Purines. LXVII.[1] An Alternative Synthesis of Adenine 7-Oxide: *N*-Oxidation of the Adenine Ring Utilizing Blocking/Deblocking at the 1-Position

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Oxidation of 1-benzyladenine (12) with *m*-chloroperoxybenzoic acid in MeOH or in MeOH–0.5 M phosphate buffer (pH 6.6) has been found to afford 1-benzyladenine 7-oxide (13) as the main product. Nonreductive debenzylation of 13 gave adenine 7-oxide (14) in 63% yield. The structure of 13 was unequivocally established by an X-ray crystallographic analysis.

Key words 1-benzyladenine 7-oxide; X-ray analysis; adenine 7-oxide synthesis; *m*-chloroperoxybenzoic acid oxidation; 1-benzyladenine *N*-oxidation; debenzylation nonreductive

Much information has been accumulated concerning the regioselectivity in *N*-oxidation of N^x-benzyladenines. Oxidation of 9-benzyladenine (**1**) with peroxyacetic acid (30 °C, 5 d) gives the N(1)-oxide **6** in 69% yield[2]; that of 9-benzyladenine-*2-d* (**2**) with *m*-chloroperoxybenzoic acid (MCPBA) (MeOH, room temp., 4 h) gives the corresponding N(1)-oxide **7** in 71% yield[3]; oxidation of 7-benzyladenine (**3**) with MCPBA (MeOH, 23 °C, 7 h) affords the N(1)-oxide **8** in 76% yield[4]; oxidation of 3-benzyladenine (**4**) with magnesium monoperoxyphthalate (MMPP) (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) provides the N(7)-oxide **9** in 40%, 24%, or 12% yield, respectively[1,5]; and oxidation of N^6-benzyladenine (**5**) with MCPBA (MeOH, 30 °C, 20 h) furnishes the N(1)-oxide **10** in 35% yield.[6] Since 1-benzyladenine (**12**), the remaining positional isomer, undergoes methylation at the 9-position,[7,8] it seemed of interest to know whether *N*-oxidation of this compound would occur at the same position. This led us to investigate the MCPBA oxidation of **12** in the present study.

Treatment of 1-benzyladenine (**12**)[7,9] with MCPBA in MeOH at 30 °C for 14 h afforded the N(7)-oxide **13** in 13% yield, together with 54% recovery of **12**. When this oxidation was carried out in MeOH–0.5 M phosphate buffer (pH 6.6) (1 : 2, v/v) at 30 °C for 20 h, the yield of **13** was improved to 19% (with 40% recovery of **12**). On exposure to air (room temp., 3 d), **13** turned into the monohydrate (**13**·H_2O).

