Purines. LXIV.[1] Syntheses of 9-Methyl-2-azaadenine 1-Oxide, Its *O*-Methyl Derivative, and 1-Substituted 5-Azidoimidazole-4-carboxamides

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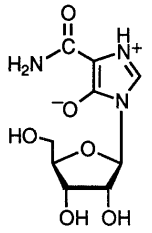
Diazotization of 5-amino-*N'*-methoxy-1-methylimidazole-4-carboxamidine (4a) with $NaNO_2$ in 1 N aqueous HCl was found to give the 1-methoxy-2-azaadenine derivative 8a · HI, which produced 5-azido-1-methylimidazole-4-carbonitrile (5a) on treatment with aqueous Na_2CO_3. The ribosyl analogue 5b, obtained from the riboside 4b by similar diazotization, was utilized for the synthesis of 5-azido-1-β-D-ribofuranosylimidazole-4-carboxamide (9b), a novel AICA riboside analogue. On heating in $HCONMe_2$ at 70°C for 10 min, 8a · HI yielded the 1-*N*-oxide 7a. Several reactions to transform the functional groups in 5a were also investigated.

Keywords diazotization; aminoimidazole; azidoimidazole-4-carbonitrile; 1-methoxy-2-azaadenine; 2-azaadenine 1-oxide; AICA riboside 5-deamino-5-azido

The imidazole nucleoside bredinin (**1**) is a potent immunosuppressive, antitumor antibiotic isolated from the culture filtrate of *Eupenicillium brefeldianum* M-2166.[2-5] Its chemical synthesis has been achieved *via* a "glycosidation route" starting from the aglycone through trimethylsilylation, glycosidation, and deprotection[6] or *via* a "photolysis route" starting from 1-β-D-ribofuranosyl-5-aminoimidazole-4-carboxamide (AICA riboside) (**10b**) and proceeding through the aminomalondiamide derivative.[7] If a direct transformation of the 5-amino group into the hydroxy group were feasible in the latter route, it should offer an efficient shortcut leading to the same goal.



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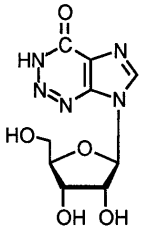

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There have been several reports[7b,8-13] on diazotization of aminoimidazole nucleosides directed toward the syntheses of **1** and other biologically active nucleosides. The diazotization of AICA riboside (**10b**) itself with $NaNO_2$ in 6 N aqueous HCl at −25°C was reported to give 2-azainosine (**2**) (86% yield) instead of the expected 5-hydroxyimidazole derivative.[8] Attempts to convert the 4-cyano analogue (with an *O*-protected ribosyl moiety) into **1** were also unsuccessful.[7b] 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 the deaminated 2-oxoimidazole derivative,[10] and that of 1-substituted 5-aminoimidazole-4-carboxamidines afforded the corresponding 2-azaadenine derivatives.[12,13] Such marked differences in reaction mode among the 5-aminoimidazole substrates with a variety of functional groups were particularly intriguing. In the present study, we therefore investigated the diazotization of 1-substituted 5-amino-*N'*-methoxyimidazole-4-carboxamidines (type **4**), readily obtainable from 9-substituted adenines (type **3**) through N(1)-oxidation,[14] *O*-methylation with MeI,[14a,15] and ring opening by mild alkaline hydrolysis.[14b,16] A brief account of a part of the results reported here has been published in a preliminary form.[17]

5-Amino-*N'*-methoxy-1-methylimidazole-4-carboxamidine (**4a**)[16a] was first treated with $NaNO_2$ in 1 N aqueous HCl at 0—3 °C for 2 h. On basification to pH 9 with aqueous Na_2CO_3, the reaction mixture afforded 5-azido-1-methylimidazole-4-carbonitrile (**5a**) in 86% yield. Treatment of the ribosyl analogue **4b**[14b] in a similar manner furnished 5-azido-1-β-D-ribofuranosylimidazole-4-carbonitrile (**5b**) in 79% yield. The correctness of the structures of **5a** and **5b** was supported by elemental analysis and by their IR spectra, which showed two absorption bands characteristic of an azido and a cyano group in the 2235—2150 cm^{-1} region. Final identification as assigned rested on their conversions into the known 5-aminoimidazole-4-carbonitriles **6a**[18] and **6b**[19] in 73% and 62% yields, respectively, by catalytic hydrogenolysis (10% Pd–C/H_2, MeOH, 1 atm, room temp., 80 min).

In considering the mechanism of the conversion of **4** into **5**, we took into account the following observations. When the primary product from the diazotization of the methyl analogue **4a** in 1 N aqueous HCl was treated with NaI instead of aqueous Na_2CO_3, 1-methoxy-9-methyl-2-azaadenine hydriodide (**8a** · HI) was isolated in 64% yield. On heating in $HCONMe_2$ at 70°C for 10 min, the 1-methoxy derivative **8a** · HI readily underwent C–O bond cleavage to give the *N*-oxide **7a** in 81% yield. This facile demethylation by nucleophilic attack of iodide anion resembled that[20,21] of 1-methoxy-9-methyladenine hydriodide (**11**) to form 9-methyladenine 1-oxide (**12**) and that[22] of 1-methoxypyridinium salt to form pyridine 1-oxide, upholding the assigned 1-methoxy structure (**8a** · HI). On the other hand, treatment of the 1-methoxy derivative **8a** · HI with aqueous Na_2CO_3 at pH 9 and room temperature for 1 h produced the azido nitrile **5a** in 57% yield. We thus propose that the conversion of **4** into **5** may proceed *via* the mechanism shown in Chart 2.

