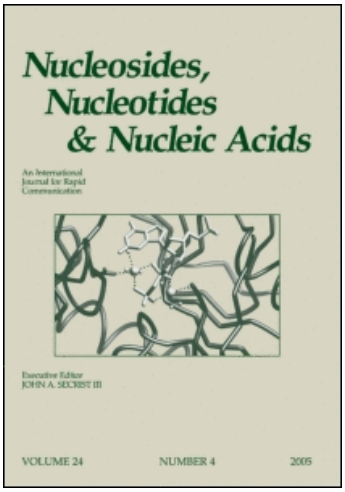

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A New Simple Synthesis of N-2-Methylguanosine and Its Analogues Via Derivatives of 4-Desmethylwyosine (Nucleosides and Nucleotides. Part 63[1])

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A NEW SIMPLE SYNTHESIS OF N-2-METHYLGUANOSINE AND ITS ANALOGUES VIA DERIVATIVES OF 4-DESMETHYLWYOSINE (NUCLEOSIDES AND NUCLEOTIDES. PART 63[1])

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ABSTRACT: Guanosine and 2'-deoxyguanosine have been converted into the corresponding N-2-methyl and N-2-ethyl derivatives in a simple, three-step procedure by N-5-alkylation of N-4-desmethylwyosines (4,5) and subsequent deprotection with N-bromosuccinimide.

N-2-Methylguanosine (1), a modified nucleoside widely occurring in ribonucleic acids[2,3], cannot be obtained by direct methylation of guanosine (2), which reacts at N-7 with methylating agents of the type MeX[4] or with diazomethane[5], and undergoes methylation at N-1 with methyl iodide in the presence of potassium carbonate[6]. Therefore, N-2-methylguanosine has been prepared indirectly from 9-(β-D-ribofuranosyl)-2-fluoropurine[7] or starting from 4-amino-1-(β-D-ribofuranosyl)-5-imidazolecarboxamide[8,9] (AICA-riboside). Those starting materials are relatively inaccessible and the discussed syntheses provide N-2-methylguanosine in rather low overall yields.

More recently, conversion of guanosine into its N-2-methyl derivative (1) has been achieved in a satisfactory yield. In the first method, 6-O-mesyl-N-2-benzoyl-2',3',5'--tri-O-benzoylguanosine has been methylated with diazomethane.[10] The second approach involves reaction of protected derivatives of guanosine with aqueous formaldehyde and

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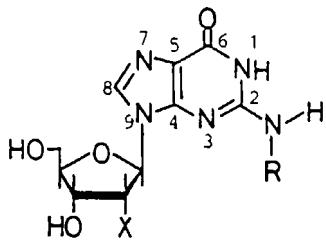
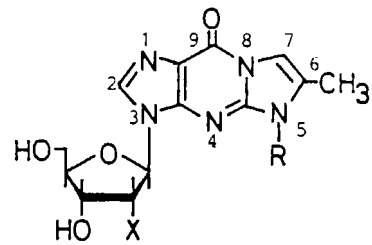


1 R=CH_3, X=OH
2 R=H, X=OH
3 R=H, X=H
10 R=CH_3, X=H
11 R=CH_2CH_3, X=OH
12 R=CH_2CH_3, X=H



4 R=H, X=OH
5 R=H, X=H
6 R=CH_3, X=OH
7 R=CH_3, X=H
8 R=CH_2CH_3, X=OH
9 R=CH_2CH_3, X=H

thiocresol in the presence of acetic acid followed by subsequent reduction with sodium borohydride or Raney nickel.[11] The two latter methods, however, are rather limited to the N-2-methyl derivatives, and it does not seem likely these approaches would be of synthetic value to obtain higher N-2-alkyl analogues.

We now report a convenient, three-step procedure for the preparation of N-2-alkyl derivatives of guanosine (**2**) and 2'-deoxyguanosine (**3**). This simple method does not require protection of hydroxyl groups of the sugar moiety.

Condensation between the N-1-sodium derivative of guanosine and bromoacetone in dimethyl sulfoxide, according to the procedure of Kasai et al.[12], afforded 4-desmethylwyosine (**4**).[13] This product, a desmethyl analogue of the hypermodified, fluorescent nucleoside wyosine[14], may be considered as a "protected" derivative of guanosine, in which its exocyclic amino group is converted into the endocyclic N-H group of the additional imidazole ring (N-5 in the numeration system of wyosine), with simultaneous protection of N-1 of guanosine. We expected this procedure for the preparation of the 2'-deoxy derivative (**5**), which was obtained from 2'-deoxyguanosine in a yield of 87%.

