Synthesis of Certain Alkenyl Purines and Purine Analogs

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Synthesis of alkenyl derivatives of certain purines and purine analogs is described. Direct alkylation of the sodium salt of 6-chloropurine (**1**) either with 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene in *N,N*-dimethylformamide furnished N-7, **4a** and N-9, **3a, 3b** alkenyl derivatives. Similar alkylation of 2-amino-6-chloropurine (**2**) provided the corresponding N-7, **4c-4e** and N-9, **3c-3e** alkenyl derivatives. Acid hydrolysis of these chloro derivatives **3a-3e, 4a,c-e** furnished the corresponding alkenyl hypoxanthines **6a, 6b** and **7a** or alkenyl guanines **6c-6e** and **7c-7e**. Treatment of **3a-3d** with thiourea in absolute ethanol provided the corresponding 6-thio derivatives **5a-5d**. Alkylation of the sodium salt of either purine-6-carboxamide (**8**) or 1,2,4-triazole-3-carboxamide (**10**) gave mainly one isomer **9a, 9b** and **11a, 11b**. The direct alkylation of pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**12**) gave N-3 alkenyl derivatives **13a, 13b**, and the N-7 alkenyl derivatives **16a, 16b** have been prepared starting from the 4-chloro derivative **14**. Synthesis of 2-amino-7-(2-penten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**19a**) has been accomplished starting from 2-amino-4-methoxypyrrolo[2,3-*d*]pyrimidine (**17**). These alkenyl derivatives were found to be devoid of anti-HCMV activity *in vitro*.

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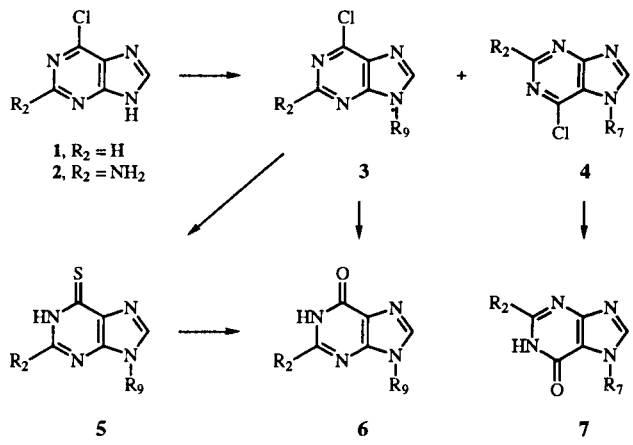
In the last few years there has been considerable interest in the synthesis of acyclic nucleoside analogs [1]. This is mainly due to the reason that a guanosine analog acyclovir was found to be active against herpes viruses [2], especially HSV-1 and HSV-2 and is the drug of choice to date, for control of HSV infections. 9-(4-Hydroxybutyl)-guanine (HBG), a carba analog of acyclovir also showed inhibition of HSV in animals [3]. Ganciclovir (DHPG), another acyclic guanosine analog is the current drug of choice for human cytomegalovirus (HCMV) infections [4]. Certain 9-alkylguanines exhibited marked antiviral activity in animal models and the antiviral activity of these guanine derivatives has been ascribed to immune potentiation [5]. A number of 6-(alkylthio)purines [6-8] and 9-alkyl-2-aminopurine-6-thiols [9-11] have been found to be active against adenocarcinoma 755 and L1210 leukemia. Recently, certain alkenyl, particularly 2-penten-1-yl and 3-methyl-2-buten-1-yl derivatives of 5-aminothiazolo[4,5-*d*]pyrimidine-2,7-dione have been found to be approximately 10 fold more active against HCMV than DHPG in similar experiments *in vitro* [12]. This observation prompted us to synthesize alkenyl derivatives of certain purines and purine analogs, which is the subject of the present communication.

Synthesis of the alkenyl derivatives of hypoxathine and guanine bases was accomplished starting from the corresponding 6-chloro derivatives. Thus, 6-chloropurine (**1**) on reaction with 1-bromo-2-pentene in *N,N*-dimethylformamide in the presence of sodium hydride afforded a product which was found to be a mixture of N-7 and N-9 alkenyl derivatives (Scheme 1). These positional isomers were separated into pure components **3a** and **4a** by silica gel column chromatography. The major component 6-chloro-9-(2-penten-1-yl)purine (**3a**) was isolated in

Scheme 1



Series **a**, $R_2 = H$; R_7 or $R_9 = -CH_2CH{=}CHCH_2CH_3$
b, $R_2 = H$; $R_9 = -CH_2CH{=}C(CH_3)_2$
c, $R_2 = NH_2$; R_7 or $R_9 = -CH_2CH{=}CHCH_2CH_3$
d, $R_2 = NH_2$; R_7 or $R_9 = -CH_2CH{=}C(CH_3)_2$
e, $R_2 = NH_2$; R_7 or $R_9 = -(CH_2)_3CH{=}CH_2$

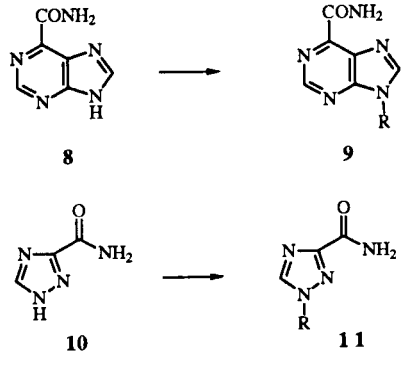
53% yield, whereas the minor component 6-chloro-7-(2-penten-1-yl)purine (**4a**) was isolated in 18% yield. Acid hydrolysis of **3a** with 1.8 *M* aqueous hydrochloric acid in tetrahydrofuran furnished 9-(2-penten-1-yl)hypoxanthine (**6a**) and the pure product was isolated in 73% yield. Similar acid hydrolysis of 6-chloro-7-(2-penten-1-yl)purine (**4a**) afforded 7-(2-penten-1-yl)hypoxanthine (**7a**) in 76% yield. The identity of these positional isomers were established by comparing the uv spectra of these compounds to those of the known alkyl purine derivatives [13]. A similar treatment of **1** with 4-bromo-2-methyl-2-butene gave 6-chloro-9-(3-methyl-2-buten-1-yl)purine (**3b**) in 49% yield. Although the formation of

N-7 isomer (very minor amount) was detected by tlc procedures it could not be obtained in the pure form. Acid hydrolysis of **3b** was accomplished with dilute aqueous hydrochloric acid and the required product 9-(3-methyl-2-buten-1-yl)hypoxanthine (**6b**) was isolated in 65% yield.