The observed ring closure of **4a** to give **8a** · HI is

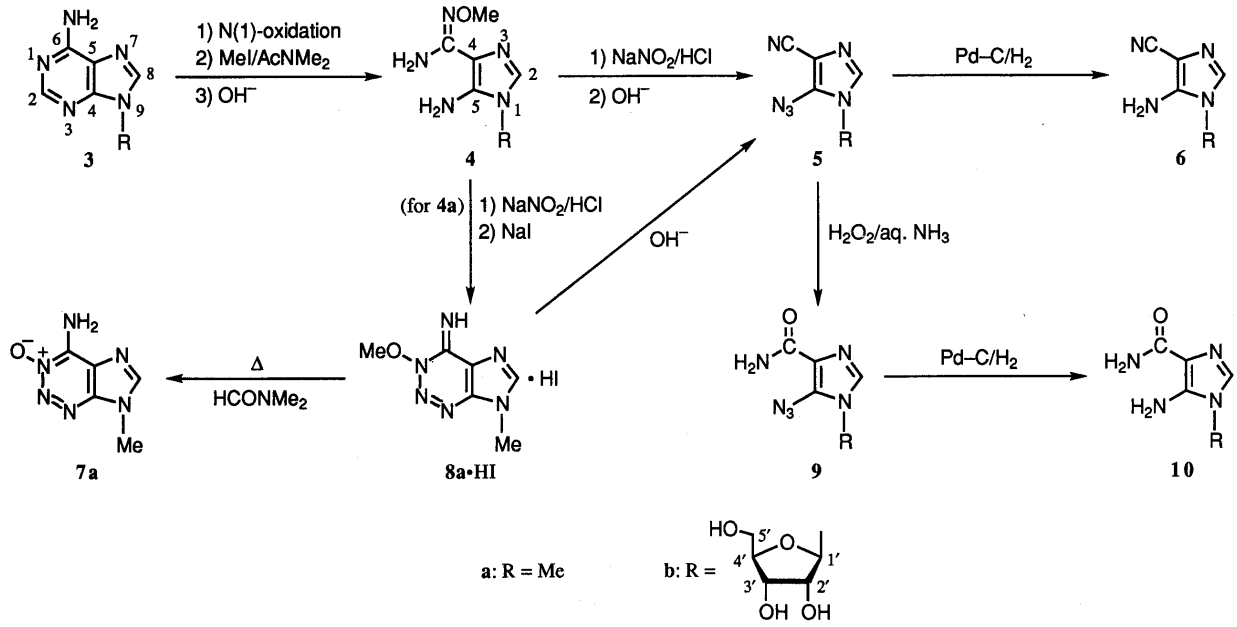

Chart 1

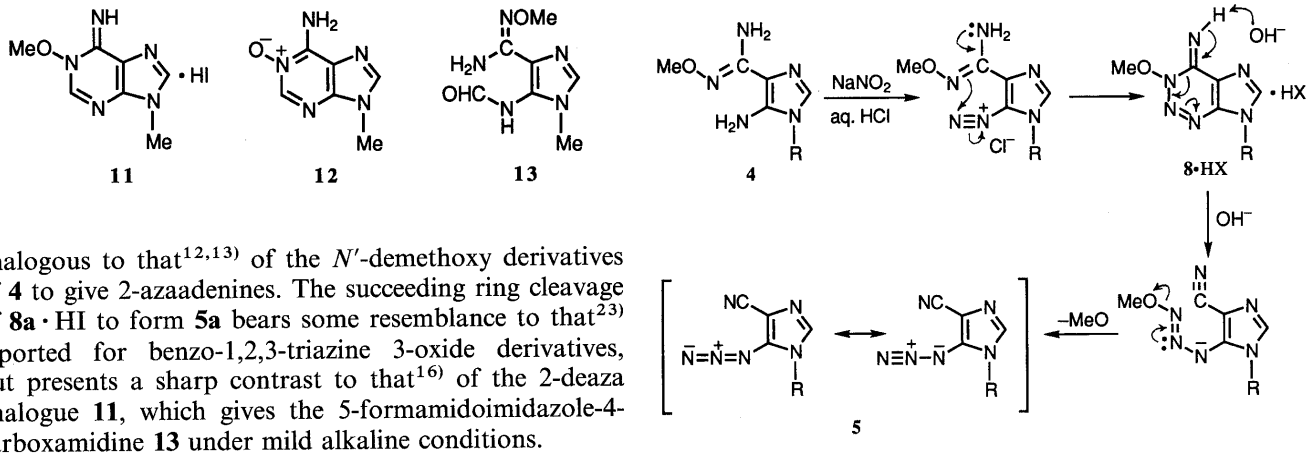

Chart 2

analogous to that[12,13] of the *N'*-demethoxy derivatives of **4** to give 2-azaadenines. The succeeding ring cleavage of **8a** · HI to form **5a** bears some resemblance to that[23] reported for benzo-1,2,3-triazine 3-oxide derivatives, but presents a sharp contrast to that[16] of the 2-deaza analogue **11**, which gives the 5-formamidoimidazole-4-carboxamidine **13** under mild alkaline conditions.

A variety of nucleosides structurally derived from AICA riboside (**10b**) by modification of the amino group at the 5-position have been reported to exhibit a broad spectrum of biological activities.[2,4,5,11,24] Therefore, we next investigated the synthesis of the 5-azido analogues **9** from **5**. On treatment with H_2O_2 in aqueous NH_3 at 2—3°C for 4 h, **5a** afforded the azido carboxamide **9a** in 76% yield. This procedure is a modification of the method of Radziszewski[25] for conversion of nitriles into carboxamides and has been successfully applied to similar conversions of the 5-halo analogues.[11] Interestingly, treatment of **5a** with aqueous H_2O_2 in the presence of CuCl at 20°C for 220 min also gave **9a**, but in only 20% yield. It is likely that a free-radical mechanism is operative in this reaction,[26] but we are unable to formulate it at the present time. Application of a similar Radziszewski procedure to the nucleoside analogue **5b** resulted in the isolation of **9a** as a hard glass in 85% yield. Characterization of **9** as the 5-azidoimidazole-4-carboxamides was readily achieved by catalytic hydrogenolyses (10% Pd–C/H_2, 65% aqueous AcOH or MeOH, 1 atm, room temp., 1—1.5 h) of **9a** and **9b**, which led to the formation of the AICA derivatives **10a**[27] and **10b**[27a] in 67% and 42% yields, respectively. The reaction sequence **3**→**4**→**5**→**9**→**10** eventually represents an alternative synthetic route to 1-substituted AICA derivatives (type **10**) from 9-substituted adenines (type **3**). Previously, we prepared **10** from 1-substituted *N'*-alkoxy-5-aminoimidazole-4-carboxamidines (type **4**) by hydrogenolytic dealkoxylation and subsequent hydrolysis of the amidine moiety.[27a]