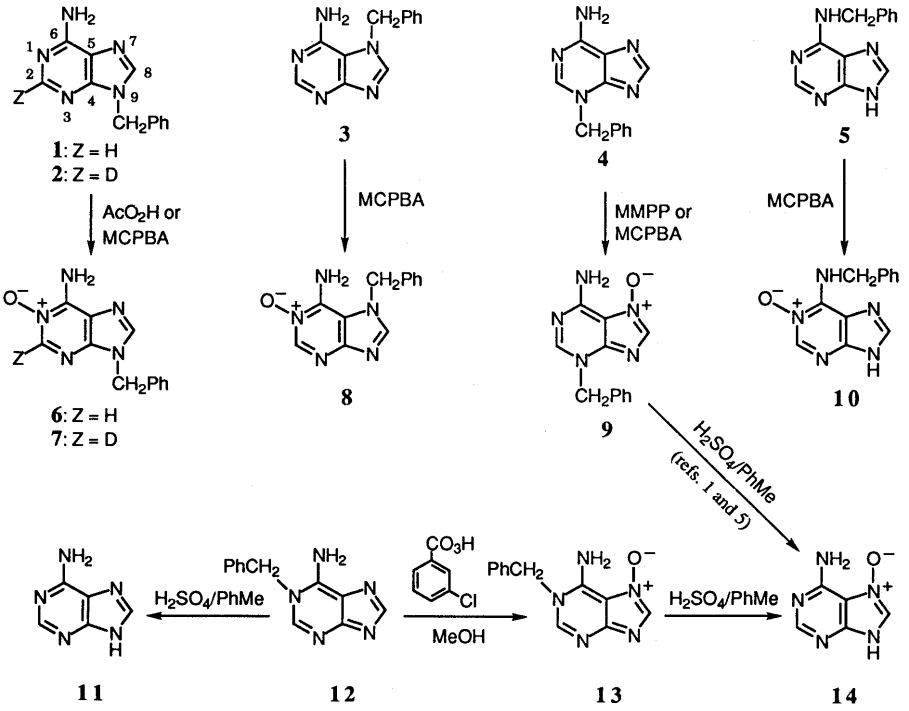

Chart 1

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If specific nonreductive debenzylation of **13** were possible, the location of the *N*-oxide function should be determined because all the four possible positional isomers of adenine *N*-oxide are known. In order to check the feasibility of removing the 1-benzyl group from the adenine nucleus, **12** was treated with conc. H_2SO_4 at 35 °C for 3 h in the presence of toluene.[1,5,6,10] This procedure turned out to be effective, giving adenine (**11**) in 53% yield. A similar debenzylation of **13** provided adenine 7-oxide (**14**) (63% yield), which was identical with a sample[1,5] prepared from 3-benzyladenine 7-oxide (**9**) by a similar debenzylation. Thus, the reaction sequence **12**→**13**→**14** afforded an alternative synthesis of **14**.

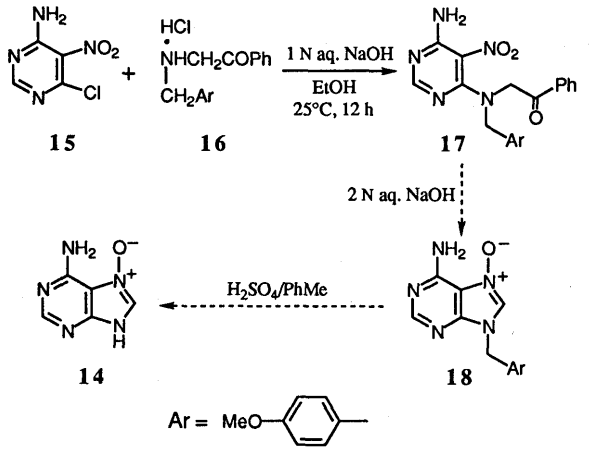

Chart 2

Yet another synthetic approach to **14** would be an extension of the "phenacylamine route", developed in our laboratory for the syntheses of guanine 7-oxide,[10c] 8-methylguanine 7-oxide,[10d] and hypoxanthine 7-*N*-oxide,[10e] as shown in Chart 2. Coupling of *N*-(4-methoxybenzyl)phenacylamine, generated *in situ* from the hydrochloride salt **16** (2 molar eq) and 1 N aqueous NaOH (2 molar eq), with 4-amino-6-chloro-5-nitropyrimidine (**15**)[11] at 25 °C for 12 h produced the phenacylaminopyrimidine **17** in 67% yield. However, treatment of **17** with 2 N aqueous NaOH in MeOH at room temperature for 2 h gave a mixture of many products, from which we were unable to isolate the cyclized product **18**, even if it were present. This led us to abandon the "phenacylamine route" approach.

We next investigated the X-ray molecular structure of **13**·H_2O in order to obtain a definitive identification and to examine its tautomeric form in the solid state. The final atomic coordinates and equivalent isotropic or isotropic thermal parameters of the atoms are listed in Table I. The bond lengths and angles are given in Tables II and III, respectively, and a computer-generated drawing of the final X-ray model, together with the atomic numbering scheme employed for the X-ray crystallographic data, is presented in Fig. 1. It may be seen that in the solid state **13**·H_2O exists in the N(7)-oxide form (**13**) rather than the N(7)-OH form (**21**).

