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Purines. LXIX.[1] Direct N(1)-Oxidation of 7-Benzyladenine and Stepwise Syntheses of Its N(1)- and N(3)-Oxides

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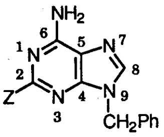
In contrast to the N(3)-selectivity in *N*-alkylation, *N*-oxidation of 7-benzyladenine (17) with *m*-chloroperoxybenzoic acid in MeOH has been found to give 7-benzyladenine 1-oxide (18) in 76% yield. Alternatively, the same *N*-oxide (18) has been synthesized in 81% yield from 1-benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (19) and hydroxylamine. Treatment of 1-benzyl-4-(hydroxyamino)imidazole-5-carbonitrile (24), obtained in 63% yield from the corresponding 4-nitro derivative (20) by catalytic hydrogenation (Pt/H_2), with formamidine acetate in boiling EtOH furnished 7-benzyladenine 3-oxide (23) in 78% yield. A UV spectroscopic approach indicated that the neutral species of 18 exists in H_2O in the N(1)-oxide form rather than the N(1)-OH form (27).

Key words 7-benzyladenine 1-oxide; 7-benzyladenine oxidation; *m*-chloroperoxybenzoic acid; 7-benzyladenine 3-oxide; acid dissociation constant; *N*-oxide tautomer

Data accumulated in the N^x-monosubstituted adenine family indicate that there is only a partial parallelism in regioselectivity between N^y-alkylation and N^y-oxidation. N(9)-Substituted adenines allow both *N*-alkylation[2] and *N*-oxidation[3] to occur preferentially at the 1-position. For instance, methylation of 9-benzyladenine (1) with MeI in $AcNMe_2$ at 50°C for 2 h gives 9-benzyl-1-methyladenine hydriodide (3) in 84% yield.[2d,k] Oxidation of 1 with 30% aqueous H_2O_2 in AcOH at 30 °C for 5 d provides 9-benzyladenine 1-oxide (4) in 69% yield[3d]; oxidation of 9-benzyladenine-*2-d* (2) with *m*-chloroperoxybenzoic acid (MCPBA) in MeOH at room temperature for 4 h affords the corresponding N(1)-oxide (5) in 71% yield.[3f] In the case of N^6-substituted adenines, alkylation under neutral conditions takes place mainly at the 3-position.[4] Although benzylation of N^6-benzyladenine (6) with $PhCH_2Br$ in $AcNMe_2$[5] or $HCONMe_2$[6] is no exception (*i.e.*, **6**→**7**), oxidation of **6** with MCPBA in MeOH at 30 °C for 20 h furnishes the N(1)-oxide (**8**) as the main product,[7] while that with 15% aqueous H_2O_2 in CF_3CO_2H at 65—70°C for 1 h produces both the N(3)-oxide (**9**) and the N(7)-oxide (**10**), but only in poor yields.[1]

Benzylation of 3-benzyladenine (**11**) with $PhCH_2Br$ in $AcNMe_2$ at 70°C for 28 h[5] or in boiling acetone for 75 h[8] to form 3,7-dibenzyladenine hydrobromide (**12**) in good yield is representative of a general 7-alkylation procedure in the N(3)-substituted adenine series.[8,9] Being in accord with this N(7)-selectivity in *N*-alkylation, oxidation of **11** with magnesium monoperoxyphthalate (MeOH, 30°C, 20 h) or with MCPBA [MeOH–1 M acetate buffer (pH 5.0), 30°C, 15 h] or with 30% aqueous H_2O_2/MeCN/$KHCO_3$ (MeOH, 25 °C, 22 h) gives the N(7)-oxide (**13**) in 40%,



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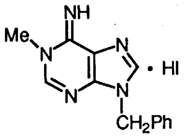

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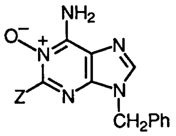

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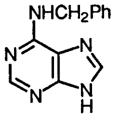

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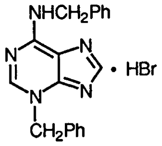

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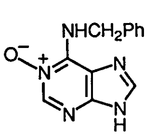