Further interest in the chemical behavior of the azido nitrile **5a** stems from its reaction in hot aqueous HCl and from its conversion into the methyl ester **19**. On treatment with 10% aqueous HCl at 72 °C for 230 min, **5a** gave the 5-amino-2-chloro derivative **16** in 7% yield. The structure of **16** was confirmed by its hydrogenolysis (10% Pd–C/H_2, MeOH/AcONa, 1 atm, 30 °C, 20 h), which led to the formation of **6a** in 43% yield with 30% recovery of **16**. The initial step in the conversion of **5a** into **16** may be assumed to involve decomposition of the protonated azide **14** to produce the cation **15** (through a nitrenium ion),[28] which may then suffer nucleophilic attack of chloride

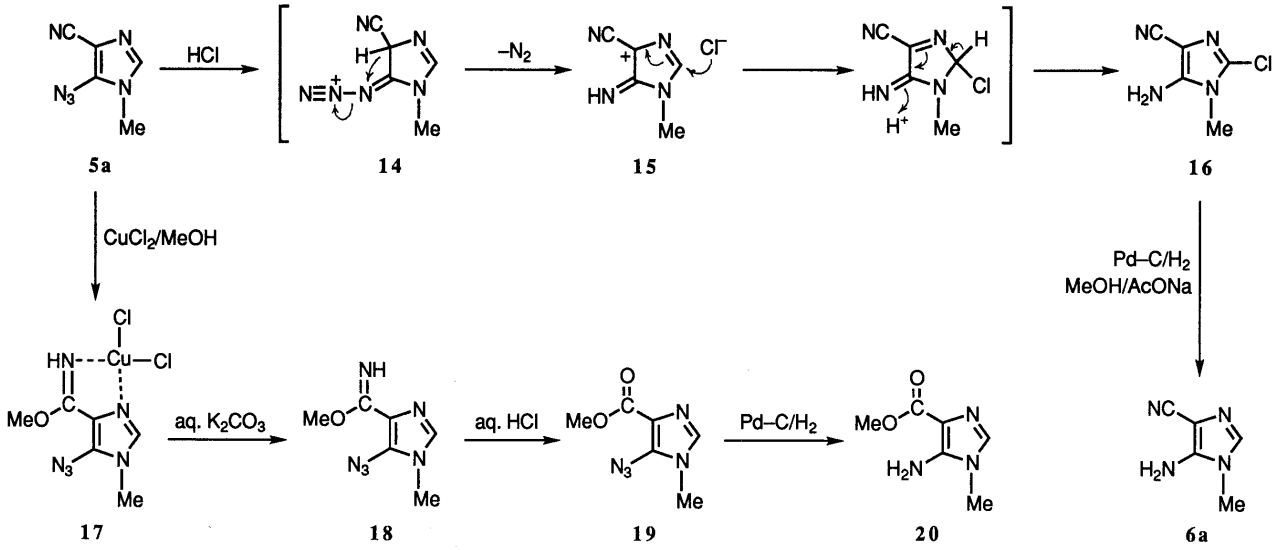

Chart 3

anion at the 2-position, as depicted in Chart 3.

Because of such instability of **5a**, the transformation of its cyano group into the methoxycarbonyl group would require mild reaction conditions. We therefore decided to apply the metal-promoted alcoholysis–hydrolysis method of Barnard.[29] Treatment of **5a** with an equimolar amount of $CuCl_2$ in MeOH at room temperature produced a complex presumed to be **17** in 79% yield. However, the direct conversion of **17** into the methyl ester **19** using EDTA[29] was found to be unsatisfactory. This led us to try an alternative two-step procedure: treatment of **17** with K_2CO_3 in H_2O at room temperature for 70 min gave the imidate **18** in 67% yield, and subsequent hydrolysis of **18** in 1 N aqueous HCl at 22°C for 3 h afforded **19** in 57% overall yield (from **17**). On catalytic hydrogenolysis (10% Pd–C/H_2, EtOH, 1 atm, room temp., 80 min), the azide **19** furnished the known 5-amino derivative **20**[30] in 74% yield.

In conclusion, the results described above reveal a peculiar behavior of 1-substituted 5-amino-*N'*-methoxyimidazole-4-carboxamidines (type **4**) upon diazotization. They have established new synthetic routes from **4a** to 9-methyl-2-azaadenine 1-oxide (**7a**) through its *O*-methyl derivative (**8a** · HI) and from **4b** to the novel AICA riboside analogue **9b**. This success enhances the value of **4a, b** as synthetic intermediates readily available from 9-substituted adenines (type **3**) by means of our favorite "fission and reclosure" technology[31] for modification of the adenine ring.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of chromatographies, instrumentation, and measurements. The solvents used for measurements of UV spectra were 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13). Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, s = singlet, sh = shoulder, t = triplet.

