A UNIQUE TRANSFORMATION OF 5-AMINO-N'-METHOXYIMIDAZOLE-4-CARBOXAMIDINES BY DIAZOTIZATION: SYNTHESIS OF THE 5-AZIDO ANALOGUE OF AICA RIBOSIDE†

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Abstract—Diazotization of 1-substituted 5-amino-N'-methoxyimidazole-4-carboxamidines (I) was found to give the 5-azidoimidazole-4-carbonitriles II through the 1-methoxy-2-azaadenine intermediates IV. The product IIb from the riboside Ib was utilized for the synthesis of 5-azido-1-β-D-ribofuranosylimidazole-4-carboxamide (Vb), a novel AICA riboside analogue.

There have been several reports on diazotization of aminoimidazole nucleosides directed toward the syntheses of the immunosuppressive antibiotic breedinin (VIIIb) and other biologically active nucleosides. Diazotization of 1-β-D-ribofuranosyl-5-aminoimidazole-4-carboxamide (AICA riboside) (VIb) with NaNO₂ in 6N aqueous HCl was reported to give 2-azainosine instead of the normal 5-hydroxy derivative.† Attempts to convert the possible 5-diazonium intermediate into VIIIb were also unsuccessful.† Similarly, 1-substituted 5-aminoimidazole-4-carboxamidines cyclized to 2-azaadenine derivatives. On the other hand, diazotization of methyl 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate resulted in an unusual reaction to yield a 2-oximidazole derivative and that of the corresponding 4-carbonitrile afforded a complex mixture containing an azo-coupled product. Such marked differences in reaction mode among substrates led us to investigate the diazotization of 1-substituted 5-amino-N'-methoxyimidazole-4-carboxamidines (type I). We wish to report here a unique reaction observed for this system and some of its synthetic applications.

†Dedicated to the memory of Professor Tetsuji Kametani.
(N$_3$); $^1$H nmr (Me$_2$SO-d$_6$) $\delta$: 3.47 (3H, s, NMe$_2$), 7.72 (1H, s, C(2)-H)]. A similar reaction of Ib$^{12}$ gave 5-azido-1-$\beta$-D-ribofuranosylimidazole-4-carbonitrile (IIb) [79%; mp ca. 136°C (dec.); uv $\lambda_{\text{max}}$ (95% aqueous EtOH) 267.5 nm ($\varepsilon$ 6300); $\lambda_{\text{max}}$ (H$_2$O) (pH 1) 268.5 (6600); $\lambda_{\text{max}}$ (H$_2$O) (pH 7) 269 (6600); $\lambda_{\text{max}}$ (H$_2$O) (pH 13) 269 (6500); ir $\nu_{\text{max}}$ (Nujol) cm$^{-1}$: 2235 (CN), 2150 (N$_3$)]. The azido nitrile structures of IIa,b were supported by the presence of two absorption bands characteristic of an azido and a cyano group in their ir spectra. Further confirmations were obtained by transformations of IIa,b into the known 5-aminoimidazole-4-carbonitriles IIIa,b$^{13}$ [73% yield; mp 203–204°C (lit. mp 195–196°C$^{13a}$ or mp 196–198°C$^{13b}$)] and IIIb$^{14}$ [62%; mp 207–208°C (lit.$^{14b}$ mp 205°C (dec.))], respectively, through hydrogenolysis (10% Pd–C/H$_2$, MeOH, 1 atm, room temp., 50–80 min).