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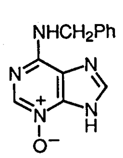

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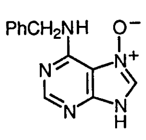

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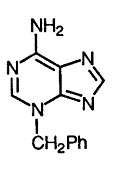

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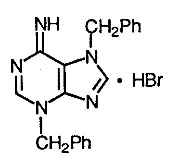

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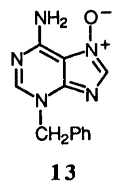

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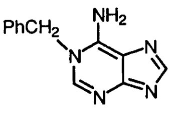

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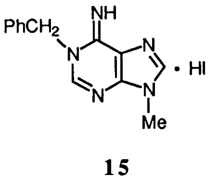

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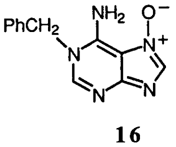

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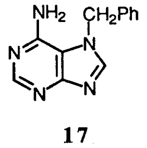

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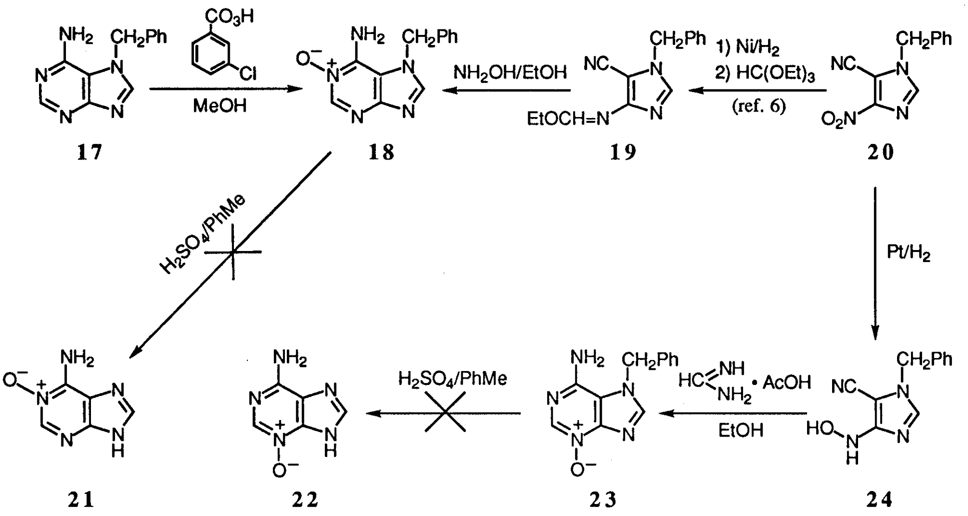

Chart 1

24%, or 12% yield, respectively.[10] In the case of N(1)-substituted adenines, *N*-alkylation usually occurs at the 9-position.[2d,h,11] Thus, methylation of 1-benzyladenine (**14**) with MeI in $AcNMe_2$ at 90—95 °C for 2 h affords 1-benzyl-9-methyladenine hydriodide (**15**) in 73% yield.[2d] However, *N*-oxidation of **14** with MCPBA in MeOH–0.5 M phosphate buffer (pH 6.6) at 30 °C for 20 h takes place at the 7-position, furnishing the N(7)-oxide (**16**) in 19% yield.[12]

N-Alkylation of N(7)-substituted adenines occurs preferentially at the 3-position, offering an alternative synthetic route to 3,7-disubstituted adenines.[2f,5,9a,11,13] For example, benzylation of 7-benzyladenine (**17**) with $PhCH_2Br$ in $AcNMe_2$ at 65 °C for 16 h produces 3,7-dibenzyladenine hydrobromide (**12**) in 81% yield.[5] Thus, it would be of interest to see whether direct *N*-oxidation of **17** could take place at the 3-position. In the present work, we investigated the MCPBA oxidation of **17** in MeOH. A brief account of a part of the results reported here has been published in a preliminary form.[14]