5-Azido-1-methyl-1*H*-imidazole-4-carbonitrile (5a) i) From **4a**: A stirred solution of **4a**[16a] (10.15 g, 60 mmol) in 1 N aqueous HCl (200 ml) was cooled to 0—3 °C, and a solution of $NaNO_2$ (of 97% purity) (5.12 g, 72 mmol) in H_2O (18 ml) was added dropwise over a period of 17 min. Stirring was continued at the same temperature for a further 2 h. The resulting dark brown solution was then brought to pH *ca.* 9 by addition of 10% aqueous Na_2CO_3 (*ca.* 120 ml), and stirring was continued for a further 1 h. The brown solid that deposited was collected by filtration, washed with H_2O, and dried to yield a first crop (6.75 g, 76%) of **5a**, mp 104 °C (dec.). The filtrate and washings were combined and extracted with AcOEt (5 × 300 ml). The AcOEt extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 in a refrigerator overnight, and concentrated *in vacuo*. The residue was dissolved in 10% aqueous HCl (28 ml), and the solution was neutralized with conc. aqueous NH_3. The pale brownish precipitate that resulted was filtered off, washed with H_2O, and dried to give a second crop (880 mg, 10%) of **5a**, mp 102.5 °C (dec.). The total yield of **5a** was 7.63 g (86%). The crude **5a** was recrystallized by dissolving it in 10% aqueous HCl and neutralizing the resulting solution with saturated aqueous $NaHCO_3$ to afford an analytical sample as an almost colorless solid, mp 105°C (dec.); MS *m/z*: 148 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 268 nm (ε 6400); $\lambda_{max}^{H_2O}$ (pH 1) 267 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 269 (6500); $\lambda_{max}^{H_2O}$ (pH 13) 269 (6400); IR ν_{max}^{Nujol} cm^{-1}: 2225 (CN), 2150 (N_3); ^{1}H-NMR (Me_2SO-d_6) δ: 3.47 [3H, s, N(1)-Me], 7.72 [1H, s, C(2)-H]. *Anal.* Calcd for $C_5H_4N_6$: C, 40.54; H, 2.72; N, 56.73. Found: C, 40.35; H, 2.65; N, 56.89.

ii) From **8a** · HI: A solution of **8a** · HI (*vide infra*) (307 mg, 0.996 mmol) in H_2O (13 ml) was brought to pH 9 by addition of 10% aqueous Na_2CO_3. The mixture was stirred at room temperature for 1 h and then extracted with AcOEt (5 × 8 ml). The AcOEt extracts were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 in a refrigerator overnight, and concentrated *in vacuo*. The residue (126 mg) was dissolved in 10% aqueous HCl (0.7 ml), and the solution was neutralized with saturated aqueous $NaHCO_3$. The almost colorless solid that deposited was filtered off, washed with H_2O, and dried to furnish **5a** (84 mg, 57%), mp 106 °C (dec.). This sample was identical (by comparison of the IR spectrum) with the one obtained by method (i).

5-Azido-1-β-D-ribofuranosyl-1*H*-imidazole-4-carbonitrile (5b) A stirred solution of **4b**[14b] (2.298 g, 8 mmol) in 1 N aqueous HCl (24 ml) was cooled to 2°C, and a solution of $NaNO_2$ (of 97% purity) (683 mg, 9.6 mmol) in H_2O (4 ml) was added dropwise over a period of 10 min. Stirring was continued at the same temperature for a further 200 min. The reaction mixture was brought to pH 9—10 by addition of conc. aqueous NH_3 (*ca.* 1.5 ml), and stirring was continued under cooling for a further 40 min. The yellowish orange solid that deposited was collected by filtration, washed with cold H_2O (7 ml), and dried to give a first crop (1.33 g, 62%) of crude **5b**, mp *ca.* 140°C (dec.). The filtrate and washings were combined, saturated with K_2CO_3, and extracted with AcOEt (10 × 50 ml). The AcOEt extracts were combined, dried over anhydrous Na_2SO_4 in a refrigerator overnight, and concentrated *in vacuo* to leave a second crop (357 mg, 17%) of crude **5b** as a reddish brown solid, mp *ca.* 140 °C (dec.). The total yield of crude **5b** was 1.687 g (79%). The

crude **5b** was dissolved in 10% aqueous HCl, and the resulting solution was neutralized with conc. aqueous NH_3. The yellowish prisms that deposited were filtered off, washed with H_2O, and dried to give an analytical sample of **5b**, mp *ca.* 136 °C (dec.); MS *m/z*: 266 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 267.5 nm (ε 6300); $\lambda_{max}^{H_2O}$ (pH 1) 268.5 (6600); $\lambda_{max}^{H_2O}$ (pH 7) 269 (6600); $\lambda_{max}^{H_2O}$ (pH 13) 269 (6500); IR ν_{max}^{Nujol} cm^{-1}: 2235 (CN), 2150 (N_3); ^{1}H-NMR (Me_2SO-d_6) (δ: 5.40 [1H, d, J=5 Hz, C(1′)-H], 8.08 [1H, s, C(2)]-H].[32] *Anal.* Calcd for $C_9H_{10}N_6O_4$: C, 40.61; H, 3.79; N, 31.57. Found: C, 40.49; H, 3.78; N, 31.67.

5-Amino-1-methyl-1*H*-imidazole-4-carbonitrile (6a) i) From **5a**: A solution of **5a** (200 mg, 1.35 mmol) in MeOH (7 ml) was hydrogenated over 10% Pd–C (200 mg) at atmospheric pressure and room temperature for 80 min. The catalyst was removed by filtration and washed with MeOH (5 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave **6a** (120 mg, 73%) as a yellowish solid, mp 198—199 °C. Recrystallization from EtOH or H_2O provided an analytical sample as yellowish plates or prisms, mp 203—204 °C (lit. mp 195—196 °C[18a]; mp 196—198 °C[18b]); MS *m/z* 122 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 245 nm (ε 12100); $\lambda_{max}^{H_2O}$ (pH 1) 233.5 (9800), 253 (8300); $\lambda_{max}^{H_2O}$ (pH 7) 243.5 (11600); $\lambda_{max}^{H_2O}$ (pH 13) 243.5 (11700); IR ν_{max}^{Nujol} cm^{-1}: 3385 and 3330 (NH_2), 2200 (CN); ^{1}H-NMR (Me_2SO-d_6) δ: 3.37 [3H, s, N(1)-Me], 6.15 (2H, dull s, NH_2), 7.14 [1H, s, C(2)-H]. *Anal.* Calcd for $C_5H_6N_4$: C, 49.17; H, 4.95; N, 45.87. Found: C, 49.10; H, 4.79; N, 46.02.

