Purines. LXXIX.[1] Synthesis and Hydrolysis of 3-Methoxyadenine and Its N^6-Benzyl Derivative Leading to the Corresponding 2-Hydroxyadenines

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Methylation of adenine 3-oxide (8a) with MeI in $AcNMe_2$ afforded 3-methoxyadenine (9a) in 44% yield. This compound (9a) underwent hydroxide-ion attack at the 2-position to give 2-hydroxyadenine (isoguanine) (10a) in 38% yield. A parallel reaction sequence starting from N^6-benzyladenine 3-oxide (8c) and proceeding through N^6-benzyl-3-methoxyadenine (9c) provided N^6-benzyl-2-hydroxyadenine (10c) in 29% overall yield, together with a small amount of N^6-benzyladenine (11c).

Key words adenine 3-oxide methylation; 3-methoxyadenine hydrolysis; isoguanine synthesis; N^6-benzyl-3-methoxyadenine hydrolysis

Chemical modification of the adenine ring by utilization of an *N*-alkoxy group as a control synthon is well documented.[2] The chemistry of 1-alkoxyadenines[3] and of their 9-substituted,[3c,e,4] 7-substituted,[5] N^6-substituted,[6] and N^6,9-disubstituted analogues[4k,7] has been extensively investigated. The most salient feature of the chemical behavior of 1-alkoxyadenines is that they suffer from hydrolytic cleavage of the N(1)–C(2) bond very easily. For example, 9-substituted 1-alkoxyadenines (**1**) underwent ring opening on treatment with H_2O at 4—5 °C to give the monocycles (**2**), which recyclized to the rearranged products **3** when heated in H_2O.[4a,e,8] The exocyclic *N*-alkoxyadenines **3** thus formed were stable under aqueous alkaline conditions.[4a,e] The reaction of **1** or **2** with hot aqueous alkali gave the deformylated monocycles **4** as the main products.[4a]

7-Methoxyadenine afforded 8-oxoadenine (**7a**) in 81% yield on treatment with boiling 0.1 N aqueous NaOH for 30 min,[9] and it was demethoxylated to give adenine (**11a**) in 81% yield when subjected to catalytic hydrogenolysis (Raney Ni–H_2, H_2O, 1 atm, 40 °C, 4 h).[10] 3-Alkyl-7-methoxyadenine perchlorates (**5**: R^1=Me) and 7-benzyloxy-3-methyladenine perchlorate (**5**: R^1=$PhCH_2$, R^2=Me) also underwent hydrolysis to give 3-alkyl-8-hydroxyadenines (**6**: R^3=H) in 37—74% yields when heated with 0.1 N aqueous NaOH for 1.5 h.[9] Similarly, ethoxide-ion attack at the 8-position was realized with 7-methoxy-3-methyladenine perchlorate (**5**: R^1=R^2=Me), which gave 8-ethoxy-3-methyladenine (**6**: R^2=Me, R^3=Et) in 89% yield on treatment with a 0.1 M EtONa solution in EtOH at 40 °C for 2 h.[9] Catalytic reduction (Raney Ni–H_2, H_2O, 1 atm, 40 °C, 4 h) of 7-methoxy-3-methyladenine perchlorate (**5**: R^1=R^2=Me) was reported to produce 3-methyladenine in 73% yield.[10]

Neither 9-methoxyadenine itself nor its derivatives have been synthesized. However, Watson obtained 9-benzyloxyadenine by treatment of 1-benzyloxy-5-[(ethoxymethylene)-amino]-1*H*-imidazole-4-carbonitrile with saturated ethanolic NH_3 at 120 °C for 3 h.[11] Under these conditions, 9-benzyloxyadenine was produced in 75% yield, suggesting the insensitivity of 9-alkoxyadenines to nucleophiles. The chemistry of 3-alkoxyadenines (type **9**), however, remained to be studied[2b] until our present work was undertaken.

