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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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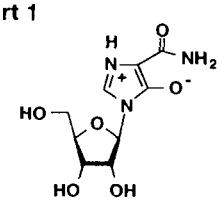
Abstract: 2'-Deoxy and 5'-phosphate derivatives of bredinin (**2** and **3**, respectively) were synthesized. UV irradiation of bredinin with a mercury lamp in aqueous HCl gave the imidazole-ring cleavage product **7** in high yield, which was converted to 2'-deoxy derivative **13**. Reconstruction of the imidazole ring of **13** with $(EtO)_3CH$ and subsequent deprotection afforded the desired 2'-deoxybredinin (**2**). Similarly, bredinin 5'-phosphate (**3**) was synthesized via the photo-product **17**.

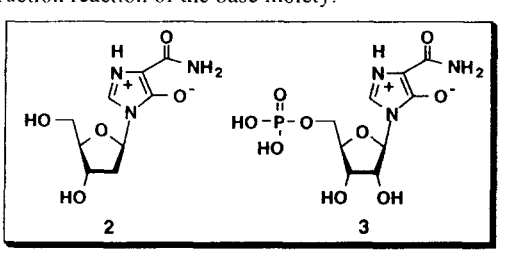
Bredinin (**1**), an imidazole nucleoside antibiotic,[2] is a clinically useful immunosuppressant[3,4] especially for transplantation of viscera[3a,b] and autoimmune disease such as rheumatism.[3c] Bredinin as well as its analogues are also known to have antitumor effects in experimental tumor models.[5] Recently, a significant antiviral effect of bredinin was also reported.[6] 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[5a,7] probably due to its unusual zwitterionic structure of the base moiety.[8] 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-aminomalonamide (**7**) which was generated by a novel photochemical imidazole-ring cleavage reaction of AICAR (**5**).[5a,7] Although **7** or its tri-*O*-acetate **8** were also efficient intermediates for preparing various bredinin derivatives,[5a] the yields of **7** and **8** were low (about 30%) and these were obtained on only a 100-mg scale by one reaction.[5a,7] In this paper, we describe the efficient preparation of **7**, **8**, and the corresponding acetonide **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

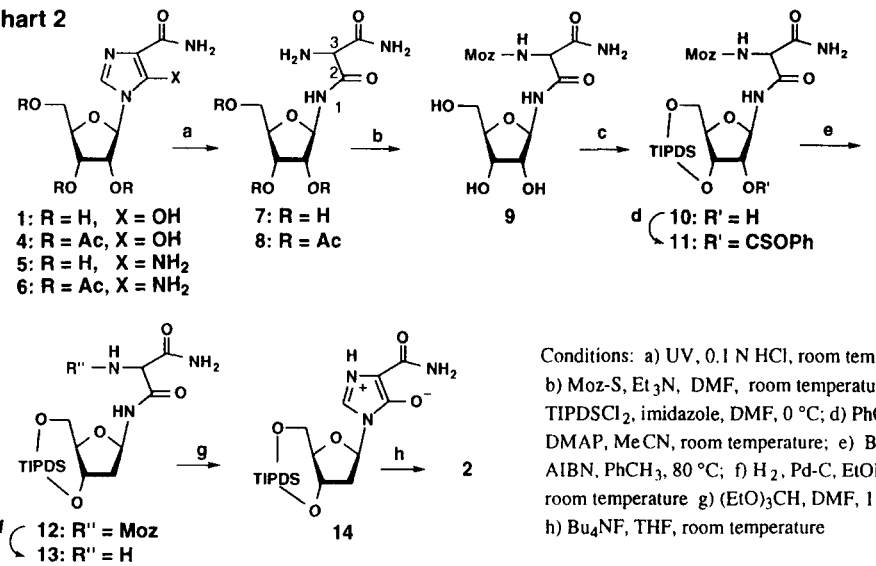


1 (bredinin)



