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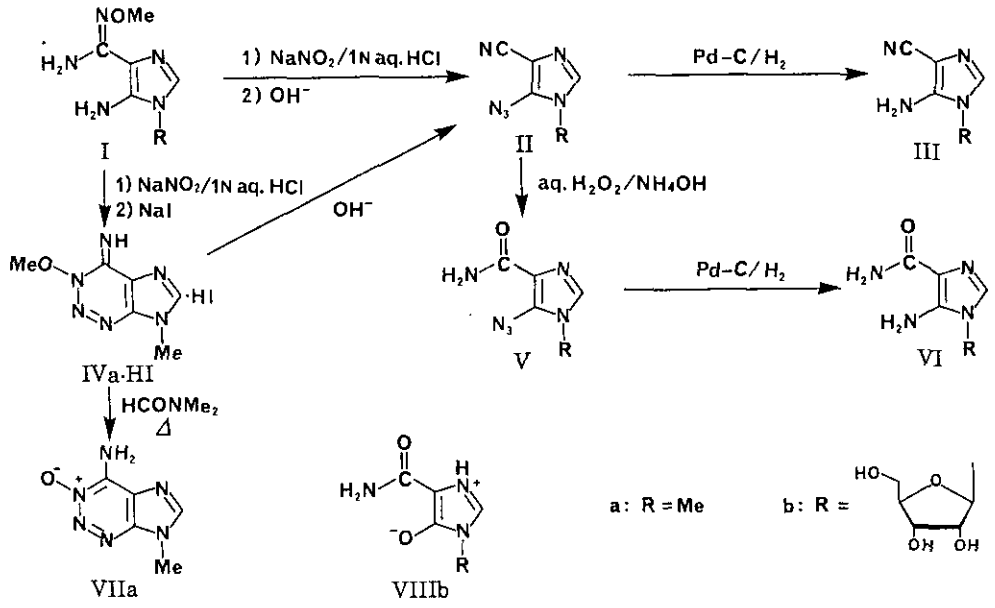
Abstract—Diazotization of 1-substituted 5-amino-*N*'-methoxyimidazole-4-carboxamidines (I) was found to give the 5-azidoimidazole-4-carbonitriles II through the 1-methoxy-2-azaadenine intermediates IV. The product IIb from the riboside Ib was utilized for the synthesis of 5-azido-1-β-D-ribofuranosylimidazole-4-carboxamide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

There have been several reports[1–7] on diazotization of aminoimidazole nucleosides directed toward the syntheses of the immunosuppressive antibiotic bredinin (VIIIb)[3,8] and other biologically active nucleosides. Diazotization of 1-β-D-ribofuranosyl-5-aminoimidazole-4-carboxamide (AICA riboside) (VIb) with $NaNO_2$ in 6 N aqueous HCl was reported to give 2-azainosine instead of the normal 5-hydroxy derivative.[1] Attempts to convert the possible 5-diazonium intermediate into VIIIb were also unsuccessful.[3] Similarly, 1-substituted 5-aminoimidazole-4-carboxamidines cyclized to 2-azaadenine derivatives.[6,7] 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-oxoimidazole derivative[4] and that of the corresponding 4-carbonitrile afforded a complex mixture containing an azo-coupled product.[3] 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.[9]

Treatment of Ia[10] with $NaNO_2$ in 1 N aqueous HCl at 0–3°C for 2 h and subsequent basification of the mixture to pH 9 with aqueous Na_2CO_3 furnished 5-azido-1-methylimidazole-4-carbonitrile (IIa)[11] [86% yield; mp 105°C (dec.); ms *m/z* : 148 (M^+); uv λ_{max} (95% aqueous EtOH) 268 nm (ε 6400); λ_{max} (H_2O) (pH 1) 267 (6500); λ_{max} (H_2O) (pH 7) 269 (6500); λ_{max} (H_2O) (pH 13) 269 (6400); ir ν_{max} (Nujol) cm^{-1}: 2225 (CN), 2150