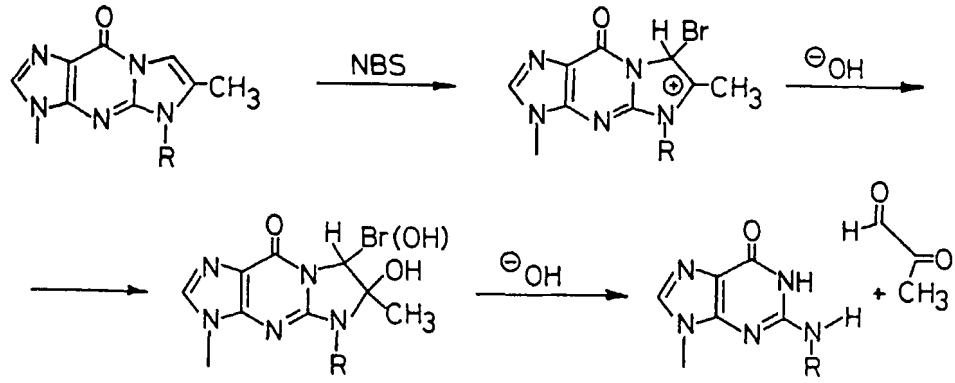
The tricyclic intermediates **4** and **5** underwent readily the selective alkylation at N-5 in the presence of potassium carbonate when treated with methyl or ethyl iodide in dimethylformamide. The respective alkylated products **6-9** crystallized easily from alcohols or water, and were isolated in yields of 81-92%. It has been also reported that reaction of the 4-desmethylwyosine system with diazomethane[12,15,16] provided N-5 methyl derivatives as the major methylation products. Similarly, the action of dimethyl sulfate on N-1-benzyl-4-desmethylwyosine resulted in a selective N-5-methylation.[17]

Transformation of N-5-alkyl tricyclic derivatives **6-9** into the corresponding N-2-alkylated guanosines (**1,11**) or 2'-deoxyguanosines (**10,12**) could be successfully achieved in a similar way as that reported by Yamaji et al.[18,19] for removal of etheno group of 1,N-6-ethenoadenosines by the action of N-bromosuccinimide (NBS). In our introductory experiment, 4-desmethylwyosine was nearly quantitatively deprotected to guanosine when treated successively with 1.5 molecular equivalents of NBS and 1 N potassium hydroxide. In a similar fashion, deblocking of the N-5-alkylated derivatives **6-9** gave the desired N-2-alkylguanosines (**1, 10-12**). Reactions of the ribonucleosides **6** and **8** were carried out in water, while the corresponding 2'-deoxyribonucleosides **7** and **9** were treated with NBS in 0.2 M acetate buffer, pH 4.5, to avoid a possible depurination. It was also observed that a smaller excess of NBS (i.e. 1.1 molar equivalents) was sufficient for an almost quantitative deblocking.

Although the mechanism of the reaction between 4-desmethylwyosines and NBS was not studied in details in the present work, it is worthy to note that: i) bromination of 4-desmethylwyosine by action of NBS is apparently faster than in the case of 1,N-6-ethenoadenosines - virtually no starting material could be detected after 10 min of reaction; ii) the slight excess of NBS necessary for a nearly quantitative conversion suggests that the discussed reaction proceeds via a monobromo intermediate (probably 7-bromo

derivative); iii) formation of an intermediate product having a C=N double bond as postulated by Yamaji et al.[19] for the reaction of ethenoadenosines seems to be very unlikely in the case of N-5-alkyl-4-desmethylwyosines since the nitrogen is substituted by an alkyl group; iv) adjustment of the reaction mixture to an alkaline pH after bromination significantly increases the yield of the final deprotection product.

