# Purines. LXXIV.[1] Syntheses and Rearrangements of 8-Oxoadenines Monomethylated at the $N^6$-, 1-, and 3-Positions

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**On treatment with boiling 2 N hydrochloric acid for 48 h, $N^6$-methyl-8-oxoadenosine (1), 1-methyl-8-oxoadenosine (5), and 7-methyl-8-oxoadenosine (8) underwent glycosidic hydrolysis, though much more slowly than the corresponding 8-unsubstituted compounds, furnishing the aglycons (2, 6, and 9) in 45%—63% yields. Under these conditions, $N^6$-methyl-8-oxoadenine (2) rearranged to 9-methyl-8-oxoadenine (3) (8% yield), presumably through fission and reclosure of the imidazole ring. Apparent methyl migration also occurred with 3-methyl-8-hydroxyadenine (7), which afforded 1-methyl-8-oxoadenine (6) in 9% yield on treatment with hydrochloric acid under similar conditions.**

**Key words** $N^x$-methyl-8-oxoadenosine hydrolysis; $N^x$-methyl-8-oxoadenine; fission–reclosure; 1-methyl-8-oxoadenine; 7-methyl-8-oxoadenine

Among the six possible *N*- or *O*-monomethylated 8-oxoadenines, 8-methoxyadenine (**11**) and $N^6$-methyl-8-oxoadenine (**2**) have already been synthesized by Robins.[2] We have reported the syntheses of 3-methyl-8-hydroxyadenine (**7**)[1] and 9-methyl-8-oxoadenine (**3**).[3] The remaining isomers, 1-methyl-8-oxoadenine (**6**) and 7-methyl-8-oxoadenine (**9**), might be prepared from the corresponding nucleosides (**5** and **8**) by glycosidic hydrolysis. However, Rizkalla *et al.*[4] reported that these nucleosides were strikingly resistant to acid hydrolysis, as was the case with the parent nucleoside, 8-oxoadenosine; the latter nucleoside was reported to be essentially unchanged after treatment with boiling 1 N hydrochloric acid for 2 h.[5]

Notwithstanding these negative reports, we found in the present study that $N^6$-methyl-8-oxoadenosine (**1**)[6] affords the known $N^6$-methyl-8-oxoadenine (**2**) in 53% yield, along with a small amount of 9-methyl-8-oxoadenine (**3**),[3] on treatment with boiling 2 N hydrochloric acid for 48 h. Being encouraged by this result, we next treated 1-methyl-8-oxoadenosine (**5**)[6] with hydrochloric acid in the same way to obtain the desired aglycon, 1-methyl-8-oxoadenine (**6**), as the hydrochloride in 78% yield. The hydrochloride gave the free base **6** in 81% yield on treatment with aqueous sodium carbonate. The correctness of the structure of **6** was established by its conversion to **2** through the Dimroth rearrangement.[7] 7-Methyl-8-oxoadenine (**9**), the last of the remaining positional isomers, was similarly prepared in 45% yield by slow hydrolysis of 7-methyl-8-oxoadenosine (**8**). The structural assignment of **9** may be made by direct comparisons with its five positional isomers [**2**, **3**, **6**, **7**, and 8-methoxyadenine (**11**)]. The requisite compound **11** had previously been synthesized from 6,8-dichloropurine through ammonolysis followed by methanolysis.[2] In the present work, we prepared **11** from 3-benzyl-8-methoxyadenine (**10**)[1] in 91% yield by hydrogenolysis using hydrogen and palladium-on-carbon. Thus, the structure of **9** was established on the basis of its nonidentity with each of the five positional isomers.

The above-mentioned formation of the by-product 9-methyl-8-oxoadenine (**3**) in the hydrolysis of $N^6$-methyl-8-oxoadenosine (**1**) deserves comment. Compound **3**