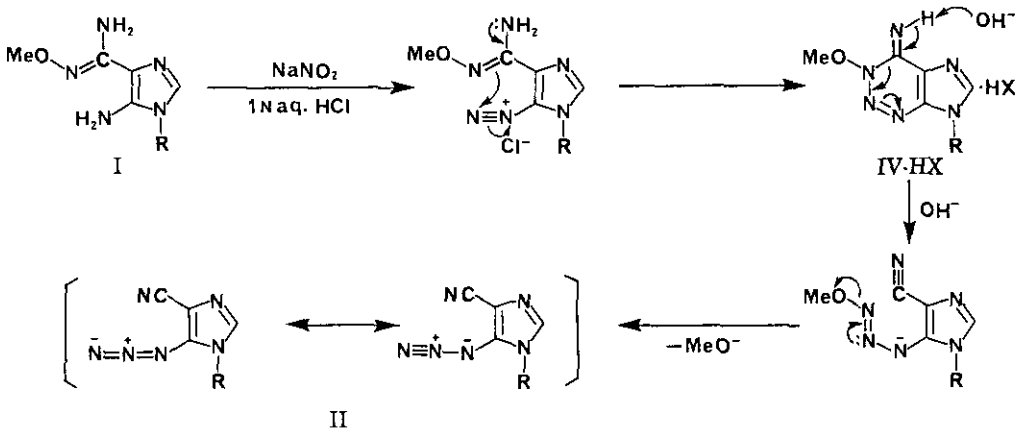
†Dedicated to the memory of Professor Tetsuji Kametani.



Scheme 1

(N_3); ^{1}H nmr (Me_2SO-d_6) δ: 3.47 (3H, s, NMe), 7.72 (1H, s, C(2)-H)]. A similar reaction of Ib[12] gave 5-azido-1-β-D-ribofuranosylimidazole-4-carbonitrile (IIb) [79%; mp *ca.* 136°C (dec.); uv λ_{max} (95% aqueous EtOH) 267.5 nm (ε 6300); λ_{max} (H_2O) (pH 1) 268.5 (6600); λ_{max} (H_2O) (pH 7) 269 (6600); λ_{max} (H_2O) (pH 13) 269 (6500); ir ν_{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[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_2SO-d_6) δ: 4.08 and 4.33 (3H each, s, NMe and OMe), 8.88 (1H, s, C(8)-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 λ_{max} (H_2O) (pH 1) 222 nm (ε 25000), 241 (shoulder) (15800), 266 (shoulder) (4000), 343 (4620); λ_{max} (H_2O) (pH 7) 222 (25400), 242 (shoulder) (17400), 270 (4450), 345 (5510); λ_{max} (H_2O) (pH 13) unstable; ^{1}H nmr (CF_3CO_2D) δ: 4.31 (3H, s, NMe), 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



I II

Scheme 2

with aqueous Na_2CO_3. 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 H_2O_2 *in aqueous* NH_3 *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} (H_2O) (pH 1) 236 (7900), 251 (shoulder) (7100); λ_{max} (H_2O) (pH 7) 268.5 (6600); λ_{max} (H_2O) (pH 13) 268.5 (6500); ir ν_{max} (Nujol) cm^{-1}: 3350 and 3175 (NH_2), 2150 (N_3), 1670 (CO); ^1H nmr (Me_2SO-d_6) δ: 3.45 (3H, s, NMe), 7.20 (br, NH_2), 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} (H_2O) (pH 1) 238 (shoulder) (6200), 258 (5200); λ_{max} (H_2O) (pH 7) 265.5 (5450); λ_{max} (H_2O) (pH 13) 265.5 (5500); ir ν_{max} (Nujol) cm^{-1}: 2150 (N_3), 1655 (CO); ^1H nmr (Me_2SO-d_6) δ: 3.57 (2H, m, C(5')-H_2), 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, NH_2), 7.92 (1H, s, C(2)-H)]. Hydrogenolyses of Va,b (10% Pd–C/H_2, 65% aqueous AcOH or MeOH, 1 atm, room temp., 1–1.5 h) furnished the AICA derivatives VIa[18] and VIb[18a] 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" technology[19] for modification of the adenine ring.

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