ii) From **16**: A solution of **16** (*vide infra*) (30 mg, 0.19 mmol) in MeOH (20 ml) containing AcONa (31.4 mg, 0.38 mmol) was hydrogenated over 10% Pd–C (30 mg) at atmospheric pressure and 30 °C for 6 h. The reaction was so slow that more catalyst (30 mg) was added at this stage, and hydrogenation was continued under similar conditions for a further 7 h. After the latter procedure had been repeated once more, the catalyst was removed by filtration and washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo*, and the residue was extracted with AcOEt (4×20 ml). The AcOEt extracts were combined and concentrated *in vacuo* to leave a yellow solid (22 mg), which was purified by preparative TLC [silica gel, AcOEt–EtOH (6:1, v/v)]. A zone that ran faster gave the starting material (**16**) (9 mg, 30% recovery), and a slower-moving zone afforded **6a** (10 mg, 43%) as a yellowish solid, mp 202 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

5-Amino-1-β-D-ribofuranosyl-1*H*-imidazole-4-carbonitrile (6b) A solution of **5b** (213 mg, 0.8 mmol) in MeOH (11 ml) was hydrogenated over 10% Pd–C (213 mg) at atmospheric pressure and 20°C for 80 min. The reaction mixture was worked up in a manner similar to that described above for **6a** under item (i), giving crude **6b** (174 mg), mp 180.5—182 °C. Purification by means of column chromatography [silica gel, AcOEt–EtOH (10:1, v/v)] afforded **6b** (120 mg, 62%) as a slightly pinkish solid, mp 198—199°C. Recrystallization of the solid from EtOH furnished an analytical sample of **6b** as a colorless crystalline solid, mp 207—208 °C [lit.[19b] mp 205 °C (dec.)]; MS *m/z*: 240 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 248 nm (ε 13000); $\lambda_{max}^{H_2O}$ (pH 1) 239.5 (10900), 249 (sh) (9800); $\lambda_{max}^{H_2O}$ (pH 7) 246 (12600); $\lambda_{max}^{H_2O}$ (pH 13) 246 (12500); IR ν_{max}^{Nujol} cm^{-1}: 3475, 3415, 3345, 3280, and 3165 (OH's and NH_2), 2212 and 2184[33] (CN and hydrogen-bonded CN[34]); ^{1}H-NMR (Me_2SO-d_6) δ: 3.57 [2H, d, J=3 Hz, C(5′)-H_2], 3.92 [1H, m, C(4′)-H], 4.03 [1H, m, C(3′)-H], 4.24 [1H, t, J=6 Hz, C(2′)-H], 5.48 [1H, d, J=6 Hz, C(1′)-H], 6.34 (br, NH_2), 7.39 [1H, s, C(2)-H].[32] *Anal.* Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 45.15; H, 5.00; N, 23.12.

3,7-Dihydro-3-methoxy-7-methyl-4*H*-imidazo[4,5-*d*]-1,2,3-triazin-4-imine Hydriodide (1-Methoxy-9-methyl-2-azaadenine Hydriodide) (8a · HI) A stirred solution of **4a**[16a] (1.015 g, 6 mmol) in 1 N aqueous HCl (24 ml) was cooled to 5 °C, and a solution of $NaNO_2$ (of 97% purity) (512 mg, 7.2 mmol) in H_2O (6 ml) was added dropwise over a period of 5 min. Stirring was continued at the same temperature for a further 45 min. The reaction mixture was then concentrated *in vacuo* at a temperature not higher than 26 °C (bath temp.), leaving a yellowish brown solid. The solid was dissolved in H_2O (8.5 ml), and a solution of NaI (6.36 g, 42.4 mmol) in H_2O (3 ml) was added. The resulting mixture was kept in an ice bath for 30 min, and the yellowish brown solid that deposited was filtered off, washed with cold H_2O (1 ml), and dried to give **8a** · HI (1.181 g, 64%), mp 222.5—223 °C (dec.). Recrystallization by dissolving the crude salt in MeOH at room temperature and adding AcOEt to the resulting solution afforded an analytical sample of **8a** · HI as almost colorless prisms, mp 223—224 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 4.08 and 4.33 (3H each, s, NMe and OMe), 8.88 (1H, s, ring proton). *Anal.* Calcd for $C_6H_8N_6O$ · HI: C, 23.39; H, 2.94; N, 27.28. Found: C, 23.45; H, 2.99; N, 27.26.

7-Methyl-7*H*-imidazo[4,5-*d*]-1,2,3-triazin-4-amine 3-Oxide (9-Methyl-2-azaadenine 1-Oxide) (7a) A suspension of **8a** · HI (154 mg, 0.5 mmol) in $HCONMe_2$ (0.5 ml) was heated in an oil bath kept at 70 °C for 10 min. The reaction mixture was then cooled in an ice bath for 1 h, and the precipitate that resulted was filtered off, washed successively with $HCONMe_2$ (0.5 ml) and ether (1 ml), and dried to afford **7a** (67 mg, 81%) as a pale yellowish solid, mp 233 °C (dec.). Recrystallization of the solid from H_2O yielded an analytical sample as slightly brownish prisms, mp 240—241 °C (dec.); MS *m/z*: 166 (M^+); UV $\lambda_{max}^{H_2O}$ (pH 1) 222 nm (ε 25000), 241 (sh) (15800), 266 (sh) (4000), 343 (4620); $\lambda_{max}^{H_2O}$ (pH 7) 222 (25400), 242 (sh) (17400), 270 (4450), 345 (5510); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (CF_3CO_2D) δ: 4.31 (3H, s, NMe), 8.88 (1H, s, ring proton). *Anal.* Calcd for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 35.87; H, 3.61; N, 50.40.