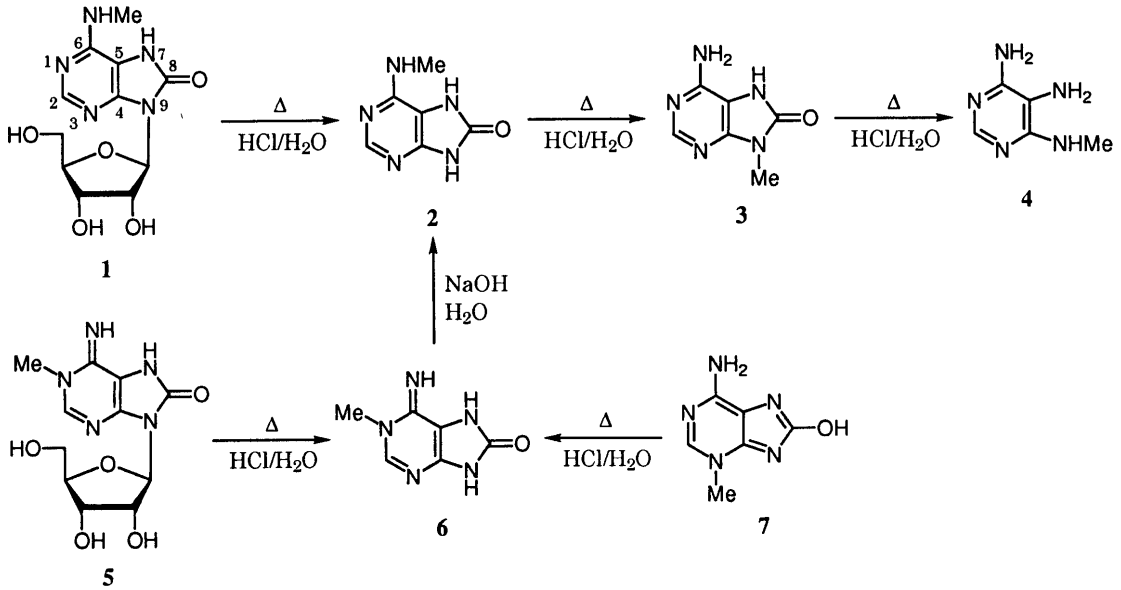


Chart 1

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appears to have been formed from the major product, $N^6$-methyl-8-oxoadenine (**2**). Indeed, **2** afforded **3** in 8% yield on treatment with boiling 2 N hydrochloric acid for 48 h. This reaction proved irreversible: under these acidic conditions, **3** yielded only a trace of a product presumed to be 5,6-diamino-4-(methylamino)pyrimidine (**4**).[8] A similar irreversible rearrangement was also realized with 3-methyl-8-hydroxyadenine (**7**), which afforded 1-methyl-8-oxoadenine (**6**) in 9% yield on treatment with boiling 2 N hydrochloric acid for 48 h. The same acid-treatment of **6** resulted in the almost quantitative recovery of this 1-methyl derivative. These rearrangements may be considered to follow a route involving hydrolytic ring-opening in the imidazole moiety and subsequent recyclization with the originally exocyclic nitrogen. Cleavage of adenine (**12**) at the C(8)–N(9) linkage would produce the symmetric monocycle **13**, through which transposition of all nitrogens other than N(7) may occur, as shown in Chart 4. This type of rearrangement under alkaline conditions has been reported for 3,7-dialkyladenines[9] and 7,9-dialkyladenines.[10] The rearrangement of 3-benzyladenine to $N^6$-benzyladenine under 2 atm of steam at 120 °C at pH 5.8 has been interpreted in terms of this type of reaction and subsequent Dimroth rearrangement.[11]

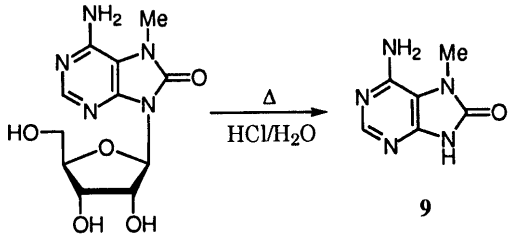


Chart 2

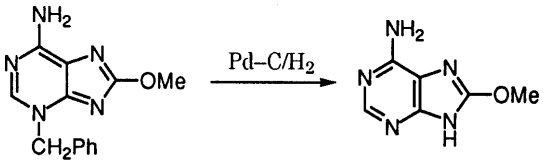


Chart 3

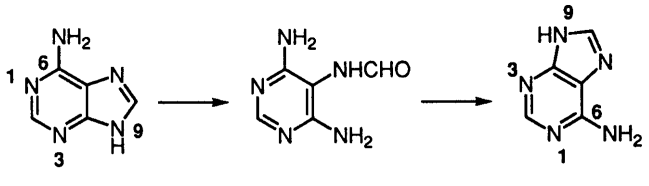


Chart 4

In conclusion, all six positional isomers possible for 8-oxoadenine monomethylated at a hetero atom have now become available. It may be seen from Table 1 that they are readily distinguishable from each other by means of UV spectroscopy. Thus, the data given in Table 1 are useful for identifying the position of monosubstitution on the 8-oxoadenine ring.

