Communications to the Editor

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SYNTHESIS OF BREDININ FROM 5-AMINOIMIDAZOLE-4-CARBOXAMIDE-RIBOFURANOSIDE (AICA-RIBOSIDE)

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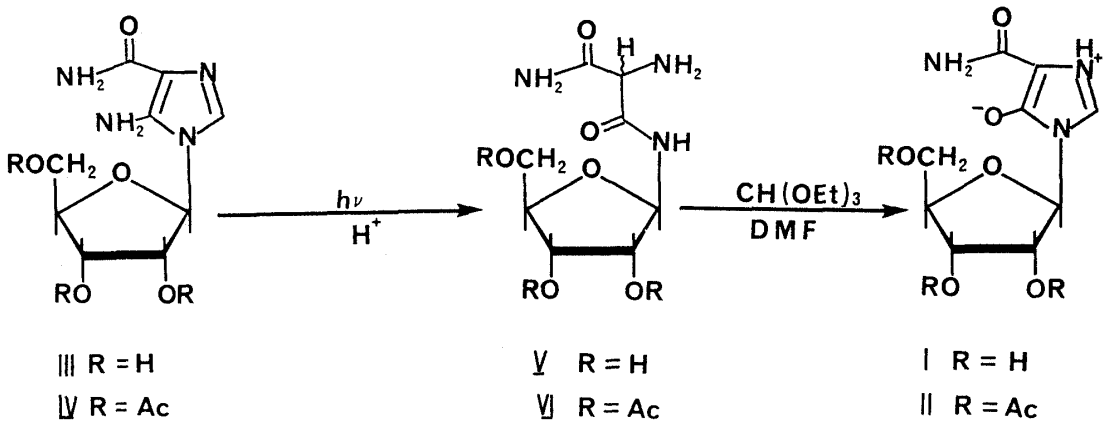
A novel synthesis of bredinin by the conversion of AICA-riboside through a photo-degradation product is described.

KEYWORDS— nucleoside antibiotic; bredinin; AICA-riboside; photochemical reaction; degradation; reconstruction

Bredinin (I), an immunosuppressive and antitumor compound isolated from Eupenicillium brefeldianum M-2166,[1-3] is a nucleoside with a unique imidazole (4-carbamoyl-imidazolium-5-olate) moiety. Compound I has been synthesized by the glycosylation of trimethylsilylated 4-carbamoylimidazolium-5-olate with 1,2,3,5-tetra-O-acetylribofuranose.[4] It is readily assumed that AICA-riboside, a commercially available imidazole nucleoside, should be a feasible starting material for the preparation of I. Recently Stevens has reported the successful synthesis of 4-carbamoylimidazolium-5-olate (aglycone of bredinin) from 5-diazoimidazole-4-carboxamide (Diazo-IC) by photolysis in an acidic condition.[5] However, the diazotization of AICA-riboside to give I has resulted in the formation of 2-azainosine as a main product,[6] and the same results were obtained in our hands.

We wish to report the first transformation of AICA-riboside (III) to bredinin (I) via photo-degradation and reconstruction of the imidazole moiety.

Because of the unsuccessful results of the diazotization of AICA-riboside, we studied the photo-degradation of AICA-riboside since we have observed the sensitive property of III to photolysis. (Chart 1) For convenient isolation and purification of the product, AICA-riboside (III) was treated with the acetic anhydride-pyridine system to afford IV. A solution of IV in 0.02N-HCl was irradiated with a high pressure mercury lamp through a Pyrex filter for 15h with argon bubbling. After standing overnight, the reaction mixture was neutralized with Dowex 1 (OH^-) and extracted several times with chloroform. The organic layer was evaporated under reduced pressure and the residue was flash chromatographed on silica gel to give an epimeric mixture (VI) as a foam in 32% yield. (CI-MS/isoBu, m/z:376 MH^+) In the CMR spectrum (25MHz, in DMSO-d_6, off resonance)



