

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

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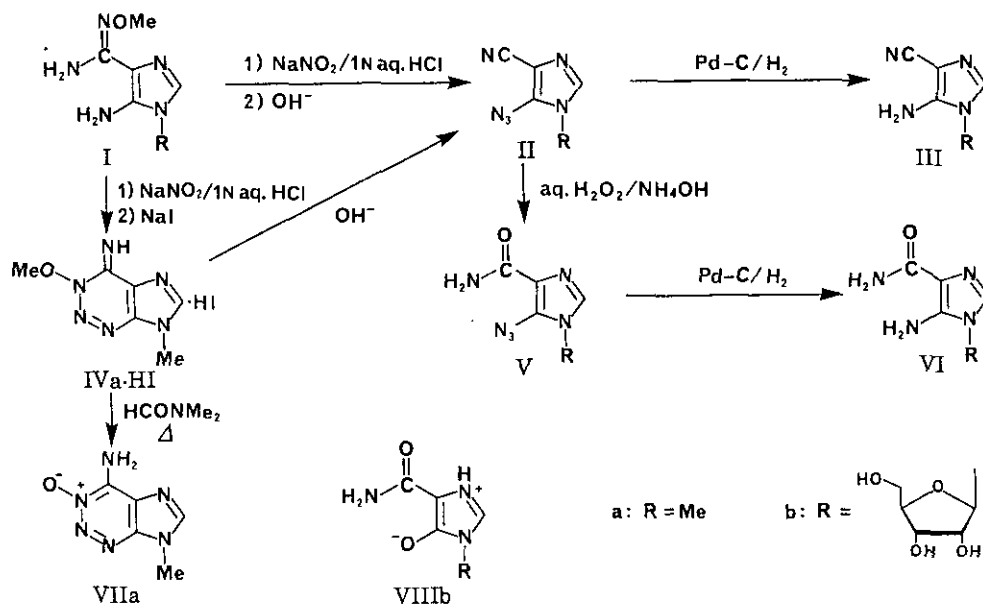
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**Abstract**—Diazotization of 1-substituted 5-amino-*N*'-methoxyimidazole-4-carboxamidines (I) was found to give the 5-azidoimidazole-4-carbonitriles II through the 1-methoxy-2-azaadenine intermediates IV. The product IIb from the riboside Ib was utilized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

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

Treatment of Ia<sup>10</sup> with NaNO<sub>2</sub> in 1 N aqueous HCl at 0–3°C for 2 h and subsequent basification of the mixture to pH 9 with aqueous Na<sub>2</sub>CO<sub>3</sub> furnished 5-azido-1-methylimidazole-4-carbonitrile (IIa)<sup>11</sup> [86% yield; mp 105°C (dec.); ms *m/z* : 148 (M<sup>+</sup>); uv λ<sub>max</sub> (95% aqueous EtOH) 268 nm (ε 6400); λ<sub>max</sub> (H<sub>2</sub>O) (pH 1) 267 (6500); λ<sub>max</sub> (H<sub>2</sub>O) (pH 7) 269 (6500); λ<sub>max</sub> (H<sub>2</sub>O) (pH 13) 269 (6400); ir ν<sub>max</sub> (Nujol) cm<sup>-1</sup>: 2225 (CN), 2150

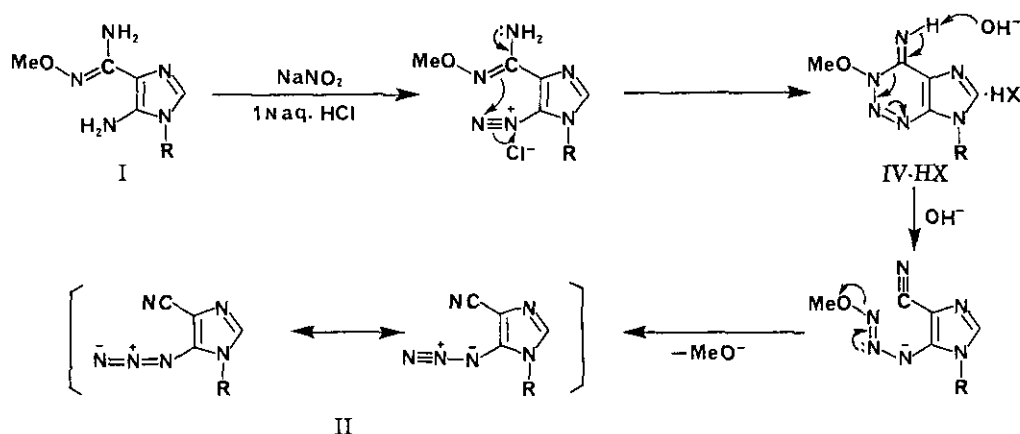
<sup>†</sup>Dedicated to the memory of Professor Tetsuji Kametani.