In a similar manner as described for **3a**, alkylation of the sodium salt of 2-amino-6-chloropurine (**2**) with 1-bromo-2-pentene, 4-bromo-2-methyl-2-butene or 5-bromo-1-pentene in dry DMF afforded the corresponding alkenyl derivatives **3c-3e** and **4c-4e**. In each case the positional isomers were resolved into the pure components by silica gel column chromatography. In all these reactions the major reaction product was found to be N-9 isomer (40-57%) and the minor product was N-7 isomer (13-20%). All these compounds were separately subjected to acid hydrolysis to provide the alkenyl guanines **6c-6e** and **7c-7e**. The site of alkylation in all these cases was established by comparing the uv data to that of the literature data [14]. The synthesis of the 6-thio analogs of hypoxanthine and guanine derivatives was achieved starting from **3**. Thus, the 6-chloro derivatives **3a-3d** on reaction with thiourea in absolute ethanol in the presence of catalytic amount of formic acid furnished the corresponding thio derivatives **5a-5d** in yields ranging from 60-87%.

Next we considered the preparation of alkenyl derivatives of purine-6-carboxamide (**8**) and 1,2,4-triazole-3-carboxamide (**10**) (Scheme 2). Both the compounds **8** and **10** are of particular interest, since the ribofuranosyl derivatives 9-β-D-ribofuranosylpurine-6-carboxamide [15] and 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin) [16] exhibited broad-spectrum antiviral activity.

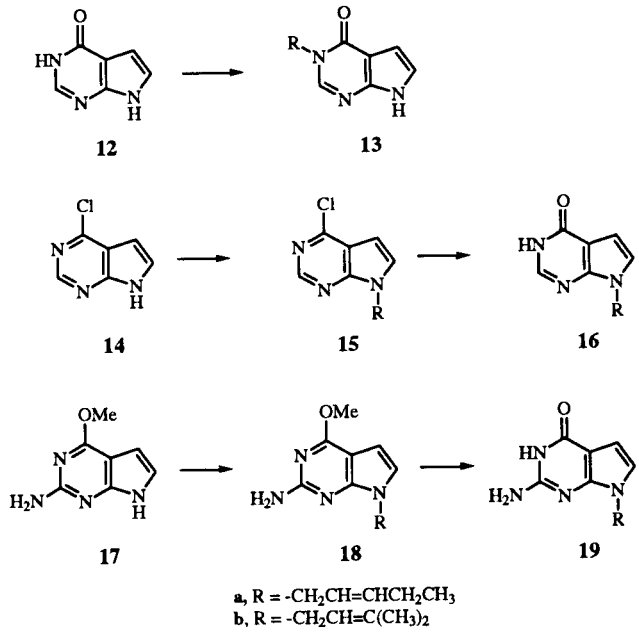
Scheme 2



Moreover it has been shown by single crystal X-ray crystallography, that ribavirin is structurally similar to inosine and guanosine [17]. In view of these observations, we initiated the synthesis of the alkenyl derivatives **9a,b** and **11a,b**. The alkylation of **8** and **10** was accomplished utilizing the sodium salt procedure. Thus, the reaction of the sodium salt of purine-6-carboxamide (**8**) [18] with 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene afforded the corresponding alkenyl derivatives **9a** and **9b**. In these reactions the product consisted of only N-9 isomer. 9-(2-Penten-1-yl)purine-6-carboxamide (**9a**) was isolated in 54% yield after silica gel column chromatography, whereas 9-(3-methyl-2-buten-1-yl)purine-6-carboxamide (**9b**) was isolated in 42% yield. The site of alkylation was established by comparison of the uv data to that of the literature data for the corresponding ribonucleoside [15]. Similarly, the sodium salt of 1,2,4-triazole-3-carboxamide (**10**) [19] on alkylation with either 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene afforded mainly the N-1 isomer. The products **11a** and **11b** were isolated in 46% and 71% yields, respectively. In these cases the site of alkylation is established based on the nmr data [20].

The synthesis of 7-deazapurine analogs was considered next (Scheme 3). Because of their structural resemblance to purines, the natural occurrence of their derivatives, and their unusual biological properties have prompted a great deal of activity directed toward the synthesis and biological evaluation of 7-deazapurine ring system [21]. The direct alkylation of the sodium salt of pyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one (**12**) [22] with either 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene in dry DMF gave a reaction product which was purified by silica gel column chromatography. The alkylated products were isolated in good yields and identified as 3-(2-penten-1-yl)-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**13a**) and 3-(3-methyl-2-buten-1-yl)-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one