Table I. Final Atomic Coordinates and Equivalent Isotropic or Isotropic Thermal Parameters for Atoms of **13**·H_2O with Estimated S.D.'s in Parentheses

Atom	*x*	*y*	*z*	B_{eq} (Å^2)
C(1)	0.4302 (3)	0.2342 (2)	0.3013 (2)	2.09 (9)
N(2)	0.4045 (3)	0.1574 (2)	0.2260 (2)	2.43 (8)
C(3)	0.2297 (4)	0.1244 (2)	0.1716 (2)	2.93 (11)
N(4)	0.0760 (3)	0.1567 (2)	0.1863 (2)	3.12 (10)
N(5)	−0.0415 (3)	0.2780 (2)	0.2938 (2)	3.00 (9)
C(6)	0.0478 (3)	0.3471 (2)	0.3678 (2)	2.68 (11)
N(7)	0.2314 (3)	0.3453 (2)	0.3843 (2)	2.25 (8)
C(8)	0.2654 (3)	0.2701 (2)	0.3178 (2)	2.10 (9)
C(9)	0.0954 (3)	0.2312 (2)	0.2631 (2)	2.44 (10)
N(10)	0.5952 (3)	0.2669 (2)	0.3521 (2)	2.68 (9)
O(11)	0.3603 (2)	0.4020 (1)	0.4506 (1)	2.93 (7)
C(12)	0.5636 (4)	0.0991 (2)	0.2095 (2)	2.57 (11)
C(13)	0.6379 (4)	0.0204 (2)	0.2958 (2)	2.87 (11)
C(14)	0.8247 (5)	−0.0015 (3)	0.3246 (2)	3.77 (13)
C(15)	0.8979 (6)	−0.0758 (3)	0.4005 (3)	5.16 (17)
C(16)	0.7835 (8)	−0.1281 (3)	0.4479 (3)	6.22 (21)
C(17)	0.5988 (8)	−0.1081 (3)	0.4214 (3)	6.51 (22)
C(18)	0.5245 (6)	−0.0338 (3)	0.3441 (3)	4.83 (17)
O(w)	0.7859 (3)	0.4165 (2)	0.5057 (2)	3.14 (9)
H(3)	0.228 (4)	0.068 (2)	0.117 (2)	1.4
H(6)	−0.008 (4)	0.392 (2)	0.407 (2)	0.8
H(10a)	0.698 (5)	0.251 (3)	0.337 (2)	1.9
H(10b)	0.605 (4)	0.314 (3)	0.405 (3)	2.4
H(12a)	0.520 (4)	0.064 (2)	0.140 (2)	0.6
H(12b)	0.661 (4)	0.149 (2)	0.203 (2)	0.5
H(14)	0.904 (4)	0.038 (3)	0.295 (2)	1.8
H(15)	1.040 (6)	−0.088 (3)	0.426 (3)	4.7
H(16)	0.839 (6)	−0.176 (4)	0.505 (4)	6.0
H(17)	0.513 (7)	−0.147 (4)	0.454 (4)	7.0
H(18)	0.396 (5)	−0.019 (3)	0.324 (2)	1.9
H(wa)	0.736 (4)	0.461 (2)	0.523 (2)	0.5
H(wb)	0.853 (5)	0.390 (3)	0.561 (3)	2.4

Table II. Selected Bond Lengths in **13**·H_2O

Bond	Length[a] (Å)	Bond	Length[a] (Å)
C(1)–N(2)	1.375 (3)	N(7)–C(8)	1.374 (3)
C(1)–C(8)	1.396 (4)	N(7)–O(11)	1.334 (2)
C(1)–N(10)	1.314 (3)	C(8)–C(9)	1.384 (3)
N(2)–C(3)	1.386 (3)	C(12)–C(13)	1.513 (4)
N(2)–C(12)	1.476 (4)	C(13)–C(14)	1.386 (4)
C(3)–N(4)	1.295 (4)	C(13)–C(18)	1.384 (5)
N(4)–C(9)	1.371 (3)	C(14)–C(15)	1.383 (4)
N(5)–C(6)	1.355 (3)	C(15)–C(16)	1.373 (6)
N(5)–C(9)	1.348 (4)	C(16)–C(17)	1.367 (7)
C(6)–N(7)	1.343 (3)	C(17)–C(18)	1.397 (5)

a) Estimated S.D.'s are given in parentheses for the last digits.

