Purines. LVIII.[1] A Synthesis of 7-Alkyl-1-methyladenines from Adenosine by Regioselective Alkylation: Utilization of a 1-Methoxy Group as a Control Synthon

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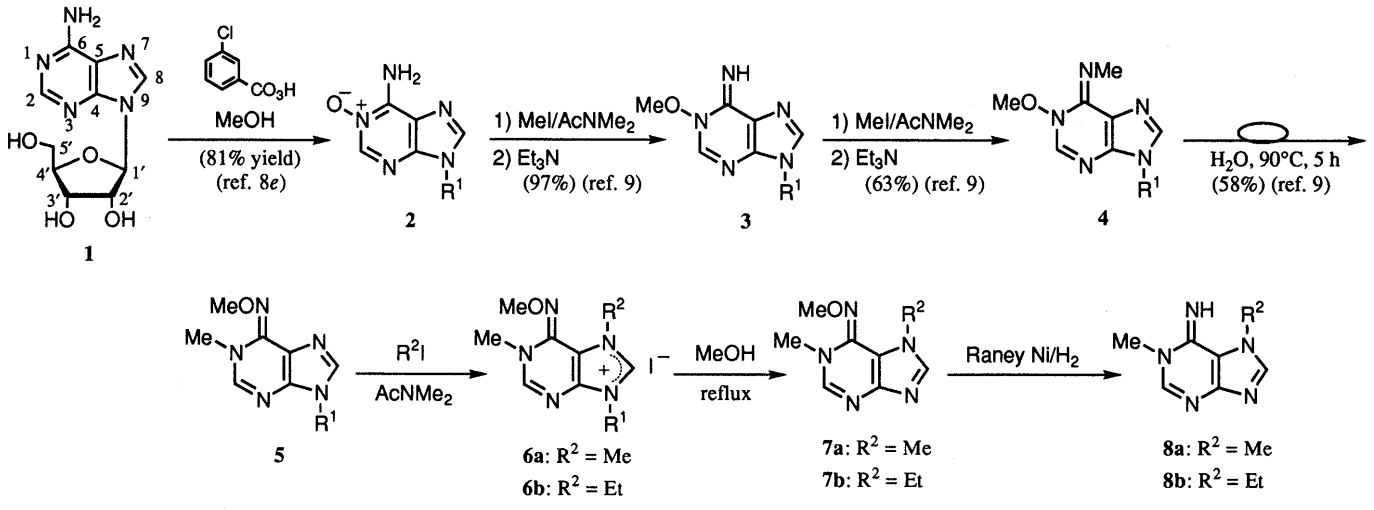
A general synthetic route to 7-alkyl-1-methyladenine (8) from N^6-methoxy-1-methyladenosine (5) in three steps [hence from adenosine (1) in seven steps] has been established. The route started with alkylation of 5, readily obtainable from 1 in four steps according to previously reported procedures, and proceeded through glycosidic methanolysis of the resulting 7-alkylated nucleoside (6) and removal of the N^6-methoxy group by catalytic hydrogenolysis.

Keywords 7-alkyl-1-methyladenine; 1-methyladenosine; alkylation regioselective; riboside methanolysis; demethoxylation; hydrogenolysis catalytic

In connection with our continuing study on the Dimroth rearrangement[1,2] and hydrolytic deamination[2b,3] in the adenine ring system, it became necessary to secure some 7-alkyl-1-methyladenines (type 8). A number of 1-alkyl-7-methyladenines have been prepared by Taylor and Loeffler[4] from 5-cyano-4-ethoxymethyleneamino-1-methylimidazole and the appropriate amine, but the application of their procedure has been limited to 7-methyl derivatives because of the route to the precursor imidazole. Leonard *et al.*[5] have extended this procedure to the synthesis of 1,7-dibenzyladenine, which includes benzylation of 4(5)-bromo-5(4)-nitroimidazole (obtainable from imidazole *via* a four-step route[6]) with $PhCH_2Br$. Although the two procedures appear to be generally applicable to the preparation of other 1,7-dialkyladenines,[7] the lengthy sequence of reactions required (possibly nine steps from the starting point) would make them less attractive. This led us to design an alternative route for the synthesis of the requisite 7-alkyl-1-methyladenines (type **8**) in the present study. The basis for the new design was afforded by our previous finding that the alkoxy group at the N(1)- or N^6-position of the adenine ring system can be a useful and convenient "control synthon"[8] for chemical modification of adenine derivatives including nucleosides.[9]