III R = H
IV R = Ac

V R = H
VI R = Ac

I R = H
II R = Ac

Chart 1

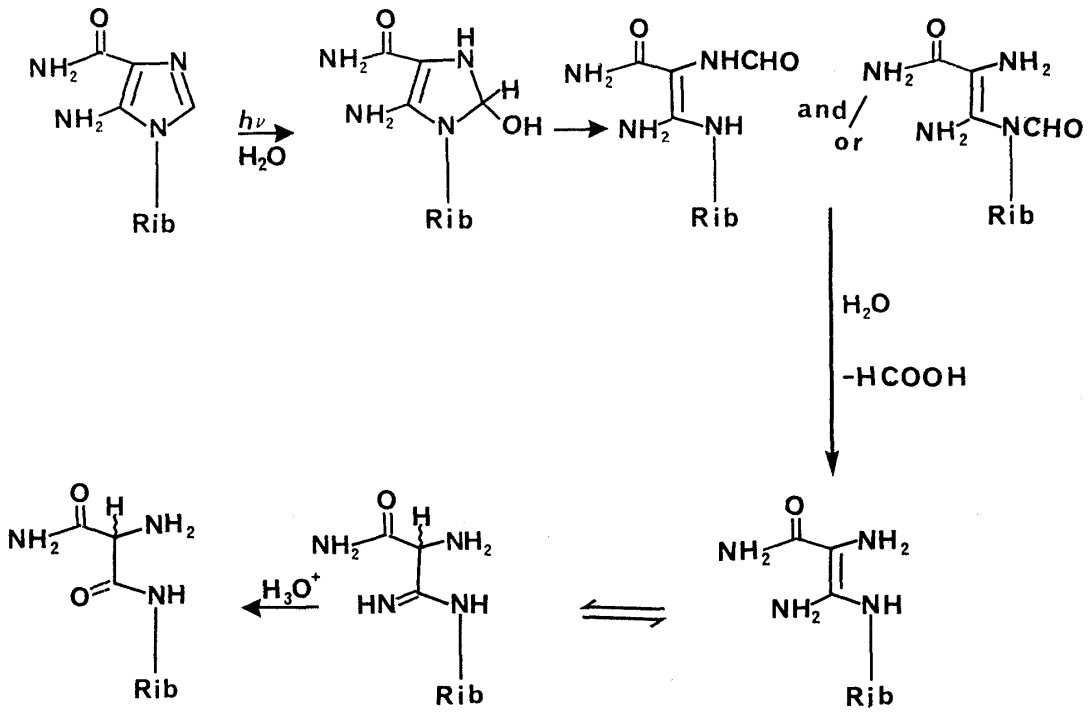


Chart 2

of one epimer (mp 122-124°C) of VI after separation of the epimer,[7] the signal of C-3 appeared at 58.7ppm as a doublet. The other epimer showed the C-3 resonance at 58.5ppm. This indicates that VI has a C-2 keto form rather than the enol form. This photoreaction most likely proceeds by the hydration of the protonated species followed by the successive hydrolysis to give the epimeric product as shown in Chart 2.

Recyclization of VI with ethyl orthoformate in dimethylformamide (110°C, 20min) afforded bredinin tri-O-acetate (II) in 75% yield as a foam, which was crystallized from MeOH. (mp 184-186°C, authentic tri-O-acetyl bredinin: mp 188-190°C) Further identification of II was accomplished by its NMR, UV and IR spectra. Deacylation of II with ammonia/methanol gave bredinin (I) in 82% yield.

More directly, a solution of AICA-riboside (III) in 0.02N-HCl was irradiated with a high pressure mercury lamp through a Pyrex filter for 15h with argon bubbling. After neutralization with Dowex 1 (OH^-), the filtrate was evaporated under reduced pressure to afford V. This photo-degradation product (V) was identical in all respects with that obtained from VI by ammonolysis. Successive reconstruction of V with ethyl orthoformate in dimethylformamide (130°C, 7min) gave bredinin (I) in 11.2% overall yield after chromatographic purification and recrystallization from H_2O-^{i}PrOH. This synthetic sample was identical with the authentic sample in all respects, including biological activity.

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7) The ^{1}H-NMR spectrum of VI showed two sets of signals due to the corresponding epimers. $[\alpha]_D^{24}$-14.3° (*c*0.5, chloroform) The separation of epimers was performed by crystallization from MeOH.

One epimer: mp 122-124°C, $[\alpha]_D^{24}$-39.8° (*c*0.5, chloroform), Anal. Calcd. for $C_{14}H_{21}N_3O_9$; C, 44.80; H, 5.64; N, 11.20% Found. C, 45.04; H, 5.73; N, 10.81%., ^{1}H-NMR(100MHz in $CDCl_3$, D_2O added) δ_{ppm}^{TMS} 2.09(s, 6H, OAc x 2), 2.15(s, 3H, OAc), 4.06(s, 1H, H-3), 4.24(m, 3H, H-4' and H-5'), 5.36-5.12(m, 2H, H-2' and H-3'), 5.67(d, 1H, H-1', J=5Hz).

Another epimer: foam, $[\alpha]_D^{24}$ -6.9° (*c*0.5, chlroform), ^{1}H-NMR; 2.09(s, 6H, OAc x 2), 2.14(s, 3H, OAc), 4.24(m, 4H, H-3, H-4' and H-5'), 5.28(m, 2H, H-2' and H-3'), 5.62(d, 1H, H-1', J=3Hz).

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