Table III. Selected Bond Angles in **13**·H_2O

Bond	Angle[a] (°)	Bond	Angle[a] (°)
N(2)–C(1)–C(8)	113.0 (2)	C(1)–C(8)–C(9)	122.6 (2)
N(2)–C(1)–N(10)	121.9 (2)	N(7)–C(8)–C(9)	106.3 (2)
C(8)–C(1)–N(10)	125.1 (2)	N(4)–C(9)–N(5)	126.5 (2)
C(1)–N(2)–C(3)	121.5 (2)	N(4)–C(9)–C(8)	122.4 (2)
C(1)–N(2)–C(12)	120.3 (2)	N(5)–C(9)–C(8)	111.1 (2)
C(3)–N(2)–C(12)	117.8 (2)	N(2)–C(12)–C(13)	111.7 (2)
N(2)–C(3)–N(4)	126.1 (2)	C(12)–C(13)–C(14)	118.9 (3)
C(3)–N(4)–C(9)	114.3 (2)	C(12)–C(13)–C(18)	122.2 (3)
C(6)–N(5)–C(9)	103.7 (2)	C(14)–C(13)–C(18)	118.8 (3)
N(5)–C(6)–N(7)	113.3 (2)	C(13)–C(14)–C(15)	121.0 (3)
C(6)–N(7)–C(8)	105.7 (2)	C(14)–C(15)–C(16)	119.4 (4)
C(6)–N(7)–O(11)	129.4 (2)	C(15)–C(16)–C(17)	120.9 (3)
C(8)–N(7)–O(11)	124.9 (2)	C(16)–C(17)–C(18)	119.7 (4)
C(1)–C(8)–N(7)	131.2 (2)	C(13)–C(18)–C(17)	120.2 (4)

a) Estimated S.D.'s are given in parentheses for the last digits.

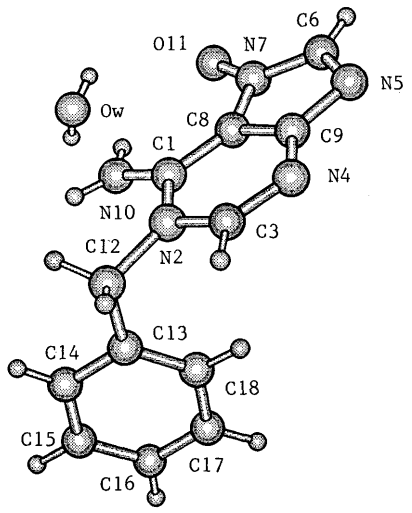

Fig. 1. A Perspective View of the Molecular Structure of **13**·H_2O and the Numbering Scheme Employed for X-ray Crystallographic Data

