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Alkylation of Adenine with Functionalized tert.-Propargyl Carbonates. Synthesis of 3'-Hydroxymethyladenallene - a New Analogue of 2'-Deoxyadenosine

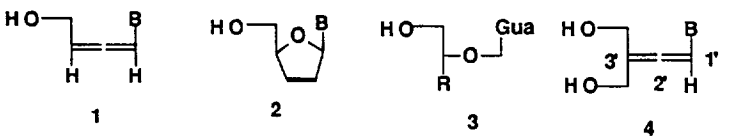
Ze-Qi Xu[1], Ramachandra V. Joshi and Jiri Zemlicka*

Department of Chemistry, Michigan Cancer Foundation and Departments of Internal Medicine and Biochemistry, Wayne State University School of Medicine, Detroit, Michigan 48201

Abstract: Esters **9d** - **9g** derived from acetylenic carbinol **5** were prepared and they were studied as potential alkylating agents with adenine (**10**), N^6-benzoyl- and N^6-dimethylamino-methyleneadenine (**16** and **17**). Carbonates **9f** and **9g** were the most suitable giving allene **11** and acetylene **12** (after N-deprotection in case of **16** and **17**). On a scale larger than 0.2 mmol, slow addition of carbonate **9f** or **9g** to a solution of **10**, **16** or **17** in DMF at 60°C was most conducive to formation of allenic derivative **11**. Such conditions also suppressed formation of by-products such as carbonate **13a** and N^9-methyladenine (**14**) observed in the case of methyl carbonate **9f**. Intermediates **11** and **12** were deprotected using BCl_3 in CH_2Cl_2 to give 3'-hydroxymethyladenallene (**4a**) and diol **15**, respectively. Compound **4a** was de-aminated with adenosine deaminase.

INTRODUCTION. Recently, we synthesized a new class of nucleoside analogues comprising an allenic system instead of a furanose moiety (**1**)[2,3]. Two of these allenols, adenallene (**1a**) and cytallene (**1b**), are potent inhibitors of human immunodeficiency virus (HIV), the etiologic agent of acquired immunodeficiency syndrome (AIDS)[2,4]. Compounds **1a** and **1b** can be regarded as analogues of the corresponding 2',3'-dideoxyribonucleosides, 2',3'-dideoxyadenosine (**2a**, ddAdo) and 2',3'-dideoxy-cytidine (**2b**, ddCyd), where the tetrahydrofuran moiety is replaced with an allene function. Indeed, the anti-HIV activity of allenols **1a** and **1b** parallels that of ddAdo (**2a**) and ddCyd (**2b**)[4]. The latter analogue was recently approved as a prescription drug for AIDS under the name zalcitabine (Hivid)[5]. Compounds **1a** and **1b** can also be viewed as mimics of open-chain nucleoside analogues, such as the antiherpetic drug acyclovir (**3a**, Zovirax)[6], where the C-O-C moiety is replaced with an isoelectronic allenic function C=C=C.

It was therefore of interest to investigate possible synthetic approaches to other functionalized allenes derived from nucleic acid bases. Allenediols **4** comprising two hydroxymethyl residues attached to an allenic system carrying a nucleic acid base could possibly mimic 2'-deoxynucleosides as well as open-chain analogues related to antiviral drug[6] ganciclovir (**3b**, Cytovene). Additional motivation for synthesis stems from the fact that compounds **4** can serve, after proper protection, as building blocks for synthesis of antisense oligonucleotides[7]. The synthesis of the first such analogue, 3'-hydroxymethyladenallene (**4a**), and related chemistry are the subject of this communication. It should be also stated that geminal bis-hydroxymethylallenes have not been described to the best of our knowledge.



1a, 2a: B = Ade
1b, 2b: B = Cyt

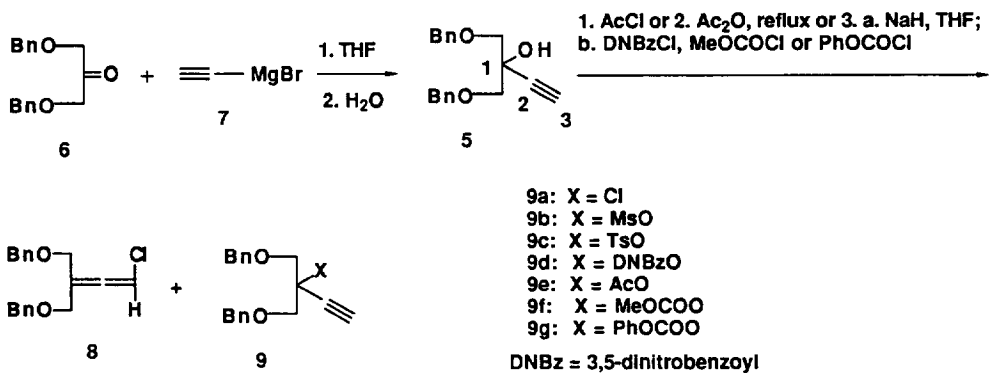
3a: R = H
3b: R = CH_2OH

4a: B = Ade

B = nucleic acid base

SYNTHESIS. Model experiments have indicated[8] that one possible approach to allenediols **4** is alkylation of nucleic acid bases with suitably functionalized propargyl derivatives. The key starting material, acetylenic carbinol **5**, was obtained readily from the known[9,10] ketone **6** and ethynylmagnesium bromide (**7**) in 80 % yield (Scheme 1). Attempted chlorination of **5** using the procedure[11] for synthesis of 1,1-dimethyl- or 1,1-diethylpropargyl chlorides led only to extensive debenzylation. Reaction of **5** with