The starting point selected for the synthesis of the first target, 1,7-dimethyladenine (**8a**), was N^6-methoxy-1-methyladenosine (**5**), which was obtainable from adenosine (**1**) in four steps through the 1-oxide **2**,[9e] the 1-methoxy derivative **3**, and the N^6-methyl derivative **4** according to the previously reported procedures.[10] Treatment of **5** with MeI in $AcNMe_2$ at 18 °C for 20 h gave the N(7)-methylated product (**6a**) in 89% yield. The occurrence of methylation in **5** at N(7) was inferred from the known preferential N(7)-methylation[10] of the 9-methyl analogue (**5**: R^1 = Me for β-D-ribofuranosyl), and the correctness of this inference was supported by a UV spectral similarity between **6a** and N^6-methoxy-1,7,9-trimethyladeninium iodide (**6a**: R^1 = Me for β-D-ribofuranosyl).[10] The 7-methylated riboside **6a** was found to be susceptible to solvolysis, as in the case[9d] of the 1-demethyl homologue: it afforded the perchlorate salt **7a**·$HClO_4$ of the aglycone in 57% yield when treated with boiling MeOH for 5 h and then with $NaClO_4$. On treatment with H_2O at 100 °C for 40 min, **6a** furnished a mixture of products, but we failed to isolate **7a** from it. The aglycone



1 2 3 4 5

6a: R^2 = Me
6b: R^2 = Et

7a: R^2 = Me
7b: R^2 = Et

8a: R^2 = Me
8b: R^2 = Et

R^1 = β-D-ribofuranosyl

Chart 1

7a·$HClO_4$ was then subjected to catalytic hydrogenolysis (Raney Ni/H_2, H_2O, 1 atm, 20 °C, 5 h), giving the desired compound **8a**·$HClO_4$ in 47% yield (in 7% overall yield from **1**).

A parallel sequence of reactions starting with ethylation of **5** was followed for the synthesis of the second target, 7-ethyl-1-methyladenine (**8b**). Thus, **5** was treated with EtI in $AcNMe_2$ at 30 °C for 30 h, and the crude product (**6b**) was heated in boiling MeOH for 6 h to form the 7-ethylated aglycone **7b**. The aglycone was isolated in the form of the perchlorate salt (**7b**·$HClO_4$) in 38% overall yield (from **5**). Finally, demethoxylation of **7b**·$HClO_4$ (Raney Ni/H_2, H_2O, 1 atm, 17 °C, 5 h) furnished **8b**·$HClO_4$ in 60% yield (in 6.5% overall yield from **1**).

In an attempt to prepare 7-benzyl-1-methyladenine (type **8**: $R^2 = PhCH_2$) by following a parallel route, **5** was treated with $PhCH_2Br$ in $AcNMe_2$ at 30 °C for 24 h and then with boiling MeOH for 5 h. Although the reaction gave a complex mixture of products, we were unable to isolate the desired 7-benzylated aglycone (type **7**: $R^2 = PhCH_2$). This failure paralleled that of a similar benzylation of the N^6-benzyloxy-N(1)-demethyl analogue.[9d]

In conclusion, the results described above have not only opened a new synthetic route to 7-alkyl-1-methyladenines (type **8**) but also exemplify the usefulness of a methoxy group as a control synthon in the synthesis of adenine derivatives. The new route consists of seven steps from adenosine (**1**) and appears to be potentially applicable to the general synthesis of 1,7-dialkyladenines.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 3*b* for details of 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 were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

N^6-Methoxy-1,7-dimethyl-9-β-D-ribofuranosyladeninium Iodide (6a) A solution of N^6-methoxy-1-methyladenosine hemihydrate (**5**·1/2H_2O)[10] (3.20 g, 10 mmol) and MeI (7.02 g, 49.5 mmol) in $AcNMe_2$ (20 ml) was stirred at 18 °C for 20 h. The reaction mixture was concentrated *in vacuo* to leave a pale yellowish solid, which was washed with ether (3 × 10 ml) and then triturated with warm MeOH (5 ml). The methanolic mixture was then kept in a refrigerator for 5 h, and the crystals that resulted were filtered off, washed with a little MeOH, and dried to give **6a** (4.03 g, 89%), mp 121—123 °C (dec.). For analysis, the crude **6a** was recrystallized by dissolving it in warm MeOH (*ca.* 40 °C) and adding ether, affording faintly yellowish pillars, mp 129.5—131 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 295 nm (ε 7810); $\lambda_{max}^{H_2O}$ (pH 1) 226 (20400), 291 (8530); $\lambda_{max}^{H_2O}$ (pH 7) 226 (20500), 291 (8560); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 3.38 [3H, s, N(1)-Me], 3.6—3.8 [2H, m, C(5′)-H's], 3.85 (3H, s, OMe), 3.9—4.2 [2H, br m, C(4′)-H and C(3′)-H], 4.00 [3H, s, N(7)-Me], 4.25—4.4 [1H, br m, C(2′)-H], 5.92 [1H, d, J = 3 Hz, C(1′)-H], 8.26 [1H, s, C(2)-H], 9.47 [1H, s, C(8)-H].[11,12] *Anal.* Calcd for $C_{13}H_{20}IN_5O_5$: C, 34.45; H, 4.45; N, 15.45. Found: C, 34.37; H, 4.47; N, 15.16.