Scheme 3



(**13b**), respectively. In these cases it was rather difficult to determine the site of alkylation based on their uv absorption data since the N-3 and N-7 alkylated products were found to have similar λ max values [23]. In order to determine the exact site of alkylation, alkenyl derivatives were synthesized starting from 4-chloropyrrolo[2,3-*d*]pyrimidine (**14**) [24] itself. Thus, reaction of the sodium salt of **14** in dry acetonitrile either with 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene afforded mainly one compound. The products 4-chloro-7-(2-penten-1-yl)pyrrolo-[2,3-*d*]pyrimidine (**15a**) and 4-chloro-7-(3-methyl-2-buten-1-yl)pyrrolo[2,3-*d*]pyrimidine (**15b**) were isolated in 50% and 55% yields, respectively. Comparison of the uv absorption data of **15a,b** to that of the corresponding ribonucleoside established the site of alkylation as N-7 [23]. Acid hydrolysis of compounds **15a** and **15b** provided 7-(2-penten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**16a**) and 7-(3-methyl-2-buten-1-yl)pyrrolo[2,3-*d*]-pyrimidin-4(3*H*)-one (**16b**). Although the uv absorption data of compounds **13a** and **13b** are similar to that of **16a** and **16b**, tlc profiles clearly indicated that they are distinctly different compounds. As it is very clear that compounds **16a** and **16b** have the alkenyl chain attached to N-7, the site of alkylation in compounds **13a** and **13b** is presumed to be N-3. The possibility for alkylation on N-1 was ruled out since it shows a considerable bathochromic shift in uv spectra. The synthesis of the alkenyl derivative of 7-deazaguanine was accomplished starting from 2-amino-4-methoxypyrrolo[2,3-*d*]pyrimidine (**17**) [25]. Thus, the sodium salt of **17** on reaction with 1-bromo-2-pentene afforded the N-7 alkylated derivative **18a** in a 28% yield. Demethylation of **18a** was achieved by the treatment with iodotrimethylsilane in dry acetonitrile and the pure product **19a** was isolated in 83% yield.

The alkenyl derivatives synthesized during this study were evaluated for their anti-HCMV (strain AD169) activity *in vitro* in MRC-5 cells using the plaque reduction assay [26], and were found to be inactive.

EXPERIMENTAL

Melting points (mp, uncorrected) were determined with a Thomas-Hoover unimelt capillary melting point apparatus. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, New Jersey. The presence of water as indicated by elemental analysis was verified by ^{1}H nmr spectroscopy. Thin layer chromatography (tlc) was performed on aluminum plates coated (0.2 mm) with silica gel 60F_{254} (EM Science). Silica gel (EM Science; 230-400 mesh) was used for flash column chromatography. All solvents and chemicals used were reagent grade and were not further dried/purified unless otherwise noted. Detection of components on tlc was by uv light. Evaporations were conducted under diminished pressure with the bath temperature below 30°. Ultraviolet spectra (uv) were recorded with a Hewlett-Packard 8452 diode array spectrophotometer. Mass spectra were obtained from Baylor College of Medicine, Houston, Texas. Nuclear magnetic resonance (^{1}H nmr) spectra were recorded in dimethyl sulfoxide-d_6 with a Bruker AM400 wide bore nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane (internal) (key: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad).

6-Chloro-9-(2-penten-1-yl)purine (**3a**) and 6-Chloro-7-(2-penten-1-yl)purine (**4a**).

To a suspension of 6-chloropurine (**1**, 3.09 g, 20 mmoles) in dry *N,N*-dimethylformamide (DMF, 50 ml) was added sodium hydride (60% dispersion in oil, 0.8 g, 20 mmoles). The mixture was protected from moisture and stirred at room temperature for 20 minutes, during which time a clear solution was obtained. To this clear solution 1-bromo-2-pentene (predominantly the *Z* olefin, 2.48 ml, 21 mmoles) was added and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated and the residue was dissolved in a mixture of dichloromethane and methanol (3:1, 20 ml). To this solution silica gel (20 g) was added and the solvents evaporated to dryness. The dried silica gel was loaded on a silica gel column (2 x 25 cm). The product which was a mixture of regio-isomers was eluted with dichloromethane containing 0-2% methanol. The appropriate fractions were collected and evaporated to give the pure positional isomers in analytically pure form.

6-Chloro-9-(2-penten-1-yl)purine (**3a**).

This compound was obtained in 53% yield (2.35 g), mp 54-56°; uv: (methanol): λ max 266 nm (ε 13,980); ^{1}H nmr: δ 0.99 (t, 3 H, CH_3), 2.23 (m, 2 H, CH_2CH$_3$), 4.96 (d, 2 H, NCH_2), 5.67 (m, 2 H, C*H*=C*H*), 8.67 (s, 1 H, C$_2$*H*), and 8.77 (s, 1 H, C$_8$*H*).

Anal. Calcd. for $C_{10}H_{11}ClN_4$: C, 53.94; H, 4.98; N, 25.16. Found: C, 53.85; H, 4.88; N, 25.01.

6-Chloro-7-(2-penten-1-yl)purine (**4a**).

This compound was obtained in 18% yield (0.8 g), mp 64-65°; uv: (methanol): λ max 246 nm (ε 13, 050), 272 (14, 030); ^{1}H nmr: δ 0.99 (t, 3 H, CH_3), 2.26 (m, 2 H, CH_2CH$_3$), 5.16 (d, 2 H, NCH_2), 5.65 (m, 2 H, C*H*=C*H*), 8.79 (s, 1 H, C$_2$*H*), and 8.80 (s, 1 H, C$_8$*H*).

Anal. Calcd. for $C_{10}H_{11}ClN_4$: C, 53.94; H, 4.98; N, 25.16. Found: C, 54.00; H, 4.94; N, 25.02.

6-Chloro-9-(3-methyl-2-buten-1-yl)purine (**3b**).

In a similar manner as described for **3a**, alkylation of **1** (1.55 g, 10 mmoles) with 4-bromo-2-methyl-2-butene (1.15ml, 10 mmoles) in dry DMF (30 ml) in the presence of sodium hydride (60%, 0.4 g, 10 mmoles) afforded **3b**, yield 1.1 g (49%), mp 56-58°; uv: (methanol): λ max 266 nm (ε 16,010); ^{1}H nmr: δ 1.72, 1.82 (2s, 6 H, 2 CH_3), 4.89 (d, 2 H, NCH_2), 5.45 (t, 1 H, C*H*), 8.64 (s, 1 H, C$_2$*H*), and 8.76 (s, 1 H, C$_8$*H*).

