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Studies on Bredinin. III.[1,2] Chemical Synthesis of Bredinin[3] (A Novel Imidazole Nucleoside)

Bredinin, a novel imidazole nucleoside, produced by *Eupenicillium brefeldianum* M-2166 was synthesized by the condensation of the trimethylsilyl derivative of 4(5)-carbamoyl imidazolium-5(4)-olate with 1,2,3,5-tetra-*O*-acyl-β-D-ribofuranose in the presence of Friedel-Crafts catalysts ($SnCl_4$, $TiCl_4$) followed by deacylation. It was identical with natural bredinin. The absolute configuration was established as 4-carbamoyl-1-β-D-ribofuranosyl imidazolium-5-olate.

Bredinin (I), a novel imidazole nucleoside, has been isolated from the culture filtrate of *Eupenicillium brefeldianum* M-2166. Bredinin has a potent immunosuppressive activity and other biological activity such as anticandida, antivirus or antitumor.[1]

The structure has been determined by X-ray crystallographic study[2] as 4-carbamoyl-1-β-ribofuranosyl imidazolium-5-olate.

In this communication, we describe the total synthesis and the absolute configuration of bredinin (I). Starting material, 4(5)-carbamoyl imidazolium-5(4)-olate (II), was prepared from aminomalonamide and ethyl orthoformate by the modified method of Schipper and Day.[4] Condensation of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (IIIa) with the trimethylsilyl derivative of II in the presence of stannic chloride in 1,2-dichloroethane according to the procedure of Niedballa and Vorbruggen[5] gave the triacetyl nucleoside (IVa).

The reaction mixture was washed with water and concentrated to dryness, then the residue was dissolved in a minimal amount of chloroform and applied to a silica gel column chromatography. The column was developed with chloroform-methanol–acetic acid (30:1:1 v/v). After evaporation of the fractions containing IVa, triacetyl nucleoside was crystallized from ethanol in 14% yield, mp 201—203°. $[\alpha]_D^{22}$ −34.3° (c=0.775, DMSO). Mass Spectrum m/e: 385 (M^+), 325 (M^+–AcOH). UV $\lambda_{max}^{ethanol}$ nm (ε): 245 (7500), 287 (11800). IR ν_{max}^{KBr} cm^{-1}: 3450, 3310, 3160, 3075, 1740, 1660, 1620, 1585, 1545, 1510, 1235. *Anal.* Calcd. for $C_{15}H_{19}O_9N_3$: C, 46.76; H, 4.97; N, 10.90. Found: C, 46.48; H, 4.97; N, 11.20. The above physical constants of IVa were identical with those of the natural 2′,3′,5′-tri-O-acetyl bredinin.

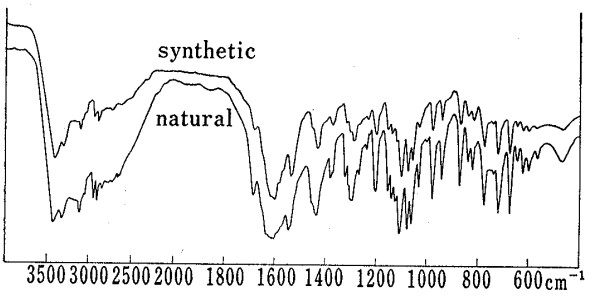

Fig. 1. IR Spectra of Synthetic and Natural Bredinin

Alternatively, treatment of the trimethylsilyl derivative of II with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (IIIb) in the presence of titanium tetrachloride in nitromethane gave a 52% yield of the 2′,3′,5′-tri-O-benzoyl bredinin (IVb), mp 141.5—143°. $[\alpha]_D^{22}$ −64.3° (c=1.073, $CHCl_3$). UV $\lambda_{max}^{ethanol}$ nm (ε): 231 (43000), 283 (15900). IR ν_{max}^{KBr} cm^{-1}. 3380, 3150, 1720, 1655, 1620, 1590, 1275. The optimal solvents, Friedel-Crafts catalysts and other conditions are presently under investigation.

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2) Part II: H. Yoshioka, K. Nakatsu, M. Hayashi and K. Mizuno, *Tetrahedron Letters*, "in press."
3) This work was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
4) E. Schipper and A.R. Day, *J. Am. Chem. Soc.*, **74**, 350 (1952).
5) U. Niedballa and H. Vorbruggen, *Angew. Chem. Intern. Ed. Engl.*, **9**, 461 (1970).

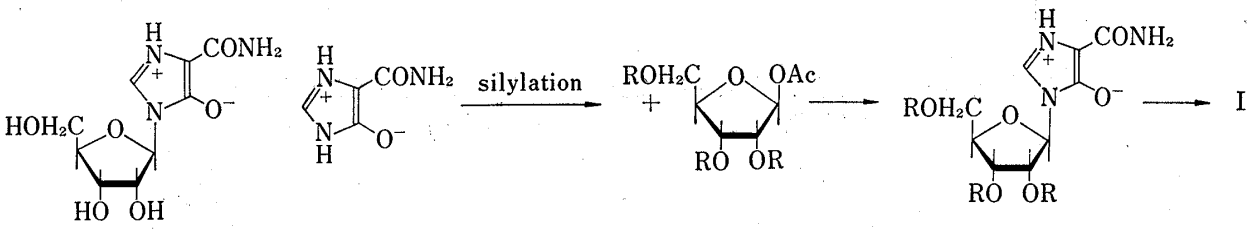

Chart 1

Deacylation of IV with methanolic ammonia gave the nucleoside, mp>200° (decomp.). $[\alpha]_D^{22}$ −27.5° (c=1.037, H_2O). UV $\lambda_{max}^{H_2O}$ nm (ε): 245 (6300), 279 (14200). IR (KBr, Fig. 1). NMR δ (DMSO-d_6): 5.53 (1H, doublet, J=5.5 Hz), 8.29 (1H, singlet). *Anal.* Calcd. for $C_9H_{13}O_6N_3 \cdot H_2O$: C, 38.99; H, 5.45; N, 15.16. Found: C, 38.99; H, 5.38; N, 15.47, which was identical with the authentic bredinin monohydrate in all respect including optical and biological properties.

From above facts, the absolute configuration of the natural bredinin was established as 4-carbamoyl-1-β-D-ribofuranosyl imidazolium-5-olate.

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