

0040-4039(95)02110-8

**NUCLEOSIDES AND NUCLEOTIDE. 145.1**  
**SYNTHESIS OF 2'-DEOXY AND 5'-PHOSPHATE DERIVATIVES OF BREDININ.**  
**A PHOTOCHEMICAL IMIDAZOLE-RING CLEAVAGE AND SUBSEQUENT**  
**RECONSTRUCTION OF THE BASE MOIETY**

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**Abstract:** 2'-Deoxy and 5'-phosphate derivatives of bredinin (2 and 3, respectively) were synthesized. UV irradiation of bredinin with a mercury lamp in aqueous HCl gave the imidazole-ring cleavage product 7 in high yield, which was converted to 2'-deoxy derivative 13. Reconstruction of the imidazole ring of 13 with (EtO)<sub>3</sub>CH and subsequent deprotection afforded the desired 2'-deoxybredinin (2). Similarly, bredinin 5'-phosphate (3) was synthesized via the photo-product 17.

Bredinin (1), an imidazole nucleoside antibiotic,<sup>2</sup> is a clinically useful immunosuppressant<sup>3,4</sup> especially for transplantation of viscera<sup>3a,b</sup> and autoimmune disease such as rheumatism.<sup>3c</sup> Bredinin as well as its analogues are also known to have antitumor effects in experimental tumor models.<sup>5</sup> Recently, a significant antiviral effect of bredinin was also reported.<sup>6</sup> Accordingly, chemical modification studies of bredinin to develop compounds with efficient pharmacological effects are important. However, the derivatization of bredinin by the usual methods known in nucleoside chemistry is troublesome<sup>5a,7</sup> probably due to its unusual zwitterionic structure of the base moiety.<sup>8</sup> Therefore, only a few studies on derivatives of 1 have been reported in spite of its biological interest.

Previously, we reported the synthesis of bredinin from 5-amino-4-carbamoylimidazole-1-β-D-ribofuranoside (AICAR, 5) via ribofuranosyl-3-aminomalonyamide (7) which was generated by a novel photochemical imidazole-ring cleavage reaction of AICAR (5).<sup>5a,7</sup> Although 7 or its tri-*O*-acetate 8 were also efficient intermediates for preparing various bredinin derivatives,<sup>5a</sup> the yields of 7 and 8 were low (about 30%) and these were obtained on only a 100-mg scale by one reaction.<sup>5a,7</sup> In this paper, we describe the efficient preparation of 7, 8, and the corresponding acetone 17 from bredinin by a photochemical reaction, and their conversion to bredinin derivatives of biological importance, namely 2'-deoxybredinin (2) and bredinin 5'-phosphate (3) via a reconstruction reaction of the base moiety.

Chart 1

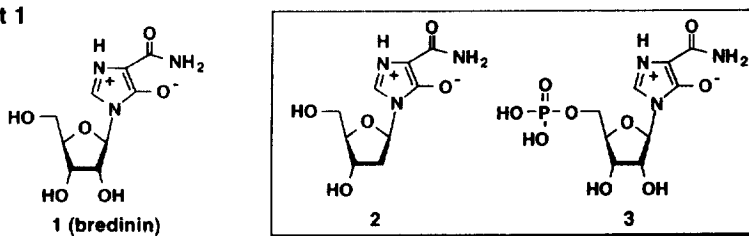
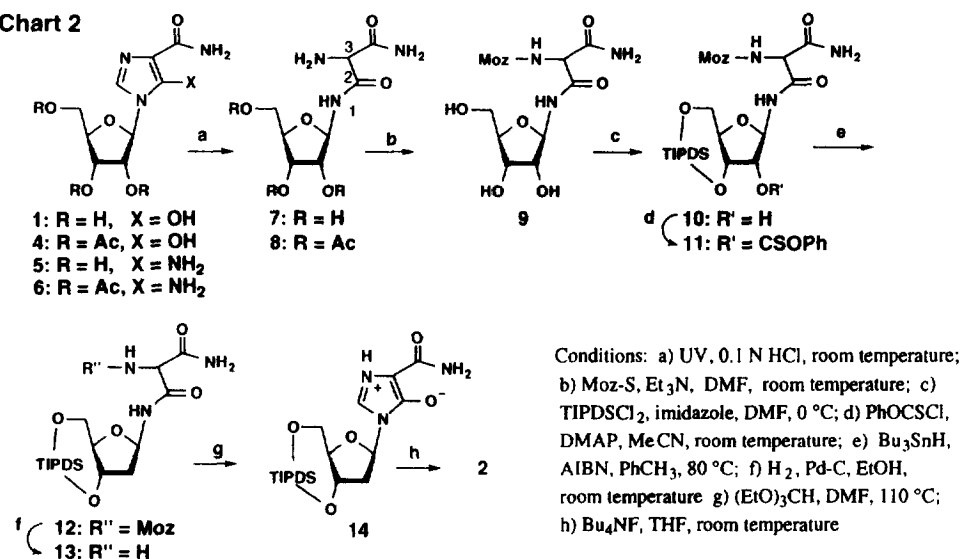