## 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. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi model 320 UV spectrophotometer [for solutions in 95% aqueous ethanol, 0.1 N hydrochloric acid (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous sodium hydroxide (pH 13)], a Shimadzu FTIR-8100 IR spectrophotometer, or either a JEOL JNM-EX-270 or a JNM-GSX-500 NMR spectrometer (measured at 25°C in hexadeuterated dimethyl sulfoxide with tetramethylsilane as an internal standard). Elemental analyses and MS measurements were performed by Dr. M. Takani and her associates at Kanazawa University. Flash chromatography was performed according to the reported procedure.[12] The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-dd's, q = quartet, s = singlet, sh = shoulder.

**$N^6$-Methyl-8-oxoadenine (2)** i) By Acid Hydrolysis of **1**: A solution of **1**·HCl[6] (200 mg, 0.599 mmol) in 2 N hydrochloric acid (15 ml) was heated under reflux for 48 h. The reaction mixture was neutralized with 10% aqueous sodium carbonate and concentrated *in vacuo*. The residue was purified by flash chromatography [chloroform–methanol (3 : 1, v/v)] to furnish **2** (32 mg) and a mixture (49 mg) of **2**, **3**, and **1**. The latter mixture was subjected again to flash chromatography to afford a second crop of **2** (15 mg), after recrystallization from 50% (v/v) methanol, and a mixture of **2** and **3**. This mixture was further purified by preparative

Table 1. UV Spectral Data for Monomethylated 8-Oxoadenines

| Compound | | UV spectra | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | Methylated site | 95% EtOH | | $H_2O$ (pH 1) | | $H_2O$ (pH 7) | | $H_2O$ (pH 13) | |
| | | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ | $\lambda_{max}$ (nm) | $\varepsilon \times 10^{-3}$ |
| **11**·2$H_2O$ | $O^8$ | 263 | 13.2 | 273 | 13.8 | 265 | 12.2 | 272 | 12.6 |
| **2** | $N^6$ | 274 | 16.4 | 276 | 14.0 | 273 | 16.9 | 282 | 18.3 |
| **6**·1.1$H_2O$ | N (1) | 220 | 16.9 | 214 | 27.7 | 216 | 22.0 | 288 | 12.4 |
| | | 230 (sh) | 15.8 | 275 | 10.7 | 226 (sh) | 18.5 | | |
| | | 294 | 12.8 | | | 288 | 14.2 | | |
| **7**[a] | N (3) | 232 | 18.8 | 217 | 22.9 | 228 | 20.4 | 231 (sh) | 9.2 |
| | | 298 | 18.3 | 287 | 19.4 | 294 | 20.1 | 306 | 14.9 |
| **9** | N (7) | 274 | 12.9 | 213 | 23.7 | 271 | 12.8 | 281 | 14.9 |
| | | | | 274 (sh) | 10.6 | | | (247)[b] | (2.7)[b] |
| | | | | 283 | 10.7 | | | | |
| **3** | N (9) | 271[c] | 13.0[c] | 218 | 24.6 | 271[c] | 13.0[c] | 280[c] | 14.9[c] |
| | | | | 270 (sh)[c] | 10.3[c] | | | (238)[b] | (1.6)[b] |
| | | | | 280[c] | 10.7[c] | | | | |

*a*) Taken from ref. 1. *b*) Absorption minimum. *c*) Taken from ref. 3.