Oxidation of 7-benzyladenine (**17**) with MCPBA was effected in MeOH at 23 °C for 7 h. Work-up of the reaction mixture gave an *N*-oxide and its *m*-chlorobenzoate salt in 40% and 36% yields, respectively. Neutralization of the salt with conc. aqueous NH_3 in 50% (v/v) aqueous MeOH furnished the *N*-oxide (in the free base form) in 85% yield. The *N*-oxide was considered to be either the N(3)-oxide (**23**) or the N(1)-oxide (**18**) rather than the N(9)-oxide, since pyrimidine compounds are usually more susceptible to *N*-oxidation than imidazoles.[15] With a view to establishing the structure of this *N*-oxide by direct comparison with authentic samples, the two candidate *N*-oxides (**18** and **23**) were synthesized in the following stepwise manner (Chart 1).

The common starting point selected for the syntheses of **18** and **23** was 1-benzyl-4-nitroimidazole-5-carbonitrile (**20**),[6] which was first converted into the 4-(ethoxymethyleneamino) derivative **19** according to the literature procedure.[6] Treatment of **19** with hydroxylamine in EtOH at room temperature for 1 h gave the desired N(1)-oxide **18** in 81% yield. This cyclization was analogous to what Yamazaki *et al.*[16] adopted for the synthesis of 2′,3′-*O*-isopropylideneadenosine 1-oxide from 5-(ethoxymethyleneamino)-1-(2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)imidazole-4-carbonitrile.

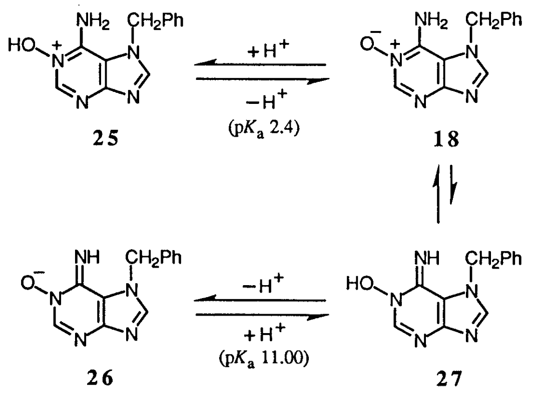

Chart 2

On the other hand, catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temp., 10 min) of **20** furnished the 4-(hydroxyamino) derivative **24** in 63% yield. On treatment with formamidine acetate in boiling EtOH for 3 h, **24** afforded the N(3)-oxide **23**, the other candidate *N*-oxide, in 78% yield.[17] The UV spectra of **23** in H_2O at pH 1 and 13 were similar to those[18] of 7-methyladenine 3-oxide, which Taylor and Loeffler[18] prepared from 1-methyl-4-nitroimidazole-5-carbonitrile *via* a parallel sequence of reactions proceeding through the corresponding 4-(hydroxyamino) derivative.

The *N*-oxide obtained directly from **17** by MCPBA oxidation was not identical with the above N(3)-oxide **23**, but was identical with a sample of the N(1)-oxide **18** synthesized from **20** through **19**, unequivocally establishing its N(1)-oxide structure. In an attempt to remove the benzyl group, **18** was treated with conc. H_2SO_4 and toluene[7,9b,10,12,19] at 35°C or 50 °C for 3 h. However, no debenzylation to form adenine 1-oxide (**21**) took place. An attempt to convert **23** into adenine 3-oxide (**22**) also failed under similar nonreductive debenzylation conditions.

As regards the tautomeric problem of 7-benzyladenine 1-oxide (**18**), its pK_a values in H_2O at 30 °C were spectrophotometrically determined to be 2.4 (basic) [for the protonated form (**25**)$\rightleftharpoons$neutral form] and 11.00 (acidic) [for the neutral form$\rightleftharpoons$monoanion (**26**)] (Chart 2). The UV spectrum of **18** in H_2O at pH 7 exhibited two absorption bands at 236 nm (ε 40900) and 279 nm (ε 8200), which may be regarded as those arising from the neutral species in view of the above pK_a values. Since the strong UV absorption of purine *N*-oxides in the 215—240 nm region is considered to be due to $>N\rightarrow O$ or the enol anion $>N\text{–}O^-$,[20] the above strong absorption of **18** at 236 nm is indicative of the overwhelming predominance of the N(1)-oxide tautomer (**18**) over the N(1)-OH tautomer (**27**) in the neutral species in H_2O.