Anal. Calcd. for $C_{10}H_{11}ClN_4$: C, 53.94; H, 4.98; N, 25.16. Found: C, 53.57; H, 4.90; N, 24.76.

2-Amino-6-chloro-9-(2-penten-1-yl)purine (**3c**) and 2-Amino-6-chloro-7-(2-penten-1-yl)purine (**4c**).

In a similar manner as described for **3a** and **3b**, treatment of the sodium salt of 2-amino-6-chloropurine (**2**, 1.27 g, 7.5 mmoles) with *Z*-1-bromo-2-pentene (0.98 ml, 8.25 mmoles) afforded the title compounds.

2-Amino-6-chloro-9-(2-penten-1-yl)purine (**3c**).

This compound was obtained in 57% yield (1.02 g), mp 94-96°; uv: (methanol): λ max 248 nm (ε 5840), 310 (7940); ^{1}H nmr: δ 0.98 (t, 3 H, CH_3), 2.20 (m, 2 H, CH_2CH_3), 4.98 (d, 2 H, NCH_2), 5.58 (m, 2 H, C*H*=C*H*), 6.63 (s, 2 H, NH_2), and 8.40 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.85; H, 5.00; N, 29.32.

2-Amino-6-chloro-7-(2-penten-1-yl)purine (**4c**).

This compound was obtained in 20% yield: (0.35 g), mp 174-176°; uv: (methanol): λ max 258 nm (ε 3825), 322 (5920); ^{1}H nmr: δ 0.98 (t, 3 H, CH_3), 2.40 (m, 2 H, CH_2CH_3), 4.70 (d, 2 H, NCH_2), 5.60 (m, 2 H, C*H*=C*H*), 6.95 (s, 2 H, NH_2), and 8.15 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.69; H, 5.04; N, 29.39.

2-Amino-6-chloro-9-(3-methyl-2-buten-1-yl)purine (**3d**) and 2-Amino-6-chloro-7-(3-methyl-2-buten-1-yl)purine (**4d**).

The title compounds were obtained by the alkylation of the sodium salt of **2** (1.70 g, 10 mmoles and 0.4 g, 10 mmoles of 60% sodium hydride) with 4-bromo-2-methyl-2-butene (1.27 ml, 11 mmoles) as described for the preparation of **3b**.

2-Amino-6-chloro-9-(3-methyl-2-buten-1-yl)purine (**3d**).

This compound was obtained in 40% yield: (0.96 g), mp 140-142°; uv: (methanol): λ max 248 nm (ε 6140), 310 (8630); ^{1}H nmr: δ 1.72, 1.77 (2s, 6 H, 2 CH_3), 4.90 (d, 2 H, NCH_2), 5.34 (t, 1 H, C*H*), 6.63 (s, 2 H, NH_2), and 8.36 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.53; H, 5.05; N, 29.38.

2-Amino-6-chloro-7-(3-methyl-2-buten-1-yl)purine (**4d**).

This compound was obtained in 18% yield (0.43 g), mp 191°; uv: (methanol): λ max 256 nm (ε 4380), 322 (6270); ^{1}H nmr: δ 1.71, 1.78 (2s, 6 H, 2 CH_3), 4.64 (d, 2 H, NCH_2), 5.37 (t, 1 H, C*H*), 6.91 (s, 2 H, NH_2), and 8.09 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.39; H, 5.04; N, 29.04.

2-Amino-6-chloro-9-(4-penten-1-yl)purine (**3e**) and 2-Amino-6-chloro-7-(4-penten-1-yl)purine (**4e**).

These compounds were obtained by the treatment of the sodium salt of **2** (1.70 g, 10 mmoles and 0.4 g, 10 mmoles of 60% sodium hydride) and 5-bromo-1-pentene (1.30 ml, 11 mmoles) as described for the preparation of **3a**.

2-Amino-6-chloro-9-(4-penten-1-yl)purine (**3e**).

This compound was obtained in 46% yield: (1.1 g), mp 120-121°; uv: (methanol): λ max 248 nm (ε 6740), 310 (9280); ^{1}H nmr: δ 1.87, 2.02 (2m, 4 H, 2 CH_2), 4.04 (t, 2 H, NCH_2), 5.01 (m, 2 H, CH_2=CH), 5.82 (m, 1 H, CH_2=C*H*), 6.79 (s, 2 H, NH_2), and 8.11 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.76; H, 5.07; N, 29.29.

2-Amino-6-chloro-7-(4-penten-1-yl)purine (**4e**).

This compound was obtained in 13% yield: (0.3 g), mp 186-188°; uv: (methanol): λ max 256 nm (ε 3360), 322 (5130); ^{1}H nmr: δ 1.89, 2.04 (2m, 4 H, 2 CH_2), 4.29 (t, 2 H, NCH_2), 5.04 (m, 2 H, CH_2=CH), 5.80 (m, 1 H, CH_2=C*H*), 6.51 (s, 2 H, NH_2), and 8.34 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.47. Found: C, 50.47; H, 4.97; N, 29.58.

9-(2-Penten-1-yl)purine-6(1*H*)-thione (**5a**).

To a suspension of **3a** (0.6 g, 2.69 mmoles) in absolute ethanol (50 ml) was added thiourea (0.36 g) followed by 3 drops of formic acid. The mixture was heated under reflux for 1 hour and then allowed to cool to room temperature. The colorless crystalline product that deposited was collected by filtration and washed with a small amount of absolute ethanol to yield 0.45 g 76% of pure **5a**, mp 272-274°; uv: (methanol): λ max 226 nm (ε 10,650), 326 (31,510); ^{1}H nmr: δ 0.96 (t, 3 H, CH_3), 2.22 (m, 2H, CH_2CH_3), 4.82 (d, 2 H, NCH_2), 5.59 (m, 2 H, C*H*=C*H*), 8.16 (s, 1 H, C_2H), 8.23 (s, 1 H, C_8H), and 13.60 (s, 1 H, N*H*).