TLC [silica gel, chloroform–methanol (10 : 1, v/v)] to give a third crop of **2** (5.6 mg; the total yield of **2** was 52.6 mg, 53%), together with **3** (2.1 mg, 2%) as a yellow solid, MS *m/z*: 165 ($M^+$). This sample of **3** was identical (by comparison of the $^1$H-NMR spectrum and TLC mobility) with an authentic specimen.[3]

Recrystallization of crude **2** from 50% (v/v) aqueous methanol afforded an analytical sample of **2** as colorless needles, mp > 300 °C (lit.[2] mp > 300 °C); MS *m/z*: 165 ($M^+$); UV (Table 1); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3326, 3212 (NH), 1701 (C=O), 1636 (C=N); $^1$H-NMR $\delta$: 2.93 (3H, d, $J$ = 4 Hz, NHMe), 6.36 (1H, br, NHMe), 8.04 [1H, s, C(2)-H], 9.83 and 11.24 (1H each, br s, two NH's). *Anal.* Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.35; H, 4.14; N, 42.15.

ii) By the Dimroth Rearrangement of **6**: A solution of **6**·1.1$H_2O$ (*vide infra*) (52.1 mg, 0.282 mmol) in 1 N aqueous sodium hydroxide (3 ml) was heated under reflux for 30 min, cooled, and neutralized with 10% hydrochloric acid. The precipitate that separated was collected by filtration, washed with water (2 × 1 ml), and dried to afford **2** (42 mg, 90%), mp > 300 °C. This sample was identical (by comparison of the $^1$H-NMR spectrum and TLC mobility) with authentic **2** described above under item (i).

**1-Methyl-8-oxoadenine Hydrochloride (6 · HCl)** Compound **5**·$H_2O$[6] (200 mg, 0.634 mmol) was heated in 2 N hydrochloric acid (15 ml) under reflux for 48 h, and the reaction mixture was concentrated *in vacuo*. The solid residue was extracted with 50% (v/v) aqueous methanol (20 ml) and then with hot methanol (10 ml). The extracts were combined, decolorized by activated charcoal powder, and concentrated *in vacuo*. The residue was washed with ethanol and dried to yield **6**·HCl (99.2 mg, 78%), mp 293—297 °C (dec.). Recrystallization of this sample from 50% (v/v) aqueous methanol afforded an analytical sample of **6**·HCl as colorless prisms, mp 298—300 °C (dec.); UV $\lambda_{max}^{95\%\ EtOH}$ 277 nm (sh) ($\varepsilon$ 9600), 287 (10400); $\lambda_{max}^{H_2O}$ (pH 1) 214 (27900), 275 (10800); $\lambda_{max}^{H_2O}$ (pH 7) 216 (22100), 227 (sh) (18200), 288 (14200); $\lambda_{max}^{H_2O}$ (pH 13) 288 (12400); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3200—3000 (NH), 1728 (C=O), 1673 (C=N); $^1$H-NMR $\delta$: 3.73 [3H, s, N(1)-Me], 8.49 [1H, s, C(2)-H], 10.13 (4H, br, four NH's). *Anal.* Calcd for $C_6H_7N_5O$·HCl: C, 35.74; H, 4.00; N, 34.74. Found: C, 35.76; H, 4.14; N, 34.52.

**1-Methyl-8-oxoadenine (6)** A solution of **6**·HCl (277 mg, 1.37 mmol) in water (2 ml) was brought to pH 8 with 10% aqueous sodium carbonate. The precipitate that separated was collected by filtration, washed with water (2 × 1 ml), recrystallized from 30% (v/v) aqueous methanol, dried over phosphorus pentoxide at 2 mmHg and 100 °C for 5 h, and exposed to air until a constant weight was reached, affording **6**·1.1$H_2O$ (207 mg, 81%), mp > 300 °C. Recrystallization and drying were repeated to give an analytical sample of **6**·1.1$H_2O$ as colorless needles, mp > 300 °C; MS *m/z*: 165 ($M^+$); UV (Table 1); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3500—3050 (NH and $H_2O$), 1707 (C=O), 1653, 1622 (C=N); $^1$H-NMR $\delta$: 3.64 [3H, s, N(1)-Me], 8.13 [1H, s, C(2)-H], 8.65 (3H, br, three NH's). *Anal.* Calcd for $C_6H_7N_5O$·1.1$H_2O$: C, 38.96; H, 5.01; N, 37.86. Found: C, 38.92; H, 4.92; N, 37.76.