5-Azido-1-methyl-1*H*-imidazole-4-carboxamide (9a) i) A stirred mixture of **5a** (148 mg, 1 mmol) and conc. aqueous NH_3 (13 ml) was cooled to 2—3 °C, and 30% aqueous H_2O_2 (1.5 ml), which had been cooled in an ice bath, was added. Stirring was continued at the same temperature for 4 h. The insoluble solid that resulted was filtered off, washed with cold H_2O (*ca.* 10 ml), and dried to give crude **9a** (140 mg) as a yellowish solid, mp *ca.* 135 °C (dec.). The solid was recrystallized by dissolving it in 10% aqueous HCl and neutralizing the resulting solution with conc. aqueous NH_3 to yield a yellowish crystalline solid (126 mg, 76%), mp *ca.* 135 °C (dec.); MS *m/z*: 166 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 268.5 nm (ε 6600); $\lambda_{max}^{H_2O}$ (pH 1) 236 (7900), 251 (sh) (7100); $\lambda_{max}^{H_2O}$ (pH 7) 268.5 (6600); $\lambda_{max}^{H_2O}$ (pH 13) 268.5 (6500); IR ν_{max}^{Nujol} cm^{-1}: 3350 and 3175 ($CONH_2$), 2150 (N_3), 1670 ($CONH_2$); ^{1}H-NMR (Me_2SO-d_6) δ: 3.45 [3H, s, N(1)-Me], 7.20 (1H, br, $CONH_2$), 7.57 [1H, s, C(2)-H]. *Anal.* Calcd for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 36.10; H, 3.68; N, 50.34.

ii) A stirred suspension of **5a** (889 mg, 6 mmol) in a mixture of H_2O (25 ml) and 30% aqueous H_2O_2 (6.80 g) was cooled to 3 °C, and CuCl (178 mg, 1.8 mmol) was added in portions over a period of 6 min. Stirring was continued at the same temperature for 20 min and then at 20 °C for 220 min, during which time two 1-g portions of 30% aqueous H_2O_2 were added at hourly intervals. The insoluble solid that resulted was filtered off, washed with H_2O, and dried to give crude **9a** (457 mg). Repeated recrystallizations of the crude solid in a manner similar to that described above under item (i) furnished **9a** (200 mg, 20%) as a pale brownish solid, mp *ca.* 130 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

5-Azido-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (9b) A stirred solution of **5b** (532 mg, 2 mmol) in conc. aqueous NH_3 (20 ml) was cooled to 1 °C, and cold 30% aqueous H_2O_2 (2.6 ml) was added. Stirring was continued at the same temperature for a further 1.5 h. The resulting yellowish orange solution was saturated with K_2CO_3, concentrated *in vacuo* to a small volume in order to remove NH_3, and then extracted with AcOEt (10×30 ml). The AcOEt extracts were combined, washed with saturated aqueous K_2CO_3 (10 ml), dried over anhydrous Na_2SO_4 in a refrigerator overnight, and concentrated *in vacuo* to leave **9b** (481 mg, 85%) as a hard glass, UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 265 nm (ε 5600); $\lambda_{max}^{H_2O}$ (pH 1) 230 (sh)[35] (6200), 258 (5200); $\lambda_{max}^{H_2O}$ (pH 7) 265.5 (5450); $\lambda_{max}^{H_2O}$ (pH 13) 265.5 (5500); IR ν_{max}^{Nujol} cm^{-1}: 2150 (N_3), 1655 ($CONH_2$); ^{1}H-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].[32]

5-Amino-1-methyl-1*H*-imidazole-4-carboxamide (10a) A solution of **9a** (116 mg, 0.698 mmol) in a mixture of AcOH (4 ml) and H_2O (2.2 ml) was hydrogenated over 10% Pd–C (116 mg) at atmospheric pressure and 21 °C for 1.5 h. The catalyst was removed by filtration and washed with H_2O. The filtrate and washings were combined and concentrated *in vacuo* to leave a pinkish solid (98.5 mg), mp 242—245 °C (dec.). Recrystallization of the solid from EtOH furnished **10a** (66 mg, 67%) as pale brownish needles, mp 251.5—252.5 °C (dec.) [lit.[27a] mp 251.5—253.5 °C (dec.)]. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10a**.[27a]

5-Amino-1-β-D-ribofuranosyl-1*H*-imidazole-4-carboxamide (AICA Riboside) (10b) The azide **9b** (100 mg, 0.352 mmol) was hydrogenated in MeOH (10 ml) over 10% Pd–C (100 mg) at atmospheric pressure and 23 °C for 1 h. The catalyst was removed by filtration and washed with MeOH (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to leave a grayish solid (88 mg). Recrystallization of the

solid from 90% (v/v) aqueous EtOH gave **10b** (38 mg, 42%) as slightly brownish prisms, mp 206—208 °C (dec.) [lit.[27a] mp 213—214.5 °C (dec.)]. This sample was identical (by comparison of the IR spectrum) with authentic **10b**.[27a]

5-Amino-2-chloro-1-methyl-1*H*-imidazole-4-carbonitrile (16) A stirred solution of **5a** (889 mg, 6 mmol) in 10% aqueous HCl (30 ml) was heated at 72 °C in an atmosphere of N_2 for 230 min. After cooling, the reaction mixture was neutralized with 10% aqueous Na_2CO_3 and extracted with AcOEt (6 × 20 ml). The AcOEt extracts were combined, dried over anhydrous Na_2SO_4 in a refrigerator for 2 d, and concentrated *in vacuo* to leave a pale brownish solid (198 mg). The solid was recrystallized from H_2O (8 ml), decolorized in EtOH (20 ml) with activated charcoal powder, and recrystallized again from H_2O (13 ml), giving **16** (67 mg, 7%) as pale yellowish needles, mp 244.5—246.5 °C (dec.). Three more recrystallizations from H_2O yielded an analytical sample of **16** as colorless needles, mp 252–253 °C (dec.); MS *m/z*: 158, 156 (M^+); UV $\lambda_{max}^{95\%\,aq.EtOH}$ 248 nm (ε 13200); $\lambda_{max}^{H_2O}$ (pH 1) 246 (13050); $\lambda_{max}^{H_2O}$ (pH 7) 246 (13200); $\lambda_{max}^{H_2O}$ (pH 13) 246 (13200); IR ν_{max}^{Nujol} cm^{-1}: 3388, 3340, 3252, and 3216 (NH_2), 2212 (CN); ^{1}H-NMR (Me_2SO-d_6) δ: 3.32 [s, N(1)-Me], 6.52 (br s, NH_2). *Anal.* Calcd for $C_5H_5ClN_4$: C, 38.36; H, 3.22; N, 35.78. Found: C, 38.06; H, 3.16; N, 35.73.