Therefore, the most probably course of the discussed conversion is as follows:



The N-2-alkylguanosines (**1**, **10-12**) were isolated from the reaction mixture in the yields of 71-82%. These compounds can be easily isolated by precipitation in acetone to obtain homogeneous by tlc preparations, which may be used for eventual further steps (i.e. protection, phosphorylation, etc.) without additional purification. However, some further purification (i.e. chromatography, crystallization) was usually required to obtain analytically pure products, as it is described in the experimental part. Despite facile formation of gels in aqueous and alcoholic solutions, all the final products were obtained in crystalline state. Their structures, as well as those of the tricyclic intermediates (**4-9**), were confirmed by mass spectra and elemental analyses, proton magnetic resonance spectroscopy (TABLE 1), ultraviolet spectra and thin-layer chromatography (TABLE 2).

TABLE 1 100 MHz ^{1}H NMR Spectra in DMSO-d_6

Compd.	Chemical shifts of the protons in ppm (δ) from TMS													
	6-CH_3[a]	N-2-R (N-5-R)[a]	5'	4'	3'	2'	1'	5'OH[b]	3'OH[b]	2'OH[b]	7[a]	8 (2)[a]	N-2[b]	N-1[b]
4	2.28 d,3	12.34[b] b,1	3.64 b,2	3.95 q,1	4.14 q,1	4.53 q,1	5.84 d,1	5.10--5.23 m,2		5.44 d,1	7.37 d,1	8.15 s,1		
5	2.27 d,3	12.33[b] b,1	3.60 b,2	3.84 q,1	4.40 b,1	2.21 m,1 2.60 m,1	6.26 t,1	4.97 t,1	5.29 d,1		7.35 d,1	8.10 s,1		
6	2.32 d,3	3.59 s,3	3.64 b,2	3.93 q,1	4.14 q,1	4.58 q,1	5.86 d,1	5.03 t,1	5.20 d,1	5.42 d,1	7.46 d,1	8.13 s,1		
7	2.33 d,3	3.59 s,3	3.62 b,2	3.87 q,1	4.39 b,1	2.22 m,1 2.62 m,1	6.33 t,1	4.94 t,1	5.32 d,1		7.45 d,1	8.12 s,1		
8	2.36 d,3	1.32 t,3 4.12 q,2	3.61 b,2	3.96 q,1	4.15 q,1	4.61 q,1	5.85 d,1	4.96 t,1	5.23 d,1	5.43 d,1	7.46 d,1	8.12 s,1		
9	2.35 d,3	1.31 t,3 4.11 q,2	3.58 b,2	3.86 q,1	4.40 b,2	2.21 m,1 2.62 m,1	6.32 t,1	4.95 t,1	5.35 d,1		7.47 d,1	8.13 s,1		
1		2.80 d,3	3.57 b,2	3.87 q,1	4.14 q,1	4.51 q,1	5.71 d,1	4.94 t,1	5.26 t,1	5.42 t,1		7.91 s,1	6.50 bq,1	10.59 bs,1
10		2.78 d,3	3.55 b,2	3.80 q,1	4.36 b,1	2.20 m,1 2.61 m,1	6.17 t,1	4.94 t,1	5.31 d,1			7.85 s,1	6.78 bq,1	10.60 bs,1
11		1.14 t,3 3.33 q,2	3.57 b,2	3.86 q,1	4.11 q,1	4.52 q,1	5.70 d,1	4.92 t,1	5.22 d,1	5.42 d,1		7.89 s,1	6.74 bt,1	10.61 bs,1
12		1.14 t,3 3.27 q,2	3.55 b,2	3.81 q,1	4.37 b,2	2.17 m,1 2.63 m,1	6.16 t,1	4.87 t,1	5.28 d,1			7.89 s,1	6.41 bt,1	10.57 bs,1

[a]Numeration system of wyosine; [b]removed by addition of D_2O. Signals are designated as: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, b-broad; figures following the observed multiplicity represent nuber of protons as estimated by integration.