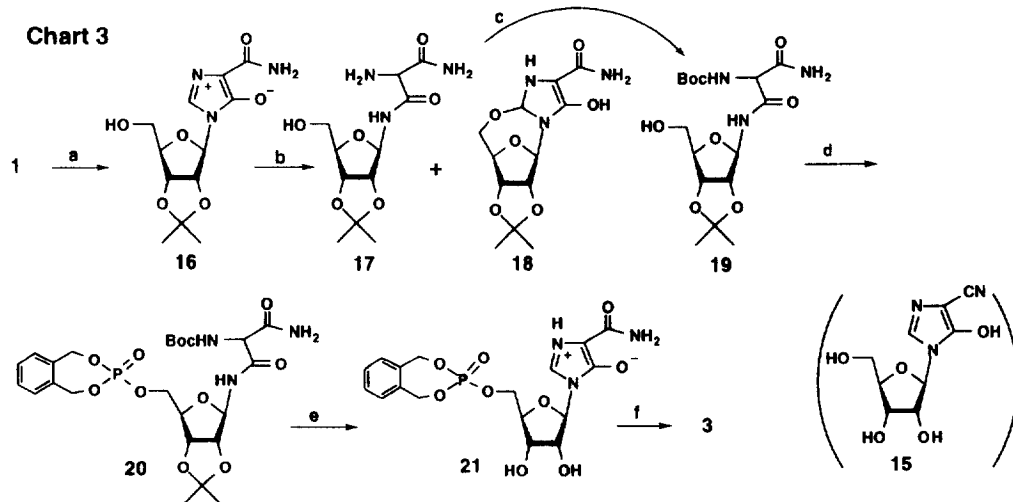
Chart 2



First, we investigated the photoreaction with 2',3',5'-tri-*O*-acetate **4**, which was prepared readily from bredinin by the usual method, for making the detection and purification of the reaction products easy. When **4** in 0.1 N HCl was irradiated with a low-pressure mercury lamp (60 W)<sup>9</sup> under bubbling of argon, the UV-absorption of the solution readily faded out to give **8** in 79% yield as a diastereomeric mixture at the 3-position. Compound **8** was identical with the photoreaction product of tri-*O*-acetyl AICAR (**6**) reported previously.<sup>7</sup> In this reaction, protonation of the base moiety would significantly facilitate the reaction (the pK<sub>a</sub> of bredinin is 6.75<sup>2a</sup>), because when the photoreaction was done under neutral conditions, it proceeded only slightly. To our knowledge, such a photochemical ring-cleavage reaction of imidazole has not been reported except for our previous results with AICAR.<sup>7</sup> In the same way, bredinin (**1**) was irradiated to give **7** in high yield, which was isolated as *N*<sup>3</sup>-*p*-methoxybenzyloxycarbonyl (Moz) derivative **9**<sup>10</sup> as crystals in 64% yield from **1**, after treating crude **7** with 4-methoxybenzyl-*S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate in the presence of Et<sub>3</sub>N in DMF. From <sup>13</sup>C NMR spectra, **9** was found to be a mixture of a pair of diastereomers at the 3-position, similarly as triacetate **8**. This photoreaction proceed very efficiently even under high concentrations of the substrate, by which more than 10 g of **9** can be prepared by one experiment.