Anal. Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.59; H, 5.39; N, 25.46; S, 14.59.

9-(3-Methyl-2-buten-1-yl)purine-6(1*H*)-thione (**5b**).

In a similar manner as described for **5a**, treatment of **3b** (0.15 g, 0.67 mmoles) with thiourea (90 mg) in absolute ethanol (10 ml) in the presence of formic acid afforded 0.11 g (74%) of **5b**, mp >250°; uv: (methanol): λ max 228 nm (ε 14,800), 326 (40,070); ^{1}H nmr: δ 1.72, 1.79 (2s, 6 H, 2 CH_3), 4.75 (d, 2 H, NCH_2), 5.39 (m, 1 H, C*H*), 8.15, 8.22 (2s, 2 H, C_2H, C_8H), and 13.58 (br s, 1 H, N*H*).

Anal. Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.29; H, 5.50; N, 25.23; S, 14.75.

2-Amino-9-(2-penten-1-yl)purine-6(1*H*)-thione (**5c**).

This compound was obtained in a similar manner as described for **5a** by the treatment of **3c** (2.37 g, 10 mmoles) with thiourea (3 g) in absolute ethanol (100 ml) in the presence of formic acid (3 drops), yield 2.05 g (87%), mp 294-296°; uv: (methanol): λ max 268 nm (ε 7300), 340 (19,000); ^{1}H nmr: δ 0.98 (t, 3 H, CH_3), 2.19 (m, 2 H, CH_2CH_3), 4.65 (d, 2 H, NCH_2), 5.54, 5.66 (2m, 2 H, C*H*=C*H*), 6.89 (br s, 2 H, NH_2), 8.23 (s, 1 H, C_8H), and 12.08 (s, 1 H, N*H*).

Anal. Calcd. for $C_{10}H_{13}N_5S$: C, 51.04; H, 5.57; N, 29.77; S, 13.63. Found: C, 51.06; H, 5.50; N, 29.81; S, 13.67.

2-Amino-9-(3-methyl-2-buten-1-yl)purine-6(1*H*)-thione (**5d**).

In a similar manner as described for **5a**, the title compound was obtained by the treatment of **3d** (0.2 g, 0.84 mmole) with thiourea (0.12 g) in absolute ethanol (10 ml) in the presence of formic acid, yield 0.12 g (61%), mp 245-246°; uv: (methanol): λ max 230 nm (ε 15,260), 268 (8,080), 346 (31,030); ^{1}H nmr: δ 1.72, 1.77 (2s, 6 H, 2 CH_3), 4.60 (d, 2 H, NCH_2), 5.37 (t, 1 H, C*H*), 7.07 (s, 2 H, NH_2), 8.41 (s, 1 H, C_8H), and 12.27 (s, 1 H, N*H*).

Anal. Calcd. for $C_{10}H_{13}N_5S \cdot H_2O$: C, 47.41; H, 5.96; N, 27.65; S, 12.66. Found: C, 47.37; H, 5.49; N, 27.37; S, 12.88.

9-(2-Penten-1-yl)hypoxanthine (**6a**).

To a suspension of **3a** (0.6 g, 2.69 mmoles) in aqueous hydrochloric acid (1.8 *M*, 15 ml) was added tetrahydrofuran (4 ml) and the mixture was heated under reflux for 1.5 hours. The reaction mixture was allowed to cool to room temperature and was neutralized with 2 *N* aqueous sodium hydoxide solution. The solid product that separated was collected by filtration and washed with a small amount of cold ethanol (5 ml). The product

was dried *in vacuo* to yield 0.4 g (73%) of pure **6a**, mp 180-182°; uv: (methanol): λ max 250 nm (ε 14,480); ^{1}H nmr: δ 0.96 (t, 3 H, CH_3), 2.21 (m, 2 H, CH_2CH_3), 4.78 (d, 2 H, NCH_2), 5.59 (m, 2 H, CH=CH), 8.00 (s, 1 H, C_2H), 8.02 (s, 1 H, C_8H), and 12.20 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.71; H, 5.84; N, 27.48.

7-(2-Penten-1-yl)hypoxanthine (**7a**).

The title compound was obtained by the acid hydrolysis of **4a** (0.5 g, 2.24 mmoles), yield 0.35 g (76%), mp 160-162°; uv: (methanol): λ max 258 nm (ε 9,340); ^{1}H nmr: δ 0.96 (t, 3 H, CH_3), 2.21 (m, 2 H, CH_2CH_3), 4.99 (d, 2 H, NCH_2), 5.60 (m, 2 H, CH=CH), 7.96 (s, 1 H, C_2H), 8.22 (s, 1 H, C_8H), and 12.30 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{12}N_4O \cdot 0.2H_2O$: C, 57.79; H, 6.01; N, 26.96. Found: C, 57.99; H, 5.81; N, 26.97.

9-(3-Methyl-2-buten-1-yl)hypoxanthine (**6b**).

The title compound was obtained by the acid hydrolysis of **3b** (0.2 g, 0.9 mmole), yield 0.12 g (65%), mp 242-244°; uv: (methanol): λ max 250 nm (ε 19,130); ^{1}H nmr: δ 1.71, 1.78 (2s, 6 H, 2 CH_3), 4.72 (d, 2 H, NCH_2), 5.38 (m, 1 H, CH), 8.03, 8.04 (2s, 2 H, C_2H, C_8H), and 12.25 (br s, 1 H, NH); ms: (FAB) m/z 205.3 (M+H).

9-(2-Penten-1-yl)guanine (**6c**).

Acid hydrolysis of **3c** (0.6 g, 2.52 mmoles) as described for **6a** afforded **6c** (0.5 g, 91%), mp >250°; uv: (methanol): λ max 256 nm (ε 16,630), 276 (10,930); ^{1}H nmr: δ 0.96 (t, 3 H, CH_3), 2.20 (m, 2 H, CH_2CH_3), 4.60 (d, 2 H, NCH_2), 5.58 (m, 2 H, CH=CH), 6.50 (s, 2 H, NH_2), 7.62 (s, 1 H, C_8H), and 10.60 (br s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{13}N_5O \cdot 0.5H_2O$: C, 52.62; H, 6.18; N, 30.69. Found: C, 52.89; H, 5.80; N, 30.62.