TABLE 2. Ultraviolet Spectra and Thin-Layer Chromatography

Compd.	solvent	λ_{max} [nm] (ε)	R_F values x 100 in systems[a]: A	B	C
4	H_2O	231 (36,900), 284 (12,300)	66[b]	58[b]	26[b]
5	H_2O	230 (38,700), 284 (12,750)	68[b]	62[b]	39[b]
6	H_2O	232 (38,600), 288 (12,800)	61	51	29
7	H_2O	232 (38,900), 288 (12,500)	68	54	40
8	H_2O	232 (36,800), 288 (12,750)	65	58	34
9	H_2O	232 (35,400), 288 (12,350)	71	62	42
1	0.1 N HCl	259 (14,100), 284 (sh; 7900)	55	54	04
	H_2O	254 (15,100), 278 (sh; 8900)			
	0.1 N NaOH	258 (12,700), 274 (sh; 11100)			
10	0.1 N HCl	259 (14,300), 283 (sh; 8100)	62	59	07
	H_2O	254 (15,100), 278 (sh; 8900)			
	0.1 N NaOH	258 (12,300), 273 (sh; 10900)			
11	0.1 N HCl	261 (14,200), 285 (sh; 7750)	60	62	05
	H_2O	255 (14,700), 278 (sh; 8900)			
	0.1 N NaOH	258 (12,200), 274 (sh; 10800)			
12	0.1 N HCl	260 (14,300), 284 (sh; 7600)	65	66	12
	H_2O	255 (15,200), 278 (sh; 9000)			
	0.1 N NaOH	258 (12,600), 274 (sh; 11100)			
2 (G)			52	51	00
3 (dG)			59	56	07

[a] see EXPERIMENTAL; [b] a spot turning dark on the light (N-5-H deriv.)

The overall yield for the synthesis of N-2-methylguanosine (**1**) from guanosine was 43%, and it was even higher in the deoxy series - 64% for synthesis of N-2-methyl-2'-deoxyguanosine (**10**) from deoxyguanosine. In this respect the present method is superior to any of the previously reported procedures. Furthermore, since a variety of N-5-alkyl or aralkyl derivatives of 4-desmethylwyosine can be easily prepared[20], this facile three-step procedure seems to be a general method for the synthesis of N-2-substituted guanosines and related heterocyclic compounds.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-S3 micro-melting point apparatus and are uncorrected. UV spectra were measured on a Shimadzu UV-260 spectrophotometer. Mass spectra were taken on a JEOL JMS-D 300 mass spectrometer at 70 eV. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100FT spectrometer. Thin-layer chromatography was conducted on Merck pre-coated silica gel F_{254} Type 60 plates using the following solvent systems (measured by volume): A, isopropanol-concd.ammonia-water (7:1:2); B, n-butanol-acetic acid-water (5:3:2); C, chloroform-methanol (4:1). For a preparative short-column chromatography Merck TLC gel HF_{254} type 60 was used. 4-Desmethylwyosine (**4**) was obtained from guanosine applying the modified procedure[15] of Kasai et al.[12] (75% of yield).

2'-Deoxy-4-desmethylwyosine (5)

Sodium hydride (472 mg, 19.64 mmol) in 60% suspension in oil was added to a solution of 2'-deoxyguanosine (**3**, 5.0 g, 18.71 mmol) in anhydrous DMSO (60 mL) and this mixture was stirred with exclusion of moisture for 1 h. The almost clear solution was treated with bromoacetone (2.69 g, 19.64 mmol) for 1 h. The reaction mixture was then made basic by addition of concd.NH_4OH (30 mL), and after 2 h at room temp. the dark red solution was concentrated <u>in vacuo</u> to a volume ca 30 mL. The solution was diluted with acetone (30 mL) and added to a stirred mixture of acetone (400 mL) and ethyl ether (100 mL). After 3 h at 0°C the oily precipitate was separated by decantation of the supernatant, washed with ether with stirring and dried under reduced pressure, then dissolved in water (200 mL) and adsorbed on a portion of silica gel (15 g, 50-100 mesh) by repeated coevaporation with ethanol. The dried gel was applied on a silica gel short column (6 X 9 cm) and the product was eluted with chloroform-methanol 6:1. Fractions containing **5** were evaporated to a white solid which was crystallized from methanol. Yield 5.023 g (87%), mp 242°C (softened). MS m/z: 189 (B), 174 (B-15), 143, 117. <u>Anal</u>. Calcd for $C_{13}H_{15}N_5O_4$ (305.29):

C, 51.15; H, 4.95; N, 22.94. Found: C, 51.14; H, 4.90; N, 22.77.

