is also observed in the electroreduction of 6-halopenicillanic acid derivatives, judging from the current efficiency.

As another application of this electrolysis, we investigated one-pot reduction/oxidation of 6,6-dibromopenicillanic acid (4a) without a diaphragm to obtain penicillanic acid 1-oxide (5a) or 1,1-dioxide (1a). Neither 5a nor 1a could be formed without complex decomposition of the starting 4a. Hence, a diaphragm was required for electroreduction of 6-halopenicillanic acid derivatives.

From the viewpoints of good yield, wide range of application, simple procedure and low cost, the present electroreduction seems to possess high potential for the synthesis of β-lactam derivatives by a reduction method. Further work is in progress.

Experimental

Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured on a Nihon Denshi PS-100 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded with a Shimadzu IR-440 spectrometer.

Materials——6-Halopenicillanic acids, 2a, ⁶ 4a, ⁷ 7a, ⁸ 7e, ⁹ 9a and ¹¹ 11a were prepared by the reported procedures. Syntheses of the esters 2b, ⁷ 4b, ⁷ 8b and ⁷ 9b were reported in our previous paper, and ⁹ 4c and ⁷ 4d were obtained in the same way. The other esters, ¹⁰ 10b and ¹¹ 11b, were prepared by the esterification of 6-halopenicillanic acid, and the sulfoxide 3b was obtained by the oxidation of 4b with 30% H₂O₂. The physical properties of new compounds were as follows.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6,6-Dibromopenicillanate 1-Oxide (3b)——mp 116—118°C. IR νmax cm⁻¹: 1820, 1815, 1805, 1755 (C=O). ¹H-NMR (CDCl₃): 1.42 (3H, s, 2-CH₃), 1.59 (3H, s, 2-CH₃), 2.23 (3H, s, C=CH₂), 4.64 (1H, s, 3-H), 4.98 (2H, s, C=CH₂). Anal. Caled for C₁₃H₁₅Br₂N₂O₅S: C, 32.04; H, 2.69; N, 2.88. Found: C, 32.26; H, 2.75; N, 2.98.

(5-Pheny1-2-oxo-1,3-dioxol-4-yl)methyl 6,6-Dibromopenicillanate (4c)——mp 95—97°C. IR νmax cm⁻¹: 1825, 1790, 1745 (C=O). ¹H-NMR (CDCl₃): 1.50 (3H, s, 2-CH₃), 1.66 (3H, s, 2-CH₃), 4.63 (1H, s, 3-H), 5.22 (2H, s, C=CH₂), 5.80 (1H, s, 5-H), 7.4—7.68 (5H, m, arom. H). Anal. Caled for C₁₆H₁₃Br₂N₂O₅S: C, 40.55; H, 2.84; N, 2.63. Found: C, 40.48; H, 2.95; N, 2.56.

(5-Terr-Buty1-2-oxo-1,3-dioxol-4-yl)methyl 6,6-Dibromopenicillanate (4d)——IR νmax cm⁻¹: 1830, 1780, 1760 (C=O). ¹H-NMR (CDCl₃): 1.35 (9H, s, C(CH₃)₃), 1.46 (3H, s, 2-CH₃), 1.61 (3H, s, 2-CH₃), 4.58 (1H, s, 3-H), 5.08.
(2H, s, C=CCH_3), 5.77 (1H, s, 5-H).

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6a-Chloropenicillanate 1,1-Dioxide (10b)—mp 90—92°C. IR ν_max cm⁻¹: 1825, 1807, 1762 (C=O). 1H-NMR (CDCl₃): 1.40 (3H, s, 2-CH₃), 1.62 (3H, s, 2-CH₃), 2.22 (3H, s, C=CCH_3), 4.45 (1H, s, 3-H), 4.65 (1H, d, J = 1.5 Hz, 6-H), 4.99 (2H, s, C=CCH_3), 5.17 (1H, d, J = 1.5 Hz, 5-H).

**Anal.** Calcd for C₁₃H₁₀ClNO₃S: C, 41.10; H, 3.72; N, 3.69. Found: C, 41.10; H, 3.76; N, 3.61.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 6b-Chloropenicillanate (11b)—mp 92—95°C. IR ν_max cm⁻¹: 1830, 1810, 1780, 1740 (C=O). 1H-NMR (CDCl₃): 1.42 (3H, s, 2-CH₃), 1.60 (3H, s, 2-CH₃), 2.18 (3H, s, C=CCH₃), 4.57 (1H, s, 3-H), 4.77 (1H, d, J = 1.5 Hz, 6-H), 4.95 (2H, s, C=CCH₃), 5.33 (1H, d, J = 1.5 Hz, 5-H).