7-(2-Penten-1-yl)guanine (**7c**).

The title compound was obtained by the acid hydrolysis of **4c** (0.25 g, 1.05 mmoles), yield 0.18 g (78%), mp >250°; uv: (methanol): λ max 248 nm (ε 11,530), 286 (11,580); ^{1}H nmr: δ 0.95 (t, 3 H, CH_3), 2.17 (m, 2 H, CH_2CH_3), 4.85 (d, 2 H, NCH_2), 5.57 (m, 2 H, CH=CH), 6.13 (s, 2 H, NH_2), 7.86 (s, 1 H, C_8H), and 10.79 (br s, 1 H, NH); ms: (FAB) m/z 220.3 (M+H).

9-(3-Methyl-2-buten-1-yl)guanine (**6d**).

This compound was obtained by the acid hydrolysis of **3d** (0.4 g, 1.68 mmoles), yield 0.25 g (68%), mp >250°; uv: (methanol): λ max 256 nm (ε 22,340), 276 (14,520); ^{1}H nmr: δ 1.70, 1.76 (2s, 6 H, 2 CH_3), 4.52 (d, 2 H, NCH_2), 5.33 (t, 1 H, CH), 6.43 (s, 2 H, NH_2), 7.63 (s, 1 H, C_8H), and 10.56 (s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.95. Found: C, 54.61; H, 5.85; N, 31.68.

7-(3-Methyl-2-buten-1-yl)guanine (**7d**).

The title compound was obtained by the acid hydrolysis of **4d** (0.17 g, 0.71 mmole), yield 0.11 g (71%), mp >250°; uv: (methanol): λ max 246 nm (ε 6390), 286 (6400); ^{1}H nmr: δ 1.69, 1.75 (2s, 6 H, 2 CH_3), 4.79 (d, 2 H, NCH_2), 5.40 (t, 1 H, CH), 6.24 (s, 2 H, NH_2), 7.87 (s, 1 H, C_8H), and 10.89 (s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.95. Found: C, 54.67; H, 5.74; N, 31.62.

9-(4-Penten-1-yl)guanine (**6e**).

The title compound was obtained from **3e** (0.5 g, 2.28 mmoles) in 64% yield, mp 268-270°; uv: (methanol): λ max 256 nm (ε 8870), 272 (6650); ^{1}H nmr: δ 1.82 (m, 2 H, CH_2), 2.00 (m, 2 H, CH_2), 3.92 (t, 2 H, NCH_2), 5.02 (m, 2 H, CH_2), 5.81 (m, 1 H, CH), 6.35 (s, 2 H, NH_2), and 7.65 (s, 1 H, C_8H).

Anal. Calcd. for $C_{10}H_{13}N_5O \cdot 1/3H_2O$: C, 53.32; H, 6.11; N, 31.09. Found: C, 53.22; H, 5.79; N, 30.93.

7-(4-Penten-1-yl)guanine (**7e**).

The title compound was obtained from **4e** (0.2 g, 0.84 mmole) in 87% yield, mp >250°; uv: (methanol): λ max 248 nm (ε 8230), 286 (8630); ^{1}H nmr: δ 1.86 (m, 2 H, CH_2), 1.97 (m, 2 H, CH_2), 4.16 (t, 2 H, NCH_2), 4.98 (m, 2 H, CH_2), 5.78 (m, 1 H, CH), 6.12 (s, 2 H, NH_2), 7.89 (s, 1 H, C_8H), and 10.76 (s, 1 H, NH).

Anal. Calcd. for $C_{10}H_{13}N_5O \cdot 0.2H_2O$: C, 53.89; H, 6.06; N, 31.43. Found: C, 53.96; H, 5.88; N, 31.38.

9-(2-Penten-1-yl)purine-6-carboxamide (**9a**).

Purine-6-carboxamide [18] (**8**, 0.5 g, 3.06 mmoles) was dried by co-evaporation with dry DMF (30 ml). The dried material was suspended in dry DMF (50 ml). To this suspension, sodium hydride (60%, 138 mg, 3.45 mmoles) was added and the mixture was stirred at room temperature for 30 minutes. 1-Bromo-2-pentene (0.5 ml, 4.16 mmoles) was added and the mixture was stirred overnight. The solvent was evaporated and the residue was purified by chromatography on a silica gel column (2 x 15 cm). The product was eluted with dichloromethane containing 0-6% methanol, yield 0.38 g (54%), mp 161-162°; uv: (methanol): λ max 284 nm (ε 9450); ^{1}H nmr: δ 0.99 (t, 3 H, CH_3), 2.27 (m, 2 H, CH_2CH_3), 4.98 (d, 2 H, NCH_2), 5.64 (m, 2 H, CH=CH), 8.04, 8.37 (2s, 2 H, NH_2), 8.76 (s, 1 H, C_8H), and 9.03 (s, 1 H, C_2H).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.66; N, 30.29. Found: C, 56.99; H, 5.57; N, 29.80.

9-(3-Methyl-2-buten-1-yl)purine-6-carboxamide (**9b**).

In a similar manner as described for compound **9a**, alkylation of **8** (0.5 g, 3.06 mmoles) with 4-bromo-2-methyl-2-butene (0.48 ml, 4.16 mmoles) gave the title compound, yield 0.3 g (42%), mp 198-200°; uv: (methanol): λ max 284 nm (ε 9300); ^{1}H nmr: δ 1.83, 1.91 (2s, 6 H, 2 CH_3), 4.99 (d, 2 H, NCH_2), 5.53 (m, 1 H, CH), 8.11, 8.45 (2s, 2 H, NH_2), 8.82 (s, 1 H, C_8H), and 9.10 (s, 1 H, C_2H).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.66; N, 30.29. Found: C, 56.89; H, 5.94; N, 30.55.