5-Methyl-4-desmethylwyosine (6)

To a solution of **4** (643 mg, 2.0 mmol) in dry DMF (10 mL) were added potassium carbonate (415 mg, 3.0 mmol) and methyl iodide (426 mg, 3.0 mmol). The resulting suspension was stirred at room temp. for 18 h, then passed through a layer of Celite. A white procipitate was carefully washed with warm DMF until no further UV absorption appeared in the filtrate. The filtrate was evaporated to an oil, and the last traces of DMF was removed by repeated coevaporation with water. The obtained white solid was crystallized from methanol to give 546 mg (81%) of **6**, mp 247-248°C. MS m/z: 335 (M^+), 203 (B), 188, 174, 148, 121. Anal. Calcd for $C_{14}H_{17}N_5O_5.0.5\ H_2O$ (344.33): C, 48.83; H, 5.26; N, 20.33. Found: C, 48.54; H, 5.13; N, 20.12.

5-Methyl-2'-deoxy-4-desmethylwyosine (7)

To a solution of **5** (4.0 g, 13.10 mmol) in dry DMF (100 mL) were added potassium carbonate (2.716 g, 19.65 mmol) and methyl iodide (2.79 g, 19.56 mmol). The reaction mixture was stirred for 12 h, then treated as in the procedure for the synthesis of **6** to obtain 3.860 g (92%) of **7**, mp 256-258°C. MS m/z: 319 (M^+), 203 (B), 188, 174, 148, 121. Anal. Calcd for $C_{14}H_{17}N_5O_4$ (319.32): C, 52.66; H, 5.37; N, 21.93. Found: C, 52.53; H, 5.32; N, 21.89.

5-Ethyl-4-desmethylwyosine (8)

To an anhydrous solution of **4** (643 mg, 2.0 mmol) in DMF (20 mL) was added potassium carbonate (553 mg, 4.0 mmol) and then ethyl iodide (624 mg, 4.0 mmol). The resulting suspension was stirred at room temp. for 3 days. Treatment of the reaction mixture as in the synthesis of **6** followed by crystallization from water afforded 486 mg (70%) of N-5-ethyl derivative **8**, mp 258-259°C (decomp.). MS m/z: 349 (M^+), 217 (B), 202, 189, 188, 162, 134. Anal. Calcd for $C_{15}H_{19}N_5O_5$ (349.35): C, 51.57; H, 5.48; N, 20.04. Found: C, 51.28; H, 5.37; N, 19.72.

5-Ethyl-2'-deoxy-4-desmethylwyosine (9)

To a solution of **5** (305.3 mg, 1.0 mmol) in DMF (8 mL) were added potassium carbonate (276 mg, 2.0 mmol) and ethyl iodide (312 mg, 2.0 mmol), and the suspension was stirred for 3 days. Treatment of the reaction mixture as in the synthesis of **6** and crystallization from ethanol gave the expected product **9** in crystalline form, yield 262.2 mg (79%), mp 217-218°C. MS m/z: 333 (M^+), 217 (B), 202, 189, 188, 162, 134. Anal. Calcd for $C_{15}H_{19}N_5O_4$ (333.35): C, 54.05; H, 5.75; N, 21.01. Found: C, 53.91; H, 5.66; N, 20.94.

Conversion of 4-desmethylwyosine (4) into guanosine (2)

To a stirred suspension of **4** (16 mg, 0.05 mmol) in 0.5 M acetate buffer, pH 4.5, (1 mL) was added NBS (13.3 mg, 0.075 mmol). After 3 h at room temp. the reaction mixture was made alkaline by addition of 1 N KOH (1 mL) and stirred for the next 1 h, then neutralized with 10% acetic acid. Thin-layer chromatography in three solvent systems and examination of the UV spectrum showed an almost quantitative conversion into guanosine, as judged by comparison with an authentic sample of **2**.

2-Methylguanosine (1)

Method A. To a stirred suspension of **6** (67.1 mg, 0.20 mmol) in water (2.5 mL) was added NBS (42.7 mg, 0.24 mmol). After 1 min a clear solution was obtained. Stirring was continued for 2.5 h, then the reaction mixture was made basic by addition of concd.NH_4OH (2 mL) and maintained at room temp. for 1 h. The solution was concentrated in vacuo to a volume ca 1 mL and diluted with acetone (10 mL), then kept at -5°C for 1 h. The solvent was removed by decantation and the white precipitate was washed with acetone and dried to obtain crude **1** (39.4 mg, 66%), homogeneous by tlc in three solvent systems, mp 221-223°C (decomp.).