In connection with our recent synthesis of the marine 8-oxoadenine aplidiamine (**7d**),[12] we intended to develop a new synthetic route to 8-oxoadenine derivatives, envisaging chemical transformation of adenine 3-oxides (**8**) into 8-oxoadenines (**7**) through hitherto unknown 3-alkoxyadenines (**9**). We first selected N^6-benzyl-8-oxoadenine (**7c**) as a target for synthesis. Thus, N^6-benzyladenine 3-oxide (**8c**)[13] was treated with five molar eq of MeI in $AcNMe_2$ at 30 °C for 20 h to provide the hydriodide of a monomethylated product in 70% yield. This compound was converted into the free base **9c** in 96% yield by treatment with Amberlite IRA-402 (HCO_3^-). The UV spectra of **9c** in various solvents resembled those of N^6-benzyl-3-methyladenine.[14] The ^{1}H-NMR spectrum of **9c** measured in $(CD_3)_2SO$ exhibited characteristics similar to those reported for N^6,3-dialkyladenines[15]: There were observed at 25 °C two sets of signals for most of the individual protons, all with identical ratios (2 : 5) of relative integral intensities, but they coalesced into one set at *ca*. 80—100 °C, indicating the existence of *syn–anti* [with respect to the N^6-CH_2Ph and N(1)] isomerism due to restricted rotation

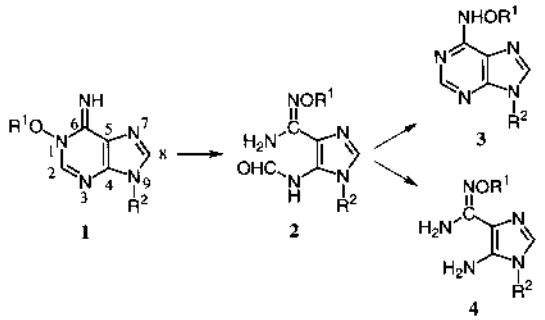

Chart 1

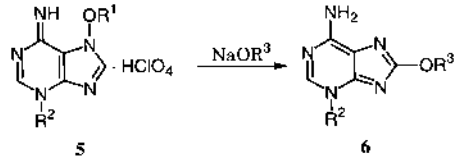

Chart 2

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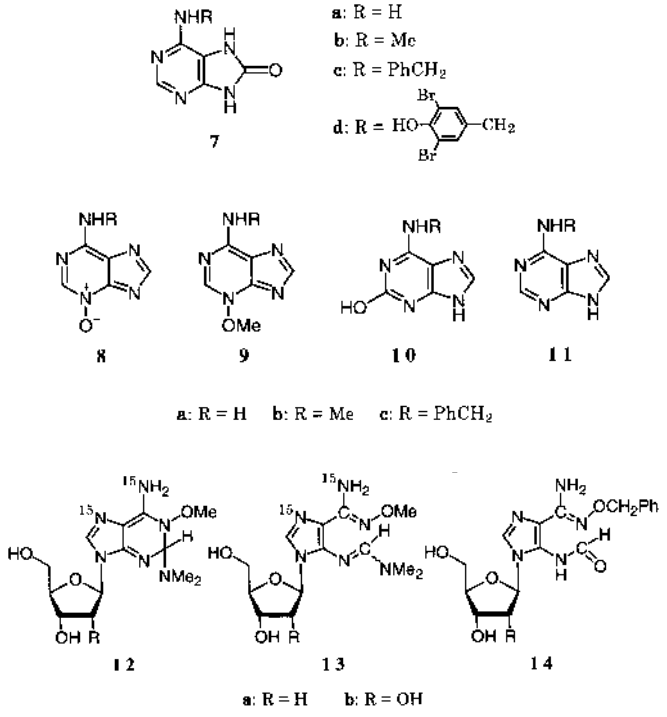

about the C(6)–N^6 bond. These results suggested that methylation of **8c** occurred at the oxygen atom, and the 3-methoxy structure for **9c** was finally confirmed by hydrogenolysis of **9c** using H_2 and Pd–C in the presence of $HClO_4$, which led to N^6-benzyladenine (**11c**) (51% yield). On treatment with 0.1 N aqueous NaOH at room temperature for 2 h, **9c** provided the hydrolyzed product **10c** in 43% yield, together with N^6-benzyladenine (**11c**) (11%). The latter compound (**11c**) was probably formed through nonreductive cleavage of the N–O bond, as in the cases of 1-benzyloxyadenine (**1**: R^1=$PhCH_2$, R^2=H),[3c] its 9-benzyl derivative (**1**: R^1=R^2=$PhCH_2$),[3c] and 1-alkoxy-9-methyl-8-oxoadenines.[16] The UV spectra of the major product **10c** in various solvents did not resemble those of N^6-methyl-8-oxoadenine (**7b**),[17] but closely resembled those of N^6-methyl-2-hydroxyadenine (**10b**).[18] The correctness of the structure of **10c** was further supported by comparison of its ^{1}H-NMR spectrum in $(CD_3)_2SO$ with that[18] of N^6-methyl-2-hydroxyadenine (**10b**). However, an attempt to convert **10c** into 2-hydroxyadenine (**10a**)[19] by treatment with $(NH_4)_2S_2O_8$[20] failed.

