An Unusual Rearrangement during Diazotization of a 5-Aminoimidazole Nucleoside

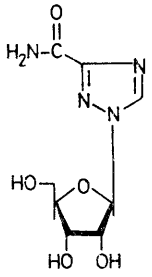
By PREM C. SRIVASTAVA,* ROBERT J. ROUSSEAU, and ROLAND K. ROBINS
(*ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute,* 2727 *Campus Drive, Irvine, California* 92715)

Summary Treatment of methyl 5-amino-1,(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate with sodium nitrite in the presence of 11N nitric acid at −20 °C yielded methyl 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-oxo-Δ^4-imidazoline-4-carboxylate.

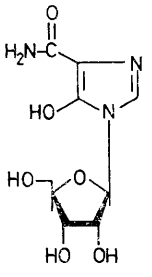
THE broad spectrum antiviral activity exhibited by 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**1**, Virazole[1]) suggested the synthesis of the imidazolecarboxamide (**2**) which could provide a hydrogen bonding site such as that found on N-2 in Virazole. We now report the unexpected formation of the carboxamide (**6**) during an attempted synthesis of (**2**).

Attempts to convert the amino-group of the carboxylate[2] (**3**) into a hydroxy-function by several well accepted procedures[3] were unsuccessful. For example, compound (**3**) was diazotized using sodium nitrite in 11N nitric acid at −20 °C and the pH adjusted to 6—7 after 2 h ($NaHCO_3$).

The mixture was extracted with ethyl acetate and the crude product was purified by silica gel column chromatography giving 72 mg of a white amorphous solid (18% yield), m.p. 150—151 °C, elemental analysis (C, H, and N) of which was consistent with the empirical formula $C_{16}H_{20}N_2O_{10}$ of the carboxylate (**4**). Treatment of this compound with



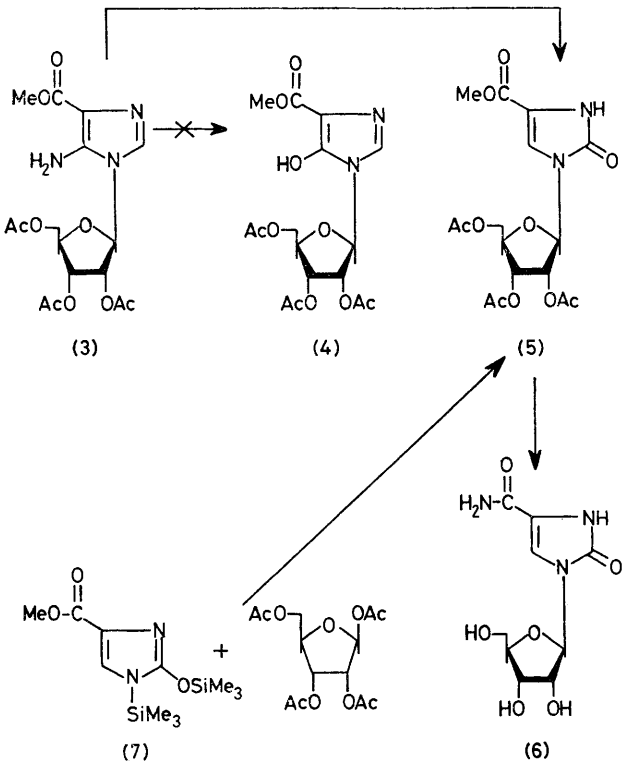
(1), Virazole



(2)

methanol–conc. ammonium hydroxide furnished a product having a m.p. 178—179 °C (from EtOH); λ_{max} 261 (pH 1) and 278 nm (pH 11). From the elemental analysis (C, H, and N), which was in agreement with the empirical formula $C_9H_{13}N_3O_6$, it seemed reasonable to assume that this compound was the desired product (**2**).

While these studies were in progress, the nucleoside antibiotic bredinin (**2**) was reported.[4] The physical properties of our final product differed from those of an authentic sample† of bredinin. The structure of our diazotization product [originally assumed to be (**4**)], on the basis of accumulated data,‡ was then assigned as the carboxylate (**5**), and is consistent with the ^{1}H n.m.r. spectral data ($CDCl_3$) δ 9·53br (s, 1H, NH); ^{1}H ($CDCl_3$–D_2O) 7·18 (s, 1H, 5-H, 5·88 (d, 1H, *J* 5 Hz, 1′-H), 5·40 (m, 2H, 2-H and 3′-H), 4·3br, (d, 3H, 4′-H and 5′-H), 3·85 (s, 3H, CO_2Me), and 2·14 (t, 9H, 2′-, 3′-, and 5′-OAc). This structural assignment was also supported by the u.v. absorption [λ_{max} 265 (pH 1) and 281 nm (pH 11)] which was similar to that of methyl 1-β-D-arabinofuranosyl-2-oxo-Δ^4-imidazoline-4-carboxylate.[5] Rigorous structural proof for the 2-oxo structure (**5**) was obtained by total synthesis. Condensation of 1 equiv. of the bistrimethylsilyl derivative (**7**) of methyl 2-oxo-Δ^4-imidazoline-4-carboxylate[5] with 1 equiv. of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of 1·4 equiv. of stannic chloride,[6] afforded, after silica gel chromatography, a 36% yield of (**5**) as the major product with physico-chemical properties‡ identical to those of (**5**) isolated by the diazotization procedure.



(3) (4) (5) (7) (6)

The ammonolysis product of (**5**) was, therefore, the carboxamide (**6**). The formation of (**5**) can be visualized as a result of nitrosation at the 2-position. The apparent reduction at the 5-position can then be linked to the attack of water at the 2-position giving (**5**).

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† An authentic sample of bredinin was kindly provided by Dr. Kimio Mizuno of Toyo Joso Co. Ltd., Ohito, Shizuoka 410-23, Japan.

‡ All compounds described herein gave analytical and spectral data in agreement with the proposed structures and were homogeneous on t.l.c.

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