2 **3**

Chart 2

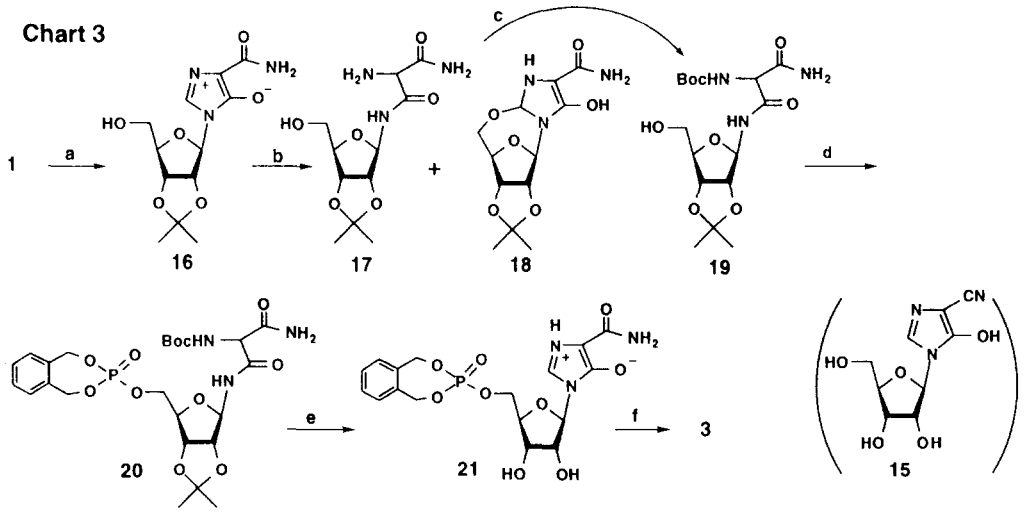


First, we investigated the photoreaction with 2',3',5'-tri-*O*-acetate **4**, which was prepared readily from bredinin by the usual method, for making the detection and purification of the reaction products easy. When **4** in 0.1 N HCl was irradiated with a low-pressure mercury lump (60 W)[9] under 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.[7] In this reaction, protonation of the base moiety would significantly facilitate the reaction (the pKa of bredinin is 6.75[2a]), 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.[7] In the same way, bredinin (**1**) was irradiated to give **7** in high yield, which was isolated as N^3-*p*-methoxybenzyloxycarbonyl (Moz) derivative **9**[10] 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_3N in DMF. From ^{13}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 sythesis, 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-tetraisopropyldisiloxane-1,3-diyl) derivative **10** in 77% yield.[11] 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_3SnH in the presence of AIBN to afford **12** in 90% yield. The N^3-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 $(EtO)_3CH$ 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 Bu_4NF in THF gave the target **2** as crystals[12] in 62% yield.

Chart 3



Conditions: a) acetone, TsOH, room temperature; b) UV, 0.1 N AcOH, room temperature; c) $(Boc)_2O$, Et_3N, DMF, room temperature; d) 1) XEPA , tetrazole, CH_2Cl_2, then I_2/H_2O, room temperature; e) 1) 90% TFA, room temperature, 2) $(EtO)_3CH$, DMF, 90 °C; f) 1) Pd-C, H_2, MeOH, room temperature, 2) Diaion WK-20 (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.[13] So, **3** is important, especially in various biochemical studies. However, the synthesis of **3** from bredinin by Yoshikawa's method,[14] 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**.[15] 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 lump (60 W)[9] 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.[16] 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*-xylylene *N,N*-diethylphosphoramidite (XEPA)[17] gave a good result; treatment of **19** with XEPA and tetrazole in CH_2Cl_2, and subsequent oxidation with 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 $(EtO)_3CH$ 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[18] 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.

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8. We attempted the protection of the phenolic hydroxyl of the base moiety of bredinin with acyl and silyl groups, but the protection was unsuccessful.
9. Use of a high-pressure mercury lump (100 W, Pyrex filter) gave similar results.
10. Physical data for **9** were as follows. mp 162-164 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (d, 1 H, N^1-H, J = 8.7 Hz), 7.38 (br s, 2 H, $CONH_2$), 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_2), 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); ^{13}C NMR (DMSO-d_6) 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$^+$). Anal. Calcd for $C_{17}H_{23}N_3O_9$: C, 49.39; H, 5.61; N, 10.16. Found: C, 49.21; H, 5.59; N, 10.20.
11. 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.
12. Physical data for **2** were as follows. mp 195-198 °C; UVλ_{max} (H_2O) 278 nm; ^{1}H NMR (DMSO-d_6, D_2O-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$^+$). Anal. Calcd for $C_9H_{13}N_3O_5 \cdot 4/5H_2O$: C, 41.96; H, 5.71; N, 16.31. Found: C, 41.68; H, 5.39; N, 16.30.
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16. It is generally recognized that the formation of 5'-cyclonucleoside is facilitated when the 2',3'-*cis*-diol of ribonucleosides is protected as acetonide due to its steric effect.
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18. Physical data for **3** were as follows. UVλ_{max} (H_2O) 279 nm; ^{1}H NMR (D_2O) 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$^+$).

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