**Rearrangement of 2 to 3** A solution of **2** (26 mg, 0.16 mmol) in 2 N hydrochloric acid (3.9 ml) was heated under reflux for 48 h and then concentrated *in vacuo*. The residue was subjected to flash chromatography [chloroform–methanol (4 : 1, v/v)] to give crude **2** and a mixture (9 mg) of **2** and **3**. Crude **2** was recrystallized from 50% (v/v) aqueous methanol to recover the starting material **2** (7 mg). The above mixture of **2** and **3** was purified by preparative TLC [silica gel, chloroform–methanol (5 : 1, v/v)] to afford a second crop of **2** (6 mg; the total recovery was 13 mg, 50%) and **3** (2 mg, 8%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **3**.[3]

On the other hand, when **3** (84 mg, 0.51 mmol) was treated with boiling 2 N hydrochloric acid (12.3 ml) for 48 h, not even a trace of **2** was detectable by means of TLC. The resulting colorless solution was concentrated *in vacuo*. The solid residue was dissolved in water (1 ml), and the solution was neutralized with 10% aqueous sodium carbonate. The precipitate that resulted was collected by filtration, washed with water (0.5 ml), and dried to recover **3** (81 mg, 96%). The filtrate and washings were combined and concentrated *in vacuo*. The solid residue was purified by flash chromatography [chloroform–methanol (3 : 1, v/v)] to afford a 1 : 6 mixture (0.6 mg) of **3** and a compound presumed to be 5,6-diamino-4-(methylamino)pyrimidine (**4**)[8] as a colorless solid, $^1$H-NMR $\delta$: 2.80 (3H, d, $J$ = 4.9 Hz, NHMe), 3.21 [1/6 × 3H, s, N(9)-Me of **3**], 3.72 [2H, br, C(5)-$NH_2$], 5.47 [2H, br s, C(6)-$NH_2$], 5.78 (1H, br q, $J$ = 4.9 Hz, NHMe), 6.50 (1/6 × 2H, br s, $NH_2$ of **3**), 7.58 [1H, s, C(2)-H], 8.01 [1/6H, s, C(2)-H of **3**], 10.35 [1/6H, br, N(7)-H of **3**].

**Rearrangement of 7 to 6** A solution of **7** (30 mg, 0.18 mmol) in 2 N hydrochloric acid (4.5 ml) was heated under reflux for 48 h. The resulting colorless solution was concentrated *in vacuo*. The solid residue was dissolved in water (1.5 ml), and the aqueous solution was passed through a column of Amberlite IRA-402 ($HCO_3^-$) (2 ml). The column was eluted with water (100 ml), and the eluate was concentrated *in vacuo* to leave a colorless solid (29 mg). This solid was subjected to flash chromatography [methanol–concentrated aqueous ammonia (30 : 1, v/v)] to afford **7** (14 mg, 47%) and **6**·1.1$H_2O$ (3.1 mg, 9%), mp > 300 °C. The latter sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **6**·1.1$H_2O$.

When **6**·1.1$H_2O$ (34 mg, 0.18 mmol) was treated with boiling 2 N hydrochloric acid (4.5 ml) for 48 h, no trace of **7** was detectable by TLC. The resulting colorless solution was concentrated *in vacuo*. The residue was washed with ethanol (1 ml) and dried to yield **6**·HCl (36 mg, 97%), mp 293—300 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **6**·HCl.

**7-Methyl-8-oxoadenosine (8)** This compound was prepared in 39% yield according to the reported method.[4] Recrystallization of crude **8** from 50% (v/v) aqueous methanol gave an analytical sample as colorless needles, mp 261—263 °C (dec.) [lit.[4] mp 266—267 °C]; MS *m/z*: 297 ($M^+$); UV $\lambda_{max}^{95\%\ EtOH}$ 273 nm ($\varepsilon$ *ca.* 9500);[13] $\lambda_{max}^{H_2O}$ (pH 1) 217 (21300), 268 (10900), 285 (sh) (9900); $\lambda_{max}^{H_2O}$ (pH 7) 211 (32800), 272 (12300); $\lambda_{max}^{H_2O}$ (pH 13) 273 (12600); IR $\lambda_{max}^{Nujol}$ cm$^{-1}$: 3424, 3320, 3218 (OH and NH), 1713 (C=O), 1651 (C=N); $^1$H-NMR $\delta$: 3.46 [1H, ddd, $J$ = 12, 8, 5 Hz, C(5')-H], 3.49 [3H, s, N(7)-Me], 3.60 [1H, ddd, $J$ = 12, 4, 4 Hz, C(5')-H], 3.86 [1H, ddd, $J$ = 5, 4, 3 Hz, C(4')-H], 4.13 [1H, ddd, $J$ = 5, 5, 3 Hz, C(3')-H], 4.87 [1H, ddd, $J$ = 6, 6, 5 Hz, C(2')-H], 5.04 [1H, d, $J$ = 5 Hz, C(3')-OH], 5.07 [1H, dd, $J$ = 8, 4 Hz, C(5')-OH], 5.22 [1H, d, $J$ = 6 Hz, C(2')-OH], 5.73 [1H, d, $J$ = 6 Hz, C(1')-H], 6.73 (2H, br s, $NH_2$), 8.02 [1H, s, C(2)-H]. *Anal.* Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.21; H, 5.06; N, 23.53.