A Complex Presumed to be Dichloro(5-azido-1-methyl-1*H*-imidazole-4-carboximidic Acid)copper Methyl Ester (17) Cupric chloride (672 mg, 5 mmol) was dissolved in MeOH (4 ml), and the solution was filtered in order to remove an insoluble material. The filtrate was mixed with a solution of **5a** (741 mg, 5 mmol) in MeOH (10 ml). The resulting mixture was diluted with MeOH (3 ml) and kept at room temperature for 3 h and then in a refrigerator overnight. The greenish blue crystals that deposited were filtered off, washed with a little MeOH, and dried to give a complex presumed to be **17** (1.25 g, 79%), mp 126 °C (dec.). The crude complex was recrystallized by dissolving it in Me_2SO and adding AcOEt to the resulting solution, yielding an analytical sample as greenish blue crystals, mp 126 °C (dec.); UV $\lambda_{max}^{95\%\,aq.EtOH}$ 280 nm (ε 11900), 740 (61); IR ν_{max}^{Nujol} cm^{-1}: 3388 (NH), 2147 (N_3), 1638 (C=N). *Anal.* Calcd for $C_6H_8N_6O \cdot CuCl_2$: C, 22.91; H, 2.56; N, 26.71. Found: C, 22.89; H, 2.55; N, 26.48.

Methyl 5-Azido-1-methyl-1*H*-imidazole-4-carboximidate (18) Saturated aqueous K_2CO_3 (3 ml) was added to a stirred solution of **17** (315 mg, 1 mmol) in H_2O (1.5 ml). The mixture was stirred at room temperature for 70 min and then extracted with AcOEt (10 × 5 ml). The AcOEt extracts were combined, washed with saturated aqueous K_2CO_3, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a reddish brown oil (144 mg). Purification of the oil by flash chromatography[36] [silica gel, CH_2Cl_2–MeOH (10 : 1, v/v)] afforded **18** (120 mg, 67%) as a pale yellowish solid. Recrystallization of the solid by dissolving it in AcOEt and adding hexane to the resulting solution gave pale yellowish crystals, mp 87—88 °C; IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 2148 (N_3), 1656 (C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 3.46 [3H, s, N(1)-Me], 3.82 (3H, s, OMe), 7.64 [1H, s, C(2)-H], 8.12 (1H, br, NH). On elemantal analysis, however, this sample failed to give a satisfactory result.

Methyl 5-Azido-1-methyl-1*H*-imidazole-4-carboxylate (19) Saturated aqueous K_2CO_3 (3 ml) was added to a stirred solution of **17** (315 mg, 1 mmol) in H_2O (1.5 ml), and the resulting mixture was extracted with AcOEt (10 × 5 ml). The AcOEt extracts were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a yellow oil (**18**) (*ca.* 160 mg). The oil was treated with 1 N aqueous HCl (10 ml) at 22 °C for 3 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The AcOEt extracts were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a yellowish solid (145 mg). Recrystallization of the solid from hexane–benzene (2 : 1, v/v) provided **19** [103 mg, 57% overall yield (from **17**)] as yellowish needles, mp 87.5—88.5 °C; MS *m/z*: 181 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 2150 (N_3), 1713 (CO); ^{1}H-NMR (Me_2SO-d_6) δ: 3.45 [3H, s, N(1)-Me], 3.77 (3H, s, OMe), 7.63 [1H, s, C(2)-H]. However, elemental analysis of this sample failed to give a satisfactory result.

Methyl 5-Amino-1-methyl-1*H*-imidazole-4-carboxylate (20) A solution of **19** (110 mg, 0.607 mmol) in EtOH (4 ml) was hydrogenated over 10% Pd–C (110 mg) at atmospheric pressure and room temperature for 80 min. The catalyst was removed by filtration and washed with a little EtOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a colorless solid (93 mg), mp 222.5—224 °C. Recrystallization of the solid from AcOEt–EtOH (2 : 1, v/v) gave **20** (70 mg, 74%) as colorless prisms, mp 226.5—229 °C. Further recrystallization from AcOEt–EtOH (3 : 1, v/v) yielded an analytical sample as colorless prisms, mp 232—237 °C (lit.[30] mp 231 °C); IR ν_{max}^{Nujol} cm^{-1}: 3475, 3280, 3225, 3150, and 3105 (NH_2), 1670 and 1633 (hydrogen-bonded $ArCO_2Me$ and C=N); ^{1}H-NMR (Me_2SO-d_6) δ: 3.39 [3H, s, N(1)-Me], 3.66 (3H, s, OMe), 6.00 (2H, br, NH_2), 7.12 [1H, s, C(2)-H]. *Anal.* Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.51; H, 5.86; N, 27.09.