Scheme 1

(N<sub>3</sub>); <sup>1</sup>H nmr (Me<sub>2</sub>SO-*d*<sub>6</sub>) δ: 3.47 (3H, s, NMe), 7.72 (1H, s, C(2)-H)]. A similar reaction of Ib<sup>12</sup> gave 5-azido-1-β-D-ribofuranosylimidazole-4-carbonitrile (Iib) [79%; mp *ca.* 136°C (dec.); uv λ<sub>max</sub> (95% aqueous EtOH) 267.5 nm (ε 6300); λ<sub>max</sub> (H<sub>2</sub>O) (pH 1) 268.5 (6600); λ<sub>max</sub> (H<sub>2</sub>O) (pH 7) 269 (6600); λ<sub>max</sub> (H<sub>2</sub>O) (pH 13) 269 (6500); ir ν<sub>max</sub> (Nujol) cm<sup>-1</sup>: 2235 (CN), 2150 (N<sub>3</sub>)]. 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<sup>13</sup> [73% yield; mp 203–204°C (lit. mp 195–196°C<sup>13a</sup> or mp 196–198°C<sup>13b</sup>)] and IIIb<sup>14</sup> [62%; mp 207–208°C (lit.<sup>14b</sup> mp 205°C (dec.))], respectively, through hydrogenolysis (10% Pd-C/H<sub>2</sub>, 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.); <sup>1</sup>H nmr (Me<sub>2</sub>SO-*d*<sub>6</sub>) 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<sub>2</sub> at 70°C for 10 min, giving the *N*-oxide VIIa [81% yield; mp 240–241°C (dec.); ms *m/z*: 166 (M<sup>+</sup>); uv λ<sub>max</sub> (H<sub>2</sub>O) (pH 1) 222 nm (ε 25000), 241 (shoulder) (15800), 266 (shoulder) (4000), 343 (4620); λ<sub>max</sub> (H<sub>2</sub>O) (pH 7) 222 (25400), 242 (shoulder) (17400), 270 (4450), 345 (5510); λ<sub>max</sub> (H<sub>2</sub>O) (pH 13) unstable; <sup>1</sup>H nmr (CF<sub>3</sub>CO<sub>2</sub>D) δ: 4.31 (3H, s, NMe), 8.88 (1H, s, C(2)-H)]. This supported the 1-methoxy structure<sup>15</sup> of IVa·HI. On the other hand, the salt IVa·HI produced Iia (57% yield) upon treatment



Scheme 2

with aqueous  $\text{Na}_2\text{CO}_3$ . 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,<sup>6,7</sup> and the succeeding ring cleavage of IV leading to II may resemble that of benzo-1,2,3-triazine 3-oxide derivatives.<sup>16</sup>

Since various nucleosides structurally derived from AICA riboside by modification at the 5-position are known to exhibit a broad spectrum of biological activities,<sup>17</sup> we next investigated the synthesis of the 5-azido analogues V from II. Thus, IIa was treated with  $\text{H}_2\text{O}_2$  in aqueous  $\text{NH}_3$  at  $2-3^\circ\text{C}$  for 4 h, affording Va [76% yield; mp ca.  $135^\circ\text{C}$  (dec.); ms  $m/z$ : 166 ( $\text{M}^+$ ); uv  $\lambda_{\text{max}}$  (95% aqueous EtOH) 268.5 nm ( $\epsilon$  6600);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 1) 236 (7900), 251 (shoulder) (7100);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 7) 268.5 (6600);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 13) 268.5 (6500); ir  $\nu_{\text{max}}$  (Nujol)  $\text{cm}^{-1}$ : 3350 and 3175 ( $\text{NH}_2$ ), 2150 ( $\text{N}_3$ ), 1670 (CO);  $^1\text{H}$  nmr ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$ : 3.45 (3H, s, NMe), 7.20 (br,  $\text{NH}_2$ ), 7.57 (1H, s, C(2)-H)]. A similar hydrolysis of IIb ( $1^\circ\text{C}$ , 1.5 h) provided the desired product Vb as a hard glass [85% yield; uv  $\lambda_{\text{max}}$  (95% aqueous EtOH) 265 nm ( $\epsilon$  5600);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 1) 238 (shoulder) (6200), 258 (5200);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 7) 265.5 (5450);  $\lambda_{\text{max}}$  ( $\text{H}_2\text{O}$ ) (pH 13) 265.5 (5500); ir  $\nu_{\text{max}}$  (Nujol)  $\text{cm}^{-1}$ : 2150 ( $\text{N}_3$ ), 1655 (CO);  $^1\text{H}$  nmr ( $\text{Me}_2\text{SO}-d_6$ )  $\delta$ : 3.57 (2H, m, C(5')- $\text{H}_2$ ), 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,  $\text{NH}_2$ ), 7.92 (1H, s, C(2)-H)]. Hydrogenolyses of Va,b (10% Pd-C/ $\text{H}_2$ , 65% aqueous AcOH or MeOH, 1 atm, room temp., 1–1.5 h) furnished the AICA derivatives VIa<sup>18</sup> and VIb<sup>18a</sup> 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,<sup>10,12</sup> demonstrating usefulness of our "fission and reclosure" technology<sup>19</sup> for modification of the adenine ring.

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Received, 29th August, 1989