In considering the mechanism of the conversion of I into II, the following observations were taken into account. When the product from the diazotization of Ia in 1 N aqueous HCl was treated with NaI, the 2-azaadenine derivative IVa-HI [64% yield; mp 223–224°C (dec.); $^1$H nmr (Me$_2$SO-d$_6$) $\delta$: 4.08 and 4.33 (3H each, s, NMe and OMe), 8.88 (1H, s, C(2)-H)] was isolated. The iodide IVa-HI readily underwent C–O bond cleavage on heating in HCONMe$_2$ at 70°C for 10 min, giving the N-oxide VIIa [81% yield; mp 240–241°C (dec.); ms m/z : 166 (M$^+$); uv $\lambda_{\text{max}}$ (H$_2$O) (pH 1) 222 nm ($\varepsilon$ 25000), 241 (shoulder) (15800), 266 (shoulder) (4000), 343 (4620); $\lambda_{\text{max}}$ (H$_2$O) (pH 7) 222 (25400), 242 (shoulder) (17400), 270 (4450), 345 (5510); $\lambda_{\text{max}}$ (H$_2$O) (pH 13) unstable; $^1$H nmr (CF$_3$CO$_2$D) $\delta$: 4.31 (3H, s, NMe$_2$), 8.88 (1H, s, C(2)-H)]. This supported the 1-methoxy structure$^{15}$ of IVa-HI. On the other hand, the salt IVa-HI produced IIa (57% yield) upon treatment
with aqueous Na₂CO₃. We thus propose the mechanism shown in Scheme 2. The observed ring closure of Ia to give IVa is analogous to that of the demethoxy derivatives of I to give 2-azaadenines,⁶ ⁷ and the succeeding ring cleavage of IV leading to II may resemble that of benzo-1,2,3-triazine 3-oxide derivatives.¹⁶

Since various nucleosides structurally derived from AICA riboside by modification at the 5-position are known to exhibit a broad spectrum of biological activities,¹⁷ we next investigated the synthesis of the 5-azido analogues V from II. Thus, IIa was treated with H₂O₂ in aqueous NH₃ at 2–3°C for 4 h, affording Va [76% yield; mp ca. 135°C (dec.); ms m/z: 166 (M⁺); uv λ_{max} (95% aqueous EtOH) 268.5 nm (ε 6600); λ_{max} (H₂O) (pH 1) 236 (7900), 251 (shoulder) (7100); λ_{max} (H₂O) (pH 7) 268.5 (6600); λ_{max} (H₂O) (pH 13) 268.5 (6500); ir ν_{max} (Nujol) cm⁻¹: 3350 and 3175 (NH₂), 1655 (CO); ¹H nmr (Me₂SO-d₆) δ: 3.45 (3H, s, NMe), 7.20 (br, NH₂), 7.57 (1H, s, C(2)-H)]. A similar hydrolysis of IIb (1°C, 1.5 h) provided the desired product Vb as a hard glass [85% yield; uv λ_{max} (95% aqueous EtOH) 265 nm (ε 5600); λ_{max} (H₂O) (pH 1) 238 (shoulder) (6200), 258 (5200); λ_{max} (H₂O) (pH 7) 265.5 (5450); λ_{max} (H₂O) (pH 13) 265.5 (5500); ir ν_{max} (Nujol) cm⁻¹: 2150 (N₂), 1655 (CO); ¹H nmr (Me₂SO-d₆) δ: 3.57 (2H, m, C(5)-H₂), 3.87 (1H, m, C(4′)-H), 4.01 (1H, m, C(3′)-H), 4.24 (1H, m, C(2′)-H), 5.01 (1H, t, J = 5 Hz, C(5′)-OH), 5.14 (1H, d, J = 5 Hz, C(3′)-OH), 5.48 (1H, d, J = 5 Hz, C(2′)-OH), 5.49 (1H, d, J = 5 Hz, C(1′)-H), 7.17 and 7.37 (1H each, dull, s, NH₂), 7.92 (1H, s, C(2)-H)]. Hydrogenolyses of Va,b (10% Pd–C/H₂, 65% aqueous AcOH or MeOH, 1 atm, room temp., 1–1.5 h) furnished the AICA derivatives VIa¹⁸ and VIb¹⁸ in 67% and 42% yields, respectively.

The results described above not only illustrate a peculiarity of I in diazotization but also enhance the value of I as synthetic intermediates readily obtainable from 9-substituted 1-methoxyadenines,¹⁰ ¹² demonstrating usefulness of our "fission and reclosure" technology¹⁹ for modification of the adenine ring.
REFERENCES


11. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.


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