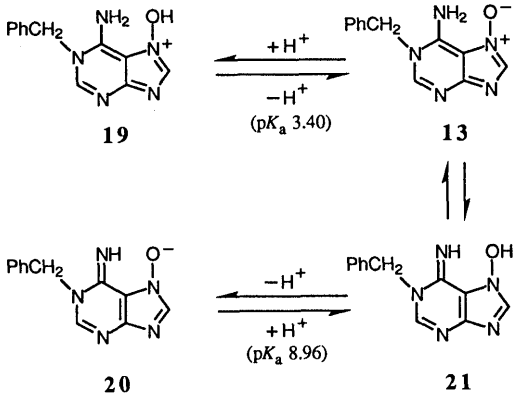

Chart 3

In approaching the tautomeric problem of 1-benzyladenine 7-oxide (**13**) in H_2O, its pK_a values in H_2O at 30 °C were spectrophotometrically determined to be 3.40 (basic) [for protonated form (**19**)⇌neutral form] and 8.96 (acidic) [for neutral form⇌monoanion (**20**)] (Chart 3). The UV spectrum of **13** in H_2O at pH 6.0 exhibited two absorption bands at 248 nm (ε 20700) and 290 nm (ε 5500), which may be regarded as those arising from the neutral species in view of the above pK_a values. Although the strong UV absorption of purine *N*-oxides in the 215—240 nm region is considered to be due to >N→O or the enol anion >N–O$^-$,[12] it is uncertain whether the above strong absorption of **13** at 248 nm reflects the predominance of the N(7)-oxide tautomer (**13**) in the neutral species in H_2O. In addition, the nonavailability of a fixed model (*e.g.*, 1-benzyl-7-methoxyadenine) for the N(7)-OH form (**21**) in the present study renders this discussion inconclusive.

In conclusion, the present results reveal that the main product from the MCPBA oxidation of 1-benzyladenine (**12**) is the N(7)-oxide **13**, which gives adenine 7-oxide (**14**) by nonreductive debenzylation. Interestingly, this regioselectivity in *N*-oxidation does not accord with that [7,8] in *N*-alkylation. Since the starting material **12** is readily obtainable from adenosine by benzylation and subsequent glycosidic hydrolysis,[7,9] the reaction sequence **12**→**13**→**14** is tantamount to a formal synthesis of adenine 7-oxide (**14**) from adenosine. The synthesis features the blocking/deblocking processes at the 1-position in *N*-oxidation of the adenine ring, because direct *N*-oxidation of adenine (**11**) itself with peroxyacetic acid occurs preferentially at the 1-position.[13]

Experimental

General Notes All melting points were taken on a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. See ref. 1 for details of chromatography, instrumentation, and measurements. Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: d = doublet, m = multiplet, s = singlet.

Debenzylation of 1-Benzyladenine (12) Leading to Adenine (11) A suspension of **12**[7,9] (120 mg, 0.533 mmol) in a mixture of toluene (1 ml) and conc. H_2SO_4 (800 mg) was vigorously stirred at 35 °C for 3 h. The reaction mixture was poured into a mixture of H_2O (5 ml) and toluene (2 ml) under ice-cooling. The toluene layer was separated from the aqueous layer and washed with H_2O (2 ml). The washings and the aqueous layer were combined and diluted with H_2O to a volume of *ca.* 20 ml. The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (16.6 ml), and the column was eluted with H_2O (60 ml). The eluates were combined and concentrated *in vacuo* to leave a colorless solid. The solid was combined with H_2O (0.5 ml), and the aqueous mixture was brought to pH 8—9 by addition of conc. aqueous NH_3 and then stirred for 1 h. The resulting insoluble solid was collected by filtration, washed with a little H_2O, and dried over P_2O_5 at 2 mmHg and 110 °C for 3 h to give adenine (**11**) (38 mg, 53%), mp > 300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **11**.

1-Benzyladenine 7-Oxide (13) i) By Oxidation of **12** in MeOH: A solution of **12**[7,9] (1.13 g, 5.02 mmol) and MCPBA (of *ca.* 80% purity) (2.17 g, 10.1 mmol) in MeOH (113 ml) was stirred at 30 °C for 14 h. The reaction mixture was concentrated *in vacuo*, and the residue was triturated with a mixture of H_2O (5 ml) and EtOH (5 ml). The insoluble solid that resulted was filtered off, washed with EtOH (1 ml), and dissolved in hot H_2O (15 ml). The aqueous solution was cooled and then brought to pH 9 with conc. aqueous NH_3. The colorless solid that deposited was filtered off, washed successively with EtOH (1 ml) and ether (1 ml), and dried to recover a first crop (173 mg, 15%) of **12**. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **12**. The first aqueous ethanolic filtrate and ethanolic washings, both of which were obtained after the above trituration, were combined and concentrated *in vacuo* to leave a yellow oil. The oil was partitioned between ether (10 ml) and a mixture of 1 N aqueous HCl (5.1 ml) and H_2O (10 ml). The aqueous layer was separated from the ethereal layer, washed with ether (10 ml), brought to pH 7 with conc. aqueous NH_3, and then concentrated *in vacuo* to leave a yellow solid, which was subjected to flash chromatography[14] [silica gel, $CHCl_3$–MeOH–conc. aqueous NH_3 (20 : 7 : 1, v/v)]. Earlier fractions afforded a second crop (436 mg, 39%) of **12**. The total recovery of **12** was 609 mg (54%).