N^6-Methoxy-1,7-dimethyladenine Perchlorate (7a·$HClO_4$) A solution of **6a** (906 mg, 2 mmol) in MeOH (30 ml) was heated under reflux for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in H_2O (0.5 ml). The resulting reddish brown solution was decolorized by addition of a little $NaHSO_3$, and then a solution of $NaClO_4$ (337 mg) in a little H_2O was added. The mixture was kept in a refrigerator overnight, and the crystals that deposited were filtered off, washed with a little H_2O, and recrystallized from EtOH to furnish a first crop (239 mg, 41%) of **7a**·$HClO_4$, mp 183.5—184.5 °C (dec.). Work-up of the above aqueous filtrate and ethanolic mother liquor in the usual manner gave a second crop (95 mg, 16%) of the perchlorate, mp 178—179 °C (dec.). The total yield of **7a**·$HClO_4$ was 334 mg (57%). Recrystallization of the crude perchlorate from EtOH provided an analytical sample of **7a**·$HClO_4$ as colorless needles, mp 187—188 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 278 nm (ε 11300); $\lambda_{max}^{H_2O}$ (pH 1) 225.5 (10300), 281 (9770); $\lambda_{max}^{H_2O}$ (pH 7) 276.5 (12100); $\lambda_{max}^{H_2O}$ (pH 13) 276.5 (11900); ^{1}H-NMR (Me_2SO-d_6) δ: 3.39 [3H, s, N(1)-Me], 3.83 (3H, s, OMe), 3.90 [3H, s, N(7)-Me], 8.27 [1H, slightly dull s, C(2)-H], 8.62 [1H, s, C(8)-H].[13] *Anal.* Calcd for $C_8H_{11}N_5O$·$HClO_4$: C, 32.72; H, 4.12; N, 23.85. Found: C, 32.54; H, 4.09; N, 23.66.

7-Ethyl-N^6-methoxy-1-methyladenine Perchlorate (7b·$HClO_4$) A solution of **5**·1/2H_2O[10] (1.28 g, 4 mmol) and EtI (3.12 g, 20 mmol) in $AcNMe_2$ (8 ml) was stirred at 30 °C for 30 h. The reaction mixture was concentrated *in vacuo* to leave a brown oil, which was washed with ether (3 × 5 ml) and dissolved in MeOH (60 ml). The resulting methanolic solution, presumed to contain the 7-ethylated product (**6b**), was heated under reflux for 6 h and then concentrated *in vacuo*. The brown oily residue, presumed to contain **7b**·HI, was dissolved in H_2O (1 ml), and the aqueous solution was successively treated with $NaHSO_3$ and a solution of $NaClO_4$ (588 mg) in H_2O (0.5 ml) in a manner similar to that described above for **7a**·$HClO_4$, giving **7b**·$HClO_4$ (465 mg, 38% overall yield from **5**·1/2H_2O) as a pale yellowish solid, mp 156—165.5 °C (dec.). Recrystallization from EtOH produced an analytical sample of **7b**·$HClO_4$ as faintly yellowish prisms, mp 172—174 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 278 nm (ε 11300); $\lambda_{max}^{H_2O}$ (pH 1) 227 (6600), 281.5 (9380); $\lambda_{max}^{H_2O}$ (pH 7) 277.5 (11800); $\lambda_{max}^{H_2O}$ (pH 13) 277.5 (11800); ^{1}H-NMR (Me_2SO-d_6) δ: 1.35 [3H, t, J = 7 Hz, N(7)-$CH_2\underline{Me}$], 3.43 [3H, dull s, N(1)-Me], 3.82 (3H, s, OMe), 4.43 [2H, q, J = 7 Hz, N(7)-$C\underline{H}_2$Me], 6.24 (br, N^+H), 8.28 [1H, br, C(2)-H], 8.75 [1H, s, C(8)-H].[13] *Anal.* Calcd for $C_9H_{13}N_5O$·$HClO_4$: C, 35.13; H, 4.59; N, 22.76. Found: C, 34.95; H, 4.66; N, 22.66.