**Anal.** Calcd for C₁₃H₁₀ClNO₃S: C, 44.90; H, 4.06; N, 4.03. Found: C, 45.08; H, 4.01; N, 4.15.

**General Procedure for Electroreduction**—Electroreduction was carried out at 0—10°C in a beaker-type cell separated by a ceramic cylinder diaphragm (30 ml), which was fitted with a cathode (Pt or Cu plate) outside the cylinder and an anode (carbon rod, Pt or Pb) inside the cylinder. Constant current (current density; 2—20 mA/cm²) was supplied by a Takasago PM-13R GP 050-2 device, until most of the starting materials had disappeared (checked by TLC or high performance liquid chromatography). The catholytes were worked up in the usual manner. The results are summarized in Tables I, II and III. A few examples of electroreduction are given below.

**Electroreduction of 4a**—A mixture of MeOH (40 ml) and Et₄N OTS (2.5 g) was added to both the cathodic and anodic compartments and 4a (1.0 g) was added to the catholyte. Electrolysis was carried out at 13.3 mA/cm² using a Pb cathode (5 × 5 cm²) and a carbon rod anode (8 mm diameter × 10 cm). After 7.0 F/mol of electricity had been passed, the catholytes were poured into a stirred mixture of AcOEt (40 ml) and saturated aqueous NaCl (20 ml) at 5°C. The pH of the mixture was adjusted to 1.5 with 6 N HCl. The organic layer was separated and the aqueous layer was extracted with AcOEt (20 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried over MgSO₄, and concentrated under reduced pressure to 1/3 volume. A solution of potassium acetate (0.3 g) in MeOH (10 ml) was added, and the mixture was concentrated again under reduced pressure to 1/2 volume and stored at 5°C overnight. The solid was filtered off and washed with ether to give 0.5 g of 6a potassium salt as colorless crystals in 75% yield. IR ν_max cm⁻¹: 1765, 1610 (C=O). 1H-NMR (DMSO-d₆): 1.44 (3H, s, 2-CH₃), 1.54 (3H, s, 2-CH₃), 2.81 (1H, dd, J = 2, 16 Hz, 6-H), 3.45 (1H, dd, J = 4, 16 Hz, 6-H), 3.88 (1H, s, 3-H), 5.12 (1H, dd, J = 2, 4 Hz, 5-H).

**Anal.** Calcd for C₁₀H₁₂KNO₃S: C, 40.15; H, 4.21; N, 5.85. Found: C, 39.93; H, 4.20; N, 5.83.

**Electroreduction of 4b**—A mixture of DMF (100 ml), AcOH (25 ml), MeOH (20 ml) and Et₄N OTS (40 g) was added to the cathodic compartment, a mixture of MeOH (15 ml) and Et₄N OTS (3 g) was added to the anodic compartment, and 4b (10 g) was added into the catholyte. Electrolysis was carried out at 2.3 mA/cm² using a Cu cathode (8.2 × 15.5 cm²) and a carbon rod anode (8 mm diameter × 10 cm). After 8.0 F/mol of electricity had been passed, the catholyte was poured into a stirred mixture of AcOEt (200 ml) and water. The organic layer was separated and washed with 5% aqueous NaCl, dried over MgSO₄, and concentrated under reduced pressure to give a syrup. The syrup was purified by column chromatography on silica gel using chloroform as an eluent to afford 6b (4.0 g, 60% yield) as a syrup, which crystallized from ether–hexane. The physical properties were in accord with the literature values.³¹

**One-Pot-Like Synthesis of 6a from 6-APA**—Bromine (4.8 ml), 2.5 N sulfuric acid (40 ml) and sodium nitrite (5.4 g) were added to dichloromethane (80 ml) with stirring at 0°C. 6-APA (12 g) was added portionwise over a period of 20 min at 5—10°C. The resultant solution was stirred at 5°C for 30 min. Aqueous 5% sodium thiosulfate was added dropwise at 5—10°C until the bromine color was discharged. The organic layer was separated and the anodic layer was extracted with dichloromethane (20 ml). Water was added to the combined organic layer, and the mixture was stirred vigorously at 5°C. The pH of the mixture was adjusted to 7.3 with saturated aqueous NaHCO₃. The aqueous layer was separated and the organic layer was extracted with water (40 ml). The pH of the combined aqueous layer was adjusted to 7.0 with 2 N HCl. This aqueous solution was added into the cathodic compartment and saturated aqueous NaHCO₃ (20 ml) was added into the anodic compartment. Electrolysis was carried out at 4.3 mA/cm² using a Pb cathode (14 × 10 cm²) and a Pt anode (1.5 × 1.5 cm²). After 3 F/mol of electricity had been passed, the catholyte was worked up in the same manner as for the electroreduction of 4a. The potassium salt of 6a was obtained as colorless crystals (8.8 g, 66%). The physical properties were in accordance with the assigned structure.

**References and Notes**

10) During this study, electroreduction of 3-haloazetidinone\(^{a}\) and 3-chlorocephem\(^{b}\) was reported. \(a\) M. A. Casadei and F. M. Moracci, J. Chem. Soc., Perkin Trans. 2, 1986, 419; \(b\) E. Lilly, UK Patent Appl. 2105720 (1983) [Chem. Abstr., 99, 70460 (1983)].