Later fractions of the chromatography gave **13** (161 mg, 13%) as pale yellowish crystals, mp 205—222 °C (dec.). Recrystallization from 50% (v/v) aqueous MeOH and drying over P_2O_5 at 2 mmHg and 100 °C for 10 h yielded an analytical sample of **13** as pale yellowish needles, mp 240—252 °C (dec.); pK_a (in H_2O at 30 °C and ionic strength 1.0): 3.40, 8.96; MS *m/z*: 241 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 251 nm (ε 16300), 283 (6500); $\lambda_{max}^{H_2O}$ (pH 1) 271 (8700); $\lambda_{max}^{H_2O}$ [pH 6.0 [in 0.045 M phosphate buffer (ionic strength 1.0)]] 248 (20700), 290 (5500); $\lambda_{max}^{H_2O}$ (pH 7) 248 (20700), 290 (5500); $\lambda_{max}^{H_2O}$ (pH 13) 245 (11200), 277 (9600); ^{1}H-NMR (Me_2SO-d_6) δ: 5.41 [2H, s, N(1)-C<u>H</u>$_2$Ph], 7.22—7.43 [6H, m, N(1)-CH$_2$<u>Ph</u> and NH], 7.98 and 8.31 (1H each, s, purine protons). *Anal.* Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.76; H, 4.66; N, 28.88.

On exposure to air at room temperature for 3 d, the anhydrous sample of **13** turned into the monohydrate **13**·H_2O, mp 240—252 °C (dec.). *Anal.* Calcd for $C_{12}H_{11}N_5O \cdot H_2O$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.77; H, 5.08; N, 27.07.

ii) By Oxidation of **12** in MeOH–Phosphate Buffer: A solution of **12**[7,9] (2.26 g, 10 mmol) and MCPBA (of *ca.* 70% purity) (4.93 g, 20

mmol) in a mixture of MeOH (60 ml) and 0.5 M phosphate buffer (pH 6.6) (120 ml) was stirred at 30 °C for 20 h. The reaction mixture was concentrated *in vacuo* to one-half its initial volume, brought to pH 1 with 10% aqueous HCl, and then shaken with ether (40 ml). The insoluble solid that resulted was collected by filtration and dissolved in MeOH (30 ml). The methanolic solution was concentrated *in vacuo*, and the residue was triturated with aqueous NH_3 (pH 10) (10 ml). The insoluble solid that resulted was filtered off, washed successively with H_2O, EtOH, and ether, and dried to recover a first crop (91 mg, 4%) of **12**. The aqueous layer of the above two-layer filtrate was separated from the ethereal layer, washed with ether (40 ml), brought to pH 7 with conc. aqueous NH_3, and then concentrated *in vacuo* to leave a yellow solid. The solid was extracted with hot MeOH (2 × 50 ml), and the methanolic extracts were combined and concentrated *in vacuo* after addition of silica gel (10 g). The residue was then subjected to flash chromatography[14] [silica gel, $CHCl_3$–MeOH–conc. aqueous NH_3 (20 : 7 : 1, v/v)]. Earlier fractions afforded a second crop (815 mg, 36%) of **12**. The total recovery of **12** was 906 mg (40%). Later fractions of the chromatography furnished **13** (455 mg, 19%) as an almost colorless solid, mp 240—247 °C (dec.). This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