1,7-Dimethyladenine Perchlorate (8a·$HClO_4$) A solution of **7a**·$HClO_4$ (200 mg, 0.681 mmol) in H_2O (35 ml) was hydrogenated over Raney Ni W-2 catalyst[14] (0.5 ml) at atmospheric pressure and 20 °C for 5 h. The catalyst was removed by filtration and washed with H_2O (30 ml). The filtrate and washings were combined and concentrated *in vacuo*, leaving a slightly greenish solid. The solid was dried and recrystallized from MeOH to furnish **8a**·$HClO_4$·1/5H_2O (85.6 mg, 47%) as colorless needles, mp 257—257.5 °C (dec.). Further recrystallization from MeOH and drying over P_2O_5 *in vacuo* (2 mmHg) first at 75 °C for 3 h and then at room temperature for 15 h afforded an analytical sample of **8a**·$HClO_4$·1/5H_2O as colorless needles, mp 263—264 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 270 nm (ε 9710), 285 (sh) (5710); $\lambda_{max}^{H_2O}$ (pH 1) 270 (9420), 282 (sh) (5400)[15]; $\lambda_{max}^{H_2O}$ (pH 7) 270 (10100), 283 (sh) (5800); $\lambda_{max}^{H_2O}$ (pH 13) 265 (12100); ^{1}H-NMR (Me_2SO-d_6) δ: 3.80 [3H, s, N(1)-Me], 4.12 [3H, s, N(7)-Me], 8.54 and 8.61 (1H each, s, purine protons), 8.82 (2H, dull s, NH's).[16] *Anal.* Calcd for $C_7H_9N_5$·$HClO_4$·1/5H_2O: C, 31.46; H, 3.92; N, 26.21. Found: C, 31.43; H, 3.75; N, 26.18.

7-Ethyl-1-methyladenine Perchlorate (8b·$HClO_4$) A solution of **7b**·$HClO_4$ (523 mg, 1.7 mmol) in H_2O (100 ml) was hydrogenated over Raney Ni W-2 catalyst[14] (1 ml) at atmospheric pressure and 17 °C for 5 h. The reaction mixture was worked up as described above for **8a**·$HClO_4$, yielding **8b**·$HClO_4$ (283 mg, 60%) as colorless prisms, mp 250—252.5 °C (dec.). Further recrystallization of the crude perchlorate from MeOH gave an analytical sample as colorless prisms, mp 255—256 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 270 nm (ε 9900), 284 (sh) (5860); $\lambda_{max}^{H_2O}$ (pH 1) 270 (10100), 282 (sh) (5920); $\lambda_{max}^{H_2O}$ (pH 7) 270 (10300), 282 (sh) (6090); $\lambda_{max}^{H_2O}$ (pH 13) 265 (12200); ^{1}H-NMR (Me_2SO-d_6) δ: 1.38 [3H, t, J = 7.5 Hz, N(7)-$CH_2\underline{Me}$], 3.83 [3H, s, N(1)-Me], 4.57 [2H, q, J = 7.5 Hz, N(7)-$C\underline{H}_2$Me], 8.66 (2H, s, purine protons), 8.80 (2H, dull s, NH's).[16] *Anal.* Calcd for $C_8H_{11}N_5$·$HClO_4$: C, 34.61; H, 4.36; N, 25.22. Found: C, 34.49; H, 4.52; N, 25.18.

References and Notes

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11) For convenience, each carbon of the sugar moiety is indicated by a primed number.
12) The assignments of these signals are based on comparison with those of the N(9)-methyl analogue,[10] the N(1)-demethyl homologue,[9d] and the N^6-benzyloxy-N(1)-demethyl analogue.[9d]
13) Assigned by comparison of the signals of **6a**, **7a**·$HClO_4$, and **7b**·$HClO_4$.
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15) Reported data[4] for the free base **8a**: UV $\lambda_{max}^{0.1\,N\,HCl}$ 270 mμ (log ε 3.86).
16) Assigned by comparison of the signals of **8a**·$HClO_4$·$1/5H_2O$ and **8b**·$HClO_4$.