Method B. The reaction was performed as in the method A. After treatment with ammonia, the reaction mixture was adsorbed on a portion of silica gel (3 g). The gel was applied on a silica gel short column (2.2 x 5 cm; prepared in

acetone-water 4:1 and washed with this solvent until no further residue after evaporation). Elution was with acetone (100 mL), then with acetone-water gradient (from 9:1 to 6:1). Fractions containing the homogeneous product were evaporated to dryness and the white residue was crystallized from aq. ethanol to give 42.3 mg (71%) of **1**, mp 234-235°C (decomp.). MS m/z: 279 (M-18), 219, 189, 165 (B), 136, 110, 109. Anal. Calcd for $C_{11}H_{15}N_5O_5.H_2O$ (315.29): C, 41.90; H, 5.43; N, 22.21. Found: C, 41.96; H, 5.28; N, 22.07.

2-Methyl-2'-deoxyguanosine (10)

Method A. NBS (735 mg, 4.13 mmol) was added to a stirred suspension of **7** (1.2 g, 3.76 mmol) in 0.2 M acetate buffer, pH 4.5 (30 mL). Stirring was continued for 20 min, and the resulting solution was made basic by addition of concd.NH_4OH (20 mL). After the next 20 min the excess of ammonia was evaporated under reduced pressure. The obtained sirup was added to an excess of acetone (1 L) and stirred at 0°C for 1 h. The supernatant was removed by decantation. The white precipitate was stirred with a fresh portion of acetone (500 mL), collected by filtration, washed with acetone and ethyl ether, then dried in vacuo to yield **10** (843 mg, 80%) as a white powder, homogeneous by tlc, mp 209-210°C (decomp.).

Method B. Compound **7** (1.0 g, 3.13 mmol) was treated with NBS (613 mg, 3.44 mmol) and with ammonia (15 mL) as in method A. The reaction mixture was then adsorbed on a portion of silica gel (10 g). the well dried gel was applied on a silica gel short column (6 x 8 cm) and the product was eluted with chloroform-methanol 3:1. Fractions containing **10** were concentrated to a volume of ca 200 mL and left at 5°C for 2 days. The crystalline product was collected by filtration, washed with ether and dried to yield 521 mg (59%), mp 219-220°C (decomp.). MS m/z: 281 (M^+), 263 (M-18), 245, 219, 202, 165 (B), 136, 110, 109. Anal. Calcd for $C_{11}H_{15}N_5O_4.H_2O$ (299.29): C, 44.14; H, 5.73; N, 23.40. Found: C, 44.09; H, 5.70; N, 23.00.

2-Ethylguanosine (11)

To a suspension of **8** (100 mg, 0.286 mmol) in water (8 mL) was added NBS (61.1 mg, 0.343 mmol) and this was stirred at room temp. for 30 min. The resulting clear solution was treated with ammonia (10 mL) for 20 min, then adsorbed on silica gel (3 g). The gel was applied on a silica gel column (3.5 x 8 cm). Elution with acetone-methanol 9:1 afforded **11** as a white solid after evaporation. The product was crystallized from ethanol; yield 73.2 mg (82%), mp 229-230°C (decomp.). MS m/z: 311 (M^+), 293 (M-18), 233, 203, 179 (B), 164, 151, 135, 110, 109. Anal. Calcd for $C_{12}H_{17}N_5O_5.H_2O$ (329.31): C, 43.77; H, 5.82; N, 21.26. Found: C, 43.82; H, 5.53; N, 21.55.

2-Ethyl-2'-deoxyguanosine (12)

Compound **9** (166.7 mg, 0.5 mmol) was treated with NBS (108 mg, 0.6 mmol) in 0.2 M acetate buffer, pH 4.5 (10 mL), then with ammonia (10 mL) and finally the reaction mixture was adsorbed on silica gel (3 g), as in the procedure of the synthesis of **10** (method B). Purification by short-column chromatography in chloroform-methanol 4:1 followed by crystallization from methanol afforded 120.0 mg (81%) of **12**, mp 232-234°C. An analytical sample was recrystallized from water, mp 236-237°C. MS m/z: 295 (M^+), 277 (M-18), 259, 203, 179 (B), 164, 151, 135, 110, 109. Anal. Calcd for $C_{12}H_{17}N_5O_4.H_2O$ (313.31): C, 46.00; H, 6.11; N, 22.35. Found: C, 45.71; H, 5.80; N, 22.07.

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