Adenine 7-Oxide (14) A suspension of **13** (446 mg, 1.85 mmol) in toluene (2 ml) was stirred at room temperature, and conc. H_2SO_4 (1.85 g) was added dropwise. The resulting mixture was stirred vigorously at 35 °C for 3 h and then poured onto ice (10 g). The aqueous mixture was washed with toluene (2 × 3 ml), diluted with H_2O to a volume of *ca.* 30 ml, and then passed through a column of Amberlite IRA-402 (HCO_3^-) (45 ml). The column was eluted first with H_2O (60 ml) and then with H_2O (120 ml) containing AcOH (6.8 g). The acidic eluates containing **14** were combined and concentrated *in vacuo* to leave a colorless solid. The solid was triturated with a little MeOH, and the insoluble solid that resulted was filtered off and recrystallized from H_2O, giving **14** (175 mg, 63%) as colorless needles, mp >300 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **14**.[1,5]

4-Amino-6-[(4-methoxybenzyl)(2-oxo-2-phenylethyl)amino]-5-nitropyrimidine (17) The hydrochloride **16**[10c] (1.67 g, 5.72 mmol) was dissolved in a stirred mixture of EtOH (12 ml) and 1 N aqueous NaOH (5.7 ml) under ice-cooling, and the 4-amino-6-chloro-5-nitropyrimidine (**15**)[11] (500 mg, 2.86 mmol) was added in small portions. The resulting mixture was stirred at 25 °C for 12 h. The pale yellow solid that deposited was filtered off, washed successively with H_2O and ether, and dried to given **17** (758 mg, 67%), mp 127—128 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3412 and 3270 (NH_2), 1701 (ArCO); ^{1}H-NMR (Me_2SO-d_6) δ: 3.72 (3H, s, OMe), 4.69 (2H, s, C$\underline{H}_2$Ar), 4.95 (2H, s, C$\underline{H}_2$COPh), 6.85 [2H, d, J=8.8 Hz, C(3′)-H and C(5′)-H],[15] 7.26 [2H, d, J=8.8 Hz, C(2′)-H and C(6′)-H],[15] 7.3—8.0 (7H, m, NH_2 and COPh), 7.93 [1H, s, C(2)-H]. This sample was homogeneous on TLC analysis, but was unstable when heated in recrystallization solvents.

X-ray Structure Determination of 13 For X-ray diffraction analysis, colorless transparent needles of **13**·H_2O were grown from aqueous MeOH. A crystal measuring 0.25 × 0.25 × 0.10 mm was selected from among them and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC-5R automatic diffractometer using graphite-monochromated Cu$K\alpha$ radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular settings of 25 2θ-values in the range of 55—65°, affording the following crystal data: a = 7.541 (1) Å; b = 12.742(1) Å; c = 13.275(1) Å; α = 90.00(0)°; β = 105.64 (1)°; γ = 90.00(0)°; U = 1228.3(2) Å^3; space group $P2_1/c$; Z = 4; D_x = 1.402 g/cm^3; $F(000)$ = 544; μ(Cu$K\alpha$) = 8.454 cm^{-1}. Out of 1832 unique reflections ($0° \leq 2\theta \leq 120°$) measured by using the $\omega/2\theta$ scan technique at a rate of 8°/min, 1564 without $|F_{obs}| = 0$ were considered unique and observed. No absorption corrections were applied.

The structure was solved by a direct method using the program SHELXS-86[16] and the difference Fourier method. Refinement of atomic parameters was carried out using the full-matrix, least-squares method with anisotropic temperature factors. All hydrogen atoms were clearly located on difference Fourier maps and refined with isotropic temperature factors. Throughout the refinement, the function $\Sigma w(|F_O| - |F_C|)^2$ was minimized, and the weight used during the final refinement stage was $\sqrt{w} = 1/\sigma(F_O)$; the final R value, 0.0410 (R_w = 0.0410). The atomic scattering factors were taken from the literature.[17] The final atomic positions and equivalent isotropic or isotropic thermal parameters for all atoms are listed in Table I. The selected bond lengths and angles are given in Tables II and III, respectively. A computer-generated,[18] perspective view of the structure of **13**·H_2O is presented in Fig. 1.

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