Because many nucleoside analogues including bredinin exhibit their biological effects as antimetabolites inhibiting DNA or RNA synthesis, 2'-deoxygenation of biologically active ribonucleosides, inhibiting RNA synthesis, would be interesting, by which the target of the compound may be changed to DNA synthesis. Therefore, we planned to synthesize 2'-deoxybredinin (**2**). The 3',5'-hydroxyls of **8** were protected by the usual method to give the corresponding 3',5'-*O*-TIPDS (1,1,3,3-tetraisopropylidisiloxane-1,3-diyl) derivative **10** in 77% yield.<sup>11</sup> Compound **10** was then converted to the 2'-*O*-phenoxythiocarbonyl derivative **11** in 74% yield. Radical deoxygenation of **11** was done by heating with Bu<sub>3</sub>SnH in the presence of AIBN to afford **12** in 90% yield. The *N*<sup>3</sup>-Moz group of **12** was removed by hydrogenation with Pd-

carbon in EtOH to give **13**. When **13** was heated with 1.3 eq. of  $(\text{EtO})_3\text{CH}$  in DMF at 110 °C for 10 min, the desired cyclization reaction proceeded to furnish **14** in 57% yield from **12**. The usual deprotection of **14** with  $\text{Bu}_4\text{NF}$  in THF gave the target **2** as crystals<sup>12</sup> in 62% yield.



Conditions: a) acetone, TsOH, room temperature; b) UV, 0.1 N AcOH, room temperature; c)  $(\text{Boc})_2\text{O}$ ,  $\text{Et}_3\text{N}$ , DMF, room temperature; d) 1) XEPA, tetrazole,  $\text{CH}_2\text{Cl}_2$ , then  $\text{I}_2/\text{H}_2\text{O}$ , room temperature; e) 1) 90% TFA, room temperature, 2)  $(\text{EtO})_3\text{CH}$ , DMF, 90 °C; f) 1) Pd-C,  $\text{H}_2$ , MeOH, room temperature, 2) Diaion WK-20 ( $\text{Na}^+$ )

Next, the synthesis of bredinin 5'-phosphate (**3**) was investigated. The 5'-phosphate **3** is produced in cells from bredinin by adenosine kinase and is the active form of bredinin, which inhibits cellular IMP dehydrogenase.<sup>13</sup> So, **3** is important, especially in various biochemical studies. However, the synthesis of **3** from bredinin by Yoshikawa's method,<sup>14</sup> the most efficient method for preparing 5'-nucleotides from nucleosides, is not successful; the reaction gave dehydrated product **15** as a major product and only 3% of **3**.<sup>15</sup> 5'-Phosphorylations of bredinin with phosphoramidite and phosphotriester methods were also tried by us, but were unsuccessful. Therefore, we investigated the synthesis of **3** via the photoreaction product. 2',3'-O-Isopropylidenebredinin (**16**), prepared readily by treating **1** with acetone/*p*-TsOH, was irradiated with a low-pressure mercury lamp (60 W)<sup>9</sup> in aqueous AcOH under bubbling of argon, gave the desired ring-cleavage product **17** in 71% yield. In this reaction, a cyclonucleoside **18** was isolated in 10% yield.<sup>16</sup> The  $N^3$ -amino group of **17** was protected by a Boc group by the usual method to give **19** in 78% yield. 5'-Phosphorylation of **19** with various methods was investigated. Thus, a phosphoramidite method with *o*-xylene *N,N*-diethylphosphoramidite (XEPA)<sup>17</sup> gave a good result; treatment of **19** with XEPA and tetrazole in  $\text{CH}_2\text{Cl}_2$ , and subsequent oxidation with  $\text{I}_2$  gave 5'-phosphotriester **20** in 70% yield. The isopropylidene and Boc groups of **20** were removed simultaneously with 90% TFA and the resulting product was heated with  $(\text{EtO})_3\text{CH}$  in DMF at 90 °C to give bredinin 5'-phosphate derivative **21** in 47% yield from **19**. Hydrogenation of **21** in the presence of Pd-carbon furnished bredinin 5'-phosphate (**3**), which was isolated as the di-sodium salt<sup>18</sup> in 89% yield.