In conclusion, the present results reveal that the main product (76% yield) from the MCPBA oxidation of 7-benzyladenine (**17**) is the N(1)-oxide **18**. Interestingly, this regioselectivity in *N*-oxidation is not in accord with that in *N*-alkylation.[2f,5,9a,11,13] At present, however, the factor(s) responsible for such an alteration in regioselectivity remain(s) uncertain. Over 35 years ago, Stevens and Brown[3b] reported that the peroxyacetic acid oxidation of 7-methyladenine did not yield an oxide. On the other hand, Scharf and Friedrich[21] reported the monoperoxyphthalic acid oxidations of adenine-cobamide (pseudovitamin B_{12}) and 2-methyladenine-cobamide, 7-substituted adenines linked to cobalt by coordination at the 9-position, in $HCONMe_2$ to form the corresponding N(1)-oxides in the adenine moieties. However, the chemical and spectroscopic evidence adduced by them appears to be insufficient, and their substrates are not exactly 7-substituted adenines because of the presence of the coordinate link with cobalt at the 9-position. Therefore, our present work can be regarded as the first valid example of direct N(1)-oxidation in the N(7)-substituted adenine series.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. Chromatography and measurements of spectra and acid dissociation constants were carried out as described previously.[10b] Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, m = multiplet, s = singlet.

Oxidation of 7-Benzyladenine (17) to Form 7-Benzyladenine 1-Oxide (18) and Its *m*-Chlorobenzoate Salt A solution of **17**[9a,b,13a] (1.20 g, 5.33 mmol) in MeOH (60 ml) was stirred at 23°C, and MCPBA (of 80% purity) (1.72 g, 8 mmol) was added in small portions. Stirring was continued at 23 °C for 7 h, and the colorless solid that deposited was collected by filtration, washed successively with MeOH (2 ml) and ether (2 × 2 ml), and dried to give **18** (520 mg, 40%), mp 237—239 °C (dec.). Recrystallization from MeOH yielded an analytical sample of **18** as colorless prisms, mp 237—242 °C (dec.); pK_a (in H_2O at 30 °C and ionic strength 1.0): 2.4 (basic), 11.00 ± 0.03 (acidic); MS *m*/*z*: 241 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 239 nm (ε 38300), 285 (7900); $\lambda_{max}^{H_2O}$ (pH 1) 268 (8500); $\lambda_{max}^{H_2O}$ (pH 7) 236 (40900), 279 (8200); $\lambda_{max}^{H_2O}$ (pH 13) 234 (24200), 287 (9700); ^{1}H-NMR ($Me_2SO\text{-}d_6$) δ: 5.74 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.10—7.16 (2H, m) and 7.25—7.38 (3H, m) [N(7)-CH$_2\underline{Ph}$], 7.89 (2H, br, NH_2), 8.51 [1H, s, C(8)-H],[22] 8.62 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.91; H, 4.68; N, 28.88.

The filtrate and washings, obtained when the crude **18** was isolated, were combined and concentrated *in vacuo* to a volume of 5 ml. The colorless crystals that deposited were filtered off, washed successively with MeOH (1 ml) and ether (3 × 3 ml), and dried to afford 7-benzyladenine 1-oxide *m*-chlorobenzoate (1 : 1) (salt) (757 mg, 36%), mp 193—194 °C. Recrystallization from 50% (v/v) aqueous MeOH furnished an analytical sample of the salt as colorless plates, mp 193—194 °C; ^{1}H-NMR ($Me_2SO\text{-}d_6$) δ: 5.74 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.1—8.0 (11H, m, aromatic protons and NH_2), 8.51 and 8.61 (1H each, s, purine protons), 13.31 (1H, br, CO_2H). *Anal.* Calcd for $C_{12}H_{11}N_5O \cdot C_7H_5ClO_2$: C, 57.37; H, 4.05; N, 17.60. Found: C, 57.55; H, 3.86; N, 17.68.