We next investigated alkaline hydrolysis of 3-methoxyadenine (**9a**), which was prepared in 44% yield by methylation of adenine 3-oxide (**8a**)[21] with MeI in $AcNMe_2$ at 30 °C for 24 h. The correctness of the methoxy structure for **9a** was established by the formation of adenine (**11a**) in 73% yield on hydrogenolysis using H_2 and Pd–C in H_2O in the presence of $HClO_4$. When treated with 0.1 N aqueous NaOH at room temperature for 1 h, **9a** afforded 2-hydroxyadenine (**10a**) (isolated in the form of the hemisulfate[19] in 38% yield) as the sole product. Although our initial attempt to convert **8a**, **c** into the corresponding 8-oxoadenines (**7a**, **c**) *via* **9a**, **c** failed, the chemical behavior observed for **9a**, **c** was in general agreement with that[22] reported for 1-alkoxypyridinium salt.

In conclusion, the present investigation has revealed that 3-methoxyadenine (**9a**) and its N^6-benzyl derivative (**9c**) are easily prepared from adenine 3-oxide (**8a**) and N^6-benzyladenine 3-oxide (**8c**), respectively, and undergo nucleophilic attack of hydroxide ion at the 2-position to give the corresponding 2-hydroxyadenines (**10a** and **10c**). Modification of this methodology may open new routes for syntheses of various types of 2-substituted adenines.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and values are corrected. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)], a JEOL JNM-EX-270 or a JNM-GSX-500 NMR spectrometer [measured at 25 °C in $(CD_3)_2SO$ with Me_4Si as an internal standard]. Elemental analyses and MS measurements were performed by Dr. Masako Takani and her associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[23] The following abbreviations are used: br=broad, d=doublet, m=multiplet, s=singlet, sh=shoulder, t=triplet.

3-Methoxyadenine (9a) A mixture of **8a**·1/2H_2O[21] (757 mg, 4.73 mmol), MeI (3.57 g, 25.2 mmol), and $AcNMe_2$ (20 ml) was stirred at 30 °C for 24 h and then concentrated *in vacuo*. The residue was purified by flash chromatography [$CHCl_3$–MeOH–5% aqueous NH_3 (20 : 7 : 1, v/v)] to afford **9a** (346 mg, 44%), mp 207—215 °C (dec.). Recrystallization from EtOH provided an analytical sample of **9a** as colorless prisms, mp 209—215 °C (dec.); MS *m/z*: 165 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 274 nm (ε 11900), 281 (sh) (11400); $\lambda_{max}^{H_2O}$ (pH 1) 277 (16800); $\lambda_{max}^{H_2O}$ (pH 7) 274 (12600); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR δ: 4.27 (3H, s, OMe), 7.79 [1H, s, C(8)-H], 8.03 (2H, br, NH_2), 8.64 [1H, s, C(2)-H]. *Anal*. Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.76; H, 4.28; N, 42.31.

***N*^{6}-Benzyl-3-methoxyadenine Hydriodide (9c·HI)** A mixture of **8c**[13] (241 mg, 1 mmol), MeI (710 mg, 5 mmol), and $AcNMe_2$ (20 ml) was stirred at 30 °C for 20 h. The resulting yellow solution was concentrated *in vacuo*, and the residue was triturated with a mixture of Et_2O (2 ml) and EtOH (1 ml) and cooled in an ice bath. The precipitate that separated was collected by filtration, washed with EtOH (1 ml), and dried to afford **9c**·HI (268 mg, 70%), mp 132—133 °C (dec.). Recrystallization of this product from EtOH gave an analytical sample of **9c**·HI as slightly yellow needles, mp 134—136 °C (dec.); UV $\lambda_{max}^{95\%\,EtOH}$ 293 nm (ε 17800); $\lambda_{max}^{H_2O}$ (pH 1) 225 (24600), 289 (22900); $\lambda_{max}^{H_2O}$ (pH 7) 224 (28700), 293 (16900); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 287 (*ca*. 11500); ^{1}H-NMR δ: 4.34 (3H, s, OMe), 4.90 (2H, d, J=5.6 Hz, PhC$\underline{H}_2$NH), 7.32—7.50 (5H, m, $\underline{Ph}CH_2$), 8.61 and 9.27 (1H each, s, purine protons), 9.71 (1H, br, $PhCH_2N\underline{H}$), 13.0 (1H, br, NH). *Anal*. Calcd for $C_{13}H_{13}N_5O$·HI: C, 40.75; H, 3.68; N, 18.28. Found: C, 40.73; H, 3.68; N, 18.15.