1-(2-Penten-1-yl)-1,2,4-triazole-3-carboxamide (**11a**).

1,2,4-Triazole-3-carboxamide [19] (**10**, 0.67 g, 6 mmoles) was dried by co-evaporation with dry DMF (20 ml) and suspended in dry DMF (30 ml). Sodium hydride (60%, 0.24 g, 6 mmoles) was added to the suspension and the mixture was stirred at room temperature for 30 minutes before 1-bromo-2-pentene (1.0 g, 6.6 mmoles) was added. The reaction was continued for 3 hours and DMF was evaporated. The residue was dissolved in water (75 ml) and the product was extracted with dichloromethane (3 x 100 ml). The combined organic layer was dried (sodium sulfate) and evaporated. The residue was purified by chromatography on a silica gel column (2 x 15 cm) and the product was eluted with dichloromethane containing 0-4% methanol to yield 0.5 g (46%) of pure **11a**, mp 108-110°; ^{1}H

nmr: δ 0.97 (t, 3 H, CH_3), 2.16 (m, 2 H, CH_2CH_3), 4.89 (d, 2 H, NCH_2), 5.57, 5.67 (2m, 2 H, CH=CH), 7.44, 7.61 (2s, 2 H, NH_2), and 8.56 (s, 1 H, C_5H).

Anal. Calcd. for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.57; H, 6.69; N, 31.20.

1-(3-Methyl-2-buten-1-yl)-1,2,4-triazole-3-carboxamide (**11b**).

Alkylation of **10** (1.0 g, 8.92 mmoles) with 4-bromo-2-methyl-2-butene (1.03 ml, 8.92 mmoles) afforded **11b** as the major component, yield 1.15 g (71%), mp 128-130°; ^{1}H nmr: δ 1.74, 1.75 (2s, 6 H, 2 CH_3), 4.82 (d, 2 H, NCH_2), 5.39 (t, 1 H, CH), 7.42, 7.61 (2s, 2 H, NH_2), and 8.54 (s, 1 H, C_5H).

Anal. Calcd. for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.37; H, 6.67; N, 31.00.

3-(2-Penten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-one (**13a**).

Pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one [22] (**12**, 0.81 g, 6 mmoles) was dried by co-evaporation with dry DMF (20 ml) and the dried substrate was suspended in dry DMF (30 ml). To this suspension was added sodium hydride (60%, 0.24 g, 6 mmoles). The mixture was stirred at room temperature for 20 minutes and 1-bromo-2-pentene (1.0 g, 6 mmoles) was added. The reaction mixture was stirred at room temperature overnight and the solvent was evaporated. The residue was dissolved in dichloromethane (200 ml) and the organic phase was washed with water (2 x 50 ml). The organic layer was dried over sodium sulfate and evaporated. The residue was purified by chromatography on a silica gel column (2 x 15 cm) and the product was eluted with dichloromethane containing 0-2% methanol to yield 0.65 g (53%) of **13a** as a colorless solid, mp 120-122°; uv: (methanol): λ max 262 nm (ε 11,200); ^{1}H nmr: δ 0.97 (t, 3 H, CH_3), 2.22 (m, 2 H, CH_2CH_3), 4.60 (d, 2 H, NCH_2), 5.42, 5.57 (2m, 2 H, CH=CH), 6.44 (d, 1 H, C_5H), 7.02 (d, 1 H, C_6H), 8.09 (s, 1 H, C_2H), and 11.80 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.21; H, 6.39; N, 20.71.

3-(3-Methyl-2-buten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-one (**13b**).

This compound was obtained by the alkylation of the sodium salt of **12** (0.81 g, 6 mmoles) with 4-bromo-2-methyl-2-butene (0.69 ml, 6 mmoles), yield 0.68 g (56%), mp 163-164°; uv: (methanol): λ max 262 nm (ε 10,900); ^{1}H nmr: δ 1.69, 1.78 (2s, 6 H, 2 CH_3), 4.54 (d, 2 H NCH_2), 5.26 (m, 1 H, CH), 6.44 (d, 1 H, C_5H), 7.05 (d, 1 H, C_6H), 8.11 (s, 1 H, C_2H), and 11.95 (br s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 64.93; H, 6.34; N, 20.49.

4-Chloro-7-(2-penten-1-yl)pyrrolo[2,3-*d*]pyrimidine (**15a**).

4-Chloropyrrolo[2,3-*d*]pyrimidine [24] (**14**, 0.5 g, 3.26 mmoles) was dried by co-evaporation with dry acetonitrile (25 ml). The dried material was suspended in dry acetonitrile (30 ml) and sodium hydride (60%, 0.13 g, 3.26 mmoles) was added. The mixture was stirred at room temperature for 30 minutes with the exclusion of moisture and 1-bromo-2-pentene (0.5 ml, 4.25 mmoles) was added. The reaction mixture was stirred at room temperature for 4 hours. The insoluble material was removed by filtration and the filtrate was evaporated. The residue was purified by chromatography on a silica gel column (2 x 15 cm) and the product was eluted with dichloromethane containing 0-2% ethyl acetate. The appropriate fractions were collected and evaporated to give 0.36 g (50%) of pure **15a** as a colorless solid, mp 46-48°; uv: (methanol): λ max 272 nm (ε 4760); ^{1}H nmr: δ 0.96 (t, 3 H, CH_3), 2.25 (m, 2 H, CH_2CH_3), 4.93 (d, 2 H, NCH_2), 5.60 (m, 2 H, CH=CH), 6.66 (d, 1 H, C_5H), 7.73 (d, 1 H, C_6H), and 8.64 (s, 1 H, C_2H).

Anal. Calcd. for $C_{11}H_{12}ClN_3$: C, 59.59; H, 5.46; N, 18.96. Found: C, 59.74; H, 5.44; N, 18.73.