**7-Methyl-8-oxoadenine (9)** A solution of **8** (200 mg, 0.673 mmol) in 2 N hydrochloric acid (20 ml) was heated under reflux for 48 h, neutralized with concentrated aqueous ammonia, and concentrated *in vacuo*. The residue was dissolved in 50% (v/v) aqueous methanol (80 ml), and the resulting solution was treated with activated charcoal powder. The charcoal was filtered off and washed with hot methanol (2 × 10 ml). The filtrate and washings were combined and concentrated to a volume of *ca.* 20 ml. The precipitate that separated was collected by filtration, washed with water (2 × 1 ml), and dried to afford **9** (36.8 mg), mp > 300 °C. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by flash chromatography, and crude **9** thus obtained was recrystallized from 50% (v/v) aqueous methanol to give a second crop of **9** (13.3 mg; the total yield was 50.1 mg, 45%), mp > 300 °C. Recrystallization from 50% (v/v) aqueous methanol furnished an analytical sample of **9** as colorless prisms, mp > 300 °C; MS *m/z*: 165 ($M^+$); UV (Table 1); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3407, 3328, 3202 (NH), 1717 (C=O), 1646 (C=N); $^1$H-NMR $\delta$: 3.42 [3H, s, N(7)-Me], 6.47 (2H, br s, $NH_2$), 7.95 [1H, s, C(2)-H], 11.45 (1H, br, NH). *Anal.* Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.55; H, 4.26; N, 42.10.

**8-Methoxyadenine (11)** A solution of **10**[1] (150 mg, 0.588 mmol) in a mixture of methanol (15 ml) and water (10 ml) was shaken with 10% palladium-on-carbon (150 mg) under hydrogen at atmospheric pressure and 50 °C for 3 h. The catalyst was filtered off and washed with hot methanol (80 ml). The filtrate and washings were combined and concentrated *in vacuo* to afford **11**·2$H_2O$ (107 mg, 91%), mp 217—218 °C (dec.). This sample was recrystallized from 5% aqueous ammonia–methanol (1 : 1, v/v), dried over phosphorus pentoxide at 2 mmHg and 100 °C for 4 h, and exposed to air until a constant weight was reached, giving an analytical sample of **11**·2$H_2O$ (reported previously as an anhydrous sample[2]) as colorless prisms, mp 231—235 °C (dec.); MS *m/z*: 165 ($M^+$); UV (Table 1); IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3181 (NH), 1673 (C=N); $^1$H-NMR $\delta$: 4.03 (3H, s, OMe), 6.68 (a total of 2H with a small broad signal at 6.42, br, $NH_2$), 7.99 [1H, br s, C(2)-H], 12.39 (a total of 1H with a small broad signal at 11.43, br, NH).[14] *Anal.* Calcd for $C_6H_7N_5O$·2$H_2O$: C, 35.82; H, 5.51; N, 34.81. Found: C, 35.76; H, 5.34; N, 34.88.

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13) The absorbance rapidly increased with time at room temperature and a constant value of $\varepsilon$ 12300 was reached 1.5 h after dissolution of **8**. This change is most likely due to keto–enol tautomerization, which might have occurred in the aqueous ethanolic solution.
14) The observed complexity of the proton signals suggests the coexistence of some NH-tautomer(s) in the hexadeuterated dimethyl sulfoxide solution.