Thus, we developed a useful method for modifying bredinin using a photoreaction. This method would be applicable to the synthesis of a variety of bredinin derivatives.

### Acknowledgment

We thank to Dr. M. Hayashi (Asahi Chemical Industry) for gift of bredinin.

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- We attempted the protection of the phenolic hydroxyl of the base moiety of bredinin with acyl and silyl groups, but the protection was unsuccessful.
- Use of a high-pressure mercury lamp (100 W, Pyrex filter) gave similar results.
- Physical data for **9** were as follows. mp 162-164 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.43 (d, 1 H, N<sup>1</sup>-H, *J* = 8.7 Hz), 7.38 (br s, 2 H, CONH<sub>2</sub>), 7.30 (d, 2 H, Ph, *J* = 8.5 Hz), 7.08 (d, 1 H, 3-NH, *J* = 8.7 Hz), 6.92 (d, 2 H, Ph, *J* = 8.5 Hz), 5.20 (dd, 1 H, H-1', *J* = 8.7 and 4.4 Hz), 5.04 (d, 1 H, OH, *J* = 5.8 Hz), 4.98 (s, 2 H, PhCH<sub>2</sub>), 4.86 (d, 1 H, OH, *J* = 5.7 Hz), 4.74 (t, OH, *J* = 5.6 Hz), 3.66 (d, 1 H, H-3, *J* = 8.7 Hz), 3.87 (m, 1 H, H-2'), 3.75 (s, 3 H, MeO), 3.73 (m, 1 H, H-3'), 3.68 (m, 1 H, H-4'), 3.53-3.99 (m, 2 H, H-5'ab); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 167.9, 166.8, 166.7, 159.0, 155.5, 129.6, 128.6, 113.7, 84.1, 84.0, 83.9, 83.4, 74.0, 73.8, 70.1, 70.0, 65.7, 61.7, 61.6, 58.8, 55.1; FAB-MS, *m/z* 414 (MH<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>23</sub>N<sub>3</sub>O<sub>9</sub>: C, 49.39; H, 5.61; N, 10.16. Found: C, 49.21; H, 5.59; N, 10.20.
- We attempted the protection of 3',5'-hydroxyls of bredinin with TIPDS group by the usual method for its subsequent 2'-deoxygenation, but the protection was unsuccessful.
- Physical data for **2** were as follows. mp 195-198 °C; UVλ<sub>max</sub> (H<sub>2</sub>O) 278 nm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, D<sub>2</sub>O-added) δ 8.23 (s, 1 H, H-2), 5.95 (dd, 1 H, H-1', *J* = 7.0 and 6.7 Hz), 4.29 (m, 1H, H-3'), 3.80 (m, 1 H, H-4'), 3.54-3.41 (m, 2 H, H-5'ab), 2.45 (m, 1 H, H-2'a), 2.15 (m, 1 H, H-2'b); FAB-MS, *m/z* 244 (MH<sup>+</sup>). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>·4/5H<sub>2</sub>O: C, 41.96; H, 5.71; N, 16.31. Found: C, 41.68; H, 5.39; N, 16.30.
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- Physical data for **3** were as follows. UVλ<sub>max</sub> (H<sub>2</sub>O) 279 nm; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 8.38 (s, 1 H, H-2), 5.81 (d, 1 H, H-1', *J* = 4.4 Hz), 4.49 (dd, 1 H, H-2', *J* = 4.4 and 4.4 Hz), 4.41 (dd, 1 H, H-3', *J* = 4.9 and 4.4 Hz), 4.28 (dd, 1 H, H-4', *J* = 4.9 and 2.4 Hz), 4.01-4.14 (m, 2 H, H-5'ab); FAB-MS, *m/z* 338 (MH<sup>+</sup>).

(Received in Japan 9 October 1995; revised 27 October 1995; accepted 2 November 1995)