***N*^{6}-Benzyl-3-methoxyadenine (9c)** A solution of **9c**·HI (101 mg, 0.264 mmol) in H_2O (10 ml) was passed through a column packed with Amberlite IRA-402 (HCO_3^-) (0.5 ml), and the column was eluted with H_2O (50 ml). The eluate was concentrated *in vacuo* to leave **9c** (64 mg, 96%), mp 169—172 °C (dec.). Recrystallization of this product from 10% aqueous EtOH provided an analytical sample of **9c** as colorless plates, mp 177—178 °C (dec.); MS *m/z*: 255 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 297 nm (ε 15900); $\lambda_{max}^{H_2O}$ (pH 1) 289 (22000); $\lambda_{max}^{H_2O}$ (pH 7) 292 (16700); $\lambda_{max}^{H_2O}$ (pH 13) (unstable) 287 (*ca*. 9500); ^{1}H-NMR δ: 4.26 (2/7×3H), 4.28 (5/7×3H) (s each, OMe), 4.75 (5/7×2H), 5.32 (2/7×2H) (d each, J=6 Hz, PhC$\underline{H}_2$NH), 7.18—7.42 (5H, m, $\underline{Ph}CH_2$), 7.82 [1H, s, C(8)-H], 8.64 (2/7H), 8.74 (5/7H) [s each, C(2)-H], 8.89 (2/7H), 9.13 (5/7H) (br t each, J=6 Hz, $PhCH_2N\underline{H}$). *Anal*. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.35; H, 5.21; N, 27.36.

Hydrogenolysis of 9a Leading to 11a A mixture of **9a** (49.5 mg, 0.3 mmol), 10% Pd–C (75 mg), 10% aqueous $HClO_4$ (300 mg), and H_2O (10 ml) was shaken under H_2 at atmospheric pressure and *ca*. 40 °C for 5 h. The catalyst was filtered off and extracted with boiling MeOH using a Soxhlet extractor. The aqueous filtrate obtained from the reaction mixture and the MeOH extracts were combined and concentrated *in vacuo* to a small volume. A solution of picric acid (68.7 mg, 0.3 mmol) in 0.1 N aqueous NaOH (3 ml) was added to the residue. The precipitate that resulted was collected by filtration, washed with H_2O (6 ml), and dried to afford adenine picrate (80 mg, 73%), as a slightly yellow solid, mp 283—288 °C (dec.). Recrystallization of this solid from H_2O afforded yellow needles, mp 288—292 °C (dec.), which were identified (by comparison of the IR spectrum and TLC mobility) with authentic adenine picrate.[3a]

Hydrogenolysis of 9c Leading to 11c A solution of **9c** (50.2 mg, 0.197 mmol) in MeOH (2 ml) was shaken under H_2 in the presence of 10% Pd–C (50 mg) and 1% aqueous $HClO_4$ (2 g) at atmospheric pressure and room

temperature for 1.5 h. The catalyst was filtered off and washed successively with hot H_2O (10 ml) and hot MeOH (20 ml). The filtrate and washings were combined and concentrated *in vacuo* to a volume of *ca*. 5 ml. Reduction of the resulting solution was again effected over another 10% Pd–C (50 mg) at atmospheric pressure and *ca*. 45 °C for a further 3.5 h. The catalyst was filtered off and washed with hot MeOH (30 ml). The filtrate and washings were combined, concentrated *in vacuo* to a volume of *ca*. 1 ml, and neutralized with saturated aqueous $NaHCO_3$. The precipitate that resulted was collected by filtration, washed with H_2O (1 ml), and dried to afford **11c** (22.6 mg, 51%), mp 229—230 °C (dec.), which was identical (by comparison of the IR spectrum and TLC mobility) with authentic **11c**.