4-Chloro-7-(3-methyl-2-buten-1-yl)pyrrolo[2,3-*d*]pyrimidine (**15b**).

In a similar manner as described for **15a**, alkylation of the sodium salt of **14** (0.5 g, 3.26 mmoles and sodium hydride 0.13 g, 3.26 mmoles, 60%) with 4-bromo-2-methyl-2-butene (0.49 ml, 4.25 mmoles) in dry acetonitrile (30 ml) afforded 0.4 g (55%) of **15b** as a light yellow oil; uv: (methanol): λ max 272 nm (ε 5300); ^{1}H nmr: δ 1.70, 1.81 (2s, 6 H, 2 CH_3), 4.87 (d, 2 H, NCH_2), 5.38 (m, 1 H, CH), 6.64 (d, 1 H, C_5H), 7.72 (d, 1 H, C_6H), and 8.64 (s, 1 H, C_2H).

Anal. Calcd. for $C_{11}H_{12}ClN_3$: C, 59.59; H, 5.46; N, 18.96. Found: C, 59.83; H, 5.48; N, 18.60.

7-(2-Penten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**16a**).

To a solution of **15a** (0.3 g) in tetrahydrofuran (4 ml) was added aqueous hydrochloric acid (1.7 *M*, 10 ml) and the mixture was heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature and neutralized with 2 *N* sodium hydroxide solution. The solvent was evaporated to dryness. The solid was extracted with dichloromethane and the insoluble material was discarded. The organic solution was evaporated and the residue was purified by chromatography on a silica gel column (2 x 15 cm). The product was eluted with dichloromethane containing 0-3% methanol. The appropriate fractions containing the product were collected and evaporated to give 0.05 g (18%) of pure **16a** as a colorless powder, mp 146-148°; uv: (methanol): λ max 262 nm (ε 11,580); ^{1}H nmr: δ 0.98 (t, 3 H, CH_3), 2.20 (m, 2 H, CH_2CH_3), 4.76 (d, 2 H, NCH_2), 5.57 (m, 2 H, CH=CH), 6.47 (d, 1 H, C_5H), 7.09 (d, 1 H, C_6H), 7.89 (s, 1 H, C_2H), and 11.85 (br s, 1 H, NH); ms: m/z 204.2 (M+H).

7-(3-Methyl-2-buten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**16b**).

In a similar manner as described for **16a**, acid hydrolysis of **15b** (0.3 g) with aqueous hydrochloric acid (1.7 *M*, 20 ml) in tetrahydrofuran (10 ml) under refluxing conditions for 12 hours afforded the title compound, 0.1 g (36%), mp 170-171°; uv: (methanol): λ max 262 nm (ε 13,800); ^{1}H nmr: δ 1.71, 1.78 (2s, 6 H, 2 CH_3), 4.70 (d, 2 H, NCH_2), 5.35 (t, 1 H, CH), 6.45 (d, 1 H, C_5H), 7.07 (d, 1 H, C_6H), 7.89 (s, 1 H, C_2H), and 11.84 (br s, 1 H, NH); ms: m/z 204.3 (M+H).

2-Amino-4-methoxy-7-(2-penten-1-yl)pyrrolo[2,3-*d*]pyrimidine (**18a**).

2-Amino-4-methoxypyrrolo[2,3-*d*]pyrimidine [25] (**17**, 0.82 g, 5 mmoles) was dried by co-evaporation with dry DMF (20 ml) before it was dissolved in DMF (30 ml). Sodium hydride (60%, 0.2 g, 5 mmoles) was added and the mixture was stirred at room temperature for 20 minutes. 1-Bromo-2-pentene (0.59 ml, 5 mmoles) was added and the reaction was continued overnight. The solvent was evaporated and the product was trit-

urated with a small amount of water (2 x 5 ml). The residue was co-evaporated with toluene and the residue was purified by silica gel column chromatography. The product was eluted with dichloromethane containing 0-4% ethyl acetate to yield 0.32 g (28%) of pure **18a**, mp 98-100°; uv: (methanol): λ max 230 nm (ε 29,990), 264 (12,230), 286 (12,000); ^{1}H nmr: δ 0.97 (t, 3 H, CH_3), 2.19 (m, 2 H, CH_2CH_3), 3.91 (s, 3 H, OCH_3), 4.63 (d, 2 H, NCH_2), 5.55 (m, 2 H, CH=CH), 6.14 (s, 2 H, NH_2), 6.22 (s, 1 H, C_5H), and 6.83 (d, 1 H, C_6H).

Anal. Calcd. for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.12. Found: C, 62.18; H, 6.91; N, 23.91.

2-Amino-7-(2-penten-1-yl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**19a**).

To a solution of **18a** (0.18 g, 0.77 mmole) in dry acetonitrile (10 ml) was added iodotrimethylsilane (0.3 ml) and the mixture was heated under reflux for 1.5 hours. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The residue was dissolved in ethyl acetate (100 ml) and washed with a solution of sodium bisulfite (0.25 g of sodium bisulfite in 25 ml of water). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic layer was evaporated to give a solid which was purified by silica gel column chromatography. The product was eluted with dichloromethane containing 0-8% methanol to yield 0.14 g (83%) of pure **19a**, mp 264-266°; uv: (methanol): λ max 264 nm (ε 15,820), 282 (10,400); ^{1}H nmr: δ 0.97 (t, 3 H, CH_3), 2.15 (m, 2 H, CH_2CH_3), 4.54 (d, 2 H, NCH_2), 5.47 (m, 2 H, CH=CH), 6.09 (s, 2 H, NH_2), 6.21 (s, 1 H, C_5H), 6.62 (d, 1 H, C_6H), and 10.18 (s, 1 H, NH).

Anal. Calcd. for $C_{11}H_{14}N_4O \cdot 0.1H_2O$: C, 60.04; H, 6.41; N, 25.46. Found: C, 59.99; H, 6.38; N, 25.37.

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