The salt (750 mg, 1.89 mmol) was dissolved in 50% (v/v) aqueous MeOH (*ca.* 30 ml) with application of heat. The resulting solution was brought to pH 8 by addition of conc. aqueous NH_3 and then allowed to stand at room temperature overnight. The colorless solid that deposited was filtered off, washed successively with MeOH (0.5 ml) and ether (2 × 1 ml), and dried to give the free base **18** (388 mg, 85%), mp 237—239 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the above analytical sample of **18**.

Conversion of 1-Benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (19) into 7-Benzyladenine 1-Oxide (18) Metallic Na (18 mg, 0.78 mg-atom) and hydroxylamine hydrochloride (54.6 mg, 0.786 mmol) were added to abs. EtOH (2 ml) in that order, and the mixture was heated under reflux for 10 min. After cooling, the insoluble solid (NaCl) that resulted was filtered off and washed with EtOH (0.5 ml). The filtrate and washings were combined and stirred, after addition of **19**[6] (100 mg, 0.393 mmol), at room temperature for 1 h. The colorless solid that deposited was filtered off, washed with EtOH (0.5 ml), and dried to yield **18** (76.9 mg, 81%), mp 235—240 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by the MCPBA oxidation of **17** (*vide supra*).

1-Benzyl-4-(hydroxyamino)imidazole-5-carbonitrile (24) A solution of **20**[6] (2.50 g, 11.0 mmol) in EtOH (250 ml) was hydrogenated over Adams catalyst (219 mg) at atmospheric pressure and room temperature for 10 min, taking up *ca.* 540 ml of H_2. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave a yellow solid. The solid was washed with EtOH (10 ml) and then recrystallized from EtOH (*ca.* 300 ml) to yield a first crop (1.16 g, 49%) of **24**, mp 166—170 °C (dec.). Concentration of the mother liquor of this recrystallization and washing of the residue with EtOH gave a second crop (327 mg, 14%) of **24**, mp 168—172 °C (dec.). The total yield of **24** was 1.487 g (63%). Recrystallization of the crude **24** from EtOH afforded an analytical sample as pale yellowish plates, mp 162—170 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3270, 3140 (NH and OH), 2208 (ArCN); ^{1}H-NMR ($Me_2SO\text{-}d_6$) δ: 5.18 [2H, s, N(1)-C$\underline{H}_2$Ph], 7.2—7.4 [5H, m, N(1)-CH$_2\underline{Ph}$], 7.84 [1H, s, C(2)-H], 8.80 (2H, br, NH and OH). *Anal.* Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.96; H, 4.79; N, 25.98.

7-Benzyladenine 3-Oxide (23) A stirred mixture of **24** (1.30 g, 6.07 mmol) and formamidine acetate (1.07 g, 10.3 mmol) in EtOH (90 ml) was heated under reflux for 3 h. After cooling, the colorless solid that deposited was collected by filtration, washed successively with EtOH (1 ml) and ether (1 ml), and dried to afford **23**·H_2O (1.22 g, 78%[17]), mp 220—230 °C (dec.). Recrystallization from MeOH, drying over P_2O_5 at 2 mmHg and 50 °C for 10 h, and subsequent moisturizing (by exposure to air until a constant weight was reached) provided an analytical sample of **23**·H_2O as pale yellowish plates, mp 225—232 °C (dec.); MS *m*/*z*: 241 (M^+), 225 ($M^+ - 16$); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 235 nm (ε 18000), 306 (13100); $\lambda_{max}^{H_2O}$ (pH 1) 226 (12900), 281 (14000); $\lambda_{max}^{H_2O}$ (pH 7) 233 (18500), 298 (13000); $\lambda_{max}^{H_2O}$ (pH 13) 232 (17900), 299 (12600); ^{1}H-NMR ($Me_2SO\text{-}d_6$) δ: 5.75 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.01 (2H, s, NH_2), 7.12—7.21 (2H, m) and 7.25—7.40 (3H, m) [N(7)-CH$_2\underline{Ph}$], 8.34 and 8.53 (1H each, s, purine protons). *Anal.* Calcd for $C_{12}H_{11}N_5O \cdot H_2O$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.75; H, 5.07; N, 27.04.

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