Hydrolysis of 9a Leading to 10a A suspension of **9a** (82.7 mg, 0.5 mmol) in 0.1 N aqueous NaOH (20 ml) was stirred at room temperature for 1 h. The resulting solution was neutralized with 10% aqueous H_2SO_4. The precipitate that separated was collected by filtration and dried to give **10a** as a dark solid (66 mg), mp >300°C; ^{1}H-NMR δ: 7.41 (2H, br, NH_2), 7.74 [1H, s, C(8)-H], 11.46 (2H, br, two NH's). This was recrystallized from 1% aqueous H_2SO_4 to afford **10a**$\cdot 1/2H_2SO4 \cdot 1/2H_2O$ (39.5 mg, 38%), mp 272—276 °C (dec.), which was identical (by comparison of the IR spectrum and TLC mobility) with an authentic specimen.[19)]

Hydrolysis of 9c Leading to 10c A suspension of **9c** (31.2 mg, 0.122 mmol) in 0.1 N aqueous NaOH (10 ml) was stirred at room temperature for 2 h. The resulting yellow solution was neutralized with 10% aqueous HCl. The precipitate that separated was collected by filtration, washed with H_2O (2×1 ml), and dried to give a yellowish solid (15.7 mg). This was subjected to preparative TLC [$CHCl_3$–MeOH–concentrated aqueous NH_3 (20 : 7 : 1, v/v)] to provide **11c** (2.9 mg, 11%), which was identical (by comparison of the ^{1}H-NMR spectrum and TLC mobility) with an authentic specimen, and **10c** (12.7 mg, 43%), mp >300 °C. The latter product was dissolved in 90% aqueous EtOH (50 ml), and the solution was concentrated to a volume of *ca.* 0.5 ml. The precipitate that deposited was collected by filtration, dried at 2 mmHg and 100 °C for 5 h to provide an analytical sample of **10c**$\cdot 1/4H_2O$ as colorless minute crystals, mp >300 °C; MS *m/z*: 241 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 245 nm (ε 12800), 284 (12500); $\lambda_{max}^{H_2O}$ (pH 1) 289 (16900); $\lambda_{max}^{H_2O}$ (pH 7) 243 (10500), 283 (12300); $\lambda_{max}^{H_2O}$ (pH 13) 288 (15400); ^{1}H-NMR δ: 4.63 (2H, d, J=4.9 Hz, PhC$\underline{H}_2$NH), 7.18—7.42 (5H, m, $\underline{Ph}CH_2$), 7.66 (2/5H), 7.84 (3/5H) [s each, C(8)-H], 7.76 (3/5H, br s), 8.15 (2/5H, br) (PhCH_2N$\underline{H}$), 10.89 (1H, br), 11.86 (br s) and 12.41 (br) (a total of 1H) (NH and OH).[24)] *Anal.* Calcd for $C_{12}H_{11}N_5O \cdot 1/4H_2O$: C, 58.65; H, 4.72; N, 28.50. Found: C, 58.86; H, 4.60; N, 28.31.

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8) Quite recently, Jones and co-workers [Pagano A. R., Zhao H., Shallop A., Jones R. A., *J. Org. Chem*., **63**, 3213—3217 (1998)] reported the syntheses of 2′-deoxyadenosine and adenosine, both labeled with ^{15}N at both the 1- and 7-positions, which adopted an "N(1)-methoxy" strategy essentially the same as that reported by us for the unlabeled species,[4e,l,o)] but without reference to most of the previous papers.[4e,f,j,m,n,o)] The key step in their syntheses was the Dimroth rearrangements of 2′-deoxy-1-methoxyadenosine and 1-methoxyadenosine, both labeled with ^{15}N at the N^6- and 7-positions, which were effected in methanolic Me_2NH and claimed to proceed through the isolable bicyclic *N*,*N*-dimethylamine adducts **12a**, **b** [representing very reactive tetrahedral [at C(2)] intermediates, presumably difficult to isolate]. However, their ^{1}H- and ^{13}C-NMR spectral data presented for the adducts, especially their complexity of signals for **12b**, may also be interpretable in terms of the isomeric monocycles **13a**, **b**, which are structurally analogous to our isolable Dimroth intermediates **14a**, **b**[4e,l,m)] [existing as *cis–trans* equilibrated mixtures (due to the formamido group) in solution].
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24) The observed complexity of the proton signals is most likely due to tautomerization, which might have occurred in the $(CD_3)_2SO$ solution.