References and Notes

1) Paper LXIII in this series, T. Fujii, T. Saito, T. Fujisawa, *Chem. Pharm. Bull.*, **42**, 1231 (1994).
2) K. Mizuno, M. Tsujino, M. Takada, M. Hayashi, K. Atsumi, K. Asano, T. Matsuda, *J. Antibiot.*, **27**, 775 (1974).
3) H. Yoshioka, K. Nakatsu, M. Hayashi, K. Mizuno, *Tetrahedron Lett.*, **1975**, 4031.
4) *a*) R. Kusaba, *Ishoku*, **16**, 517 (1981); *b*) References cited in *Ishoku*, **17**, (suppl.) (1982).
5) *a*) K. Sakaguchi, M. Tsujino, M. Yoshizawa, K. Mizuno, K. Hayano, *Cancer Res.*, **35**, 1643 (1975); *b*) H. Koyama, M. Tsuji, *Biochem. Pharmacol.*, **32**, 3547 (1983).
6) *a*) M. Hayashi, T. Hirano, M. Yaso, K. Mizuno, T. Ueda, *Chem. Pharm. Bull.*, **23**, 245 (1975); *b*) Y. Tarumi, K. Moriguchi, T. Atsumi, *J. Heterocycl. Chem.*, **21**, 529 (1984); *c*) Y. Tarumi Y. Takebayashi, T. Atsumi, *ibid.*, **21**, 849 (1984); *d*) R. Gu, W. Tang, J. Pu, Z. Li, *Yiyao Gongye*, **17**, 129 (1986) [*Chem. Abstr.*, **105**, 191521*q* (1986)].
7) *a*) K. Fukukawa, S. Shuto, T. Hirano, T. Ueda, *Chem. Pharm. Bull.*, **32**, 1644 (1984); *b*) *Idem*, *ibid.*, **34**, 3653 (1986).
8) M. Kawana, G. A. Ivanovics, R. J. Rousseau, R. K. Robins, *J. Med. Chem.*, **15**, 841 (1972).
9) P. C. Srivastava, G. A. Ivanovics, R. J. Rousseau, R. K. Robins, *J. Org. Chem.*, **40**, 2920 (1975).
10) P. C. Srivastava, R. J. Rousseau, R. K. Robins, *J. Chem. Soc., Chem. Commun.*, **1977**, 151.
11) P. C. Srivastava, D. G. Streeter, T. R. Matthews, L. B. Allen, R. W. Sidwell, R. K. Robins, *J. Med. Chem.*, **19**, 1020 (1976).
12) J. A. Montgomery, H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972).
13) R. B. Meyer, Jr., D. A. Shuman, R. K. Robins, *J. Am. Chem. Soc.*, **96**, 4962 (1974).
14) *a*) T. Fujii, C. C. Wu, T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971); *b*) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, T. Fujisawa, *ibid.*, **39**, 301 (1991).
15) T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, K. Yamamoto, *Chem. Pharm. Bull.*, **31**, 3149 (1983).
16) *a*) T. Fujii, T. Itaya, C. C. Wu, F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *b*) T. Itaya, F. Tanaka, T. Fujii, *ibid.*, **28**, 535 (1972).
17) T. Saito, Y. Asahi, S. Nakajima, T. Fujii, *Heterocycles*, **30**, 329 (1990).
18) *a*) G. Shaw, D. N. Butler, *J. Chem. Soc.*, **1959**, 4040; *b*) M. Greenhalgh, G. Shaw, D. V. Wilson, N. J. Cusack, *J. Chem. Soc. (C)*, **1969**, 2198.
19) *a*) M. P. Groziak, J.-W. Chern, L. B. Townsend, *J. Org. Chem.*, **51**, 1065 (1986); *b*) J. P. Ferris, B. Devadas, C.-H. Huang, W.-Y. Ren, *ibid.*, **50**, 747 (1985); *c*) K. Suzuki, I. Kumashiro, Japan. Patent 6905225 [*Chem. Abstr.*, **71**, 12561*n* (1969)].
20) *a*) T. Fujii, T. Itaya, S. Yamada, *Chem. Pharm. Bull.*, **14**, 1452 (1966); *b*) T. Fujii, T. Itaya, *ibid.*, **19**, 1611 (1971).
21) *a*) T. Fujii, T. Itaya, S. Moro, *Chem. Pharm. Bull.*, **20**, 958 (1972); *b*) For similar *O*-dealkylations of 1-alkoxyadenine derivatives, see T. Fujii, F. Tanaka, K. Mohri, T. Itaya, *ibid.*, **22**, 2211 (1974); T. Fujii, I. Inoue, T. Itaya, T. Saito, *ibid.*, **28**, 3443 (1980); T. Fujii, T. Itaya, T. Saito, S. Kawakatsu, *ibid.*, **32**, 4842 (1984).
22) A. R. Katritzky, E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
23) *a*) J. Meisenheimer, O. Senn, P. Zimmermann, *Ber. Dtsch. Chem. Ges.*, **60**, 1736 (1927); *b*) D. Harrison, A. C. B. Smith, *J. Chem. Soc.*, **1960**, 2157.
24) A. Matsuda, N. Minakawa, T. Sasaki, T. Ueda, *Chem. Pharm. Bull.*, **36**, 2730 (1988).
25) *a*) B. Radziszewski, *Ber. Dtsch. Chem. Ges.*, **18**, 355 (1885); *b*) P. Friedlaender, J. Weisberg, *ibid.*, **28**, 1838 (1895).
26) G. Sosnovsky, D. J. Rawlinson, "Organic Peroxides," Vol. II, ed. by D. Swern, Wiley–Interscience, New York, 1971, Chapter III.
27) *a*) T. Fujii, T. Itaya, T. Saito, M. Kawanishi, *Chem. Pharm. Bull.*, **26**, 1929 (1978); *b*) G. Shaw, R. N. Warrener, D. N. Butler, R. K. Ralph, *J. Chem. Soc.*, **1959**, 1648; *c*) A. H. Cook, J. D. Downer,

I. Heilbron, *ibid.*, **1948**, 2028.
28) P. T. Lansbury, "Nitrenes," ed. by W. Lwowski, Interscience, New York, 1970, Chapter 11.
29) P. F. B. Barnard, *J. Chem. Soc.* (*A*), **1969**, 2140.
30) J. L. Wong, D. S. Fuchs, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1284.
31) *a*) For a review, see T. Fujii, T. Itaya, T. Saito, *Yuki Gosei Kagaku Kyokai Shi*, **41**, 1193 (1983); *b*) Ref. 1 and references cited therein.
32) For convenience, each carbon of the sugar moiety is indicated by a primed number.
33) Depending on the nature of crystals, this absorption band often disappeared.
34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Vol. 2, 2nd ed., Chapman and Hall, London, 1980, pp. 269—270.
35) Our previous communication[17] has erroneously described this shoulder wavelength to be 238 nm.
36) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).