Scheme 1



9a: X = Cl
9b: X = MsO
9c: X = TsO
9d: X = DNBzO
9e: X = AcO
9f: X = MeOCOO
9g: X = PhOCOO

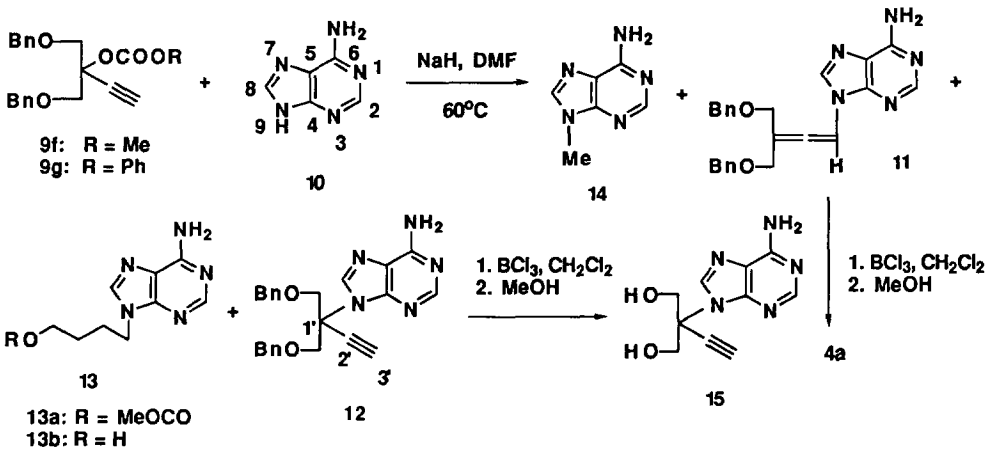
DNBz = 3,5-dinitrobenzoyl

$SOCl_2$ in DMF afforded a mixture of chloroallene **8** and chloroacetylene **9a** as indicated by IR spectrum. This product as well as the corresponding mesylate **9b** and tosylate **9c** were not sufficiently stable to permit alkylation of adenine (**10**) either with or without catalysis by $Pd(PPh_3)_4$. 3,5-Dinitrobenzoate **9d** produced only traces of allene **11** and acetylene **12** (Scheme 2) although this reagent had been successfully used to prepare an unstable allenic thioether[12]. Acetylation of carbinol **5** with AcCl or Ac_2O gave a stable acetate **9e** in 83 - 87 % yield. Nevertheless, attempted alkylation of adenine (**10**) using **9e** and $Pd(PPh_3)_4$ in DMF was fruitless.

By contrast, **leaving groups of the carbonate type provided the necessary balance between the stability (9e) and reactivity (9a - 9d) and were found suitable for alkylation of adenine (10, Scheme 2).** Methyl and ethyl carbonates **9f** and **9g** were prepared from the respective chloroformates and the sodium salt of **5** in THF. Of particular advantage is a direct quenching of the Grignard intermediate from the reaction of ketone **6** and ethynylmagnesium bromide (**7**) with chloroformate **9f** or **9g**. A similar procedure was recently employed for the synthesis of methyl carbonates derived from acetylenic carbinols of nucleosides[13].

In the initial small scale experiments (0.15 mmol) carried out at 60°C in DMF with the sodium salt of adenine (**10**), both methyl and phenyl carbonate **9f** and **9g** gave a very clean reaction, yielding N^9-allene

Scheme 2



11 and N^9-acetylene **12** as shown by TLC and UV spectra (Scheme 2). On a larger scale, when 0.9 mmol of sodium salt of adenine (**10**) was reacted with an equivalent of methyl carbonate **9f** in DMF (20 mL) at 60°C for 20 h, N^9-acetylene **12** (1 %), carbonate **13a** (3 %) and N^9-methyladenine (**14**, 18 %) were obtained, but no allene **11**. Ammonolysis of **13a** readily furnished the known[3] 4-hydroxybutyladenine **13b**. A prolonged reaction time increased only the yield of **14**. Changing the ratio of NaH and carbonate **9f** did not affect the outcome.

Formation of saturated carbonate **13a** with a transposed methyl carbonate function lacking both benzyl groups and one carbon atom of the original side chain of allene **11** was unexpected and may be indicative of a free radical reaction. An allenic derivative seems to be a logical intermediate in the formation of **13a** which contains a straight chain of carbons. Assuming that NaH was the source of hydrogen, four molar equivalents of H_2 would have been necessary to remove benzyl groups and reduce the allene function. Loss of a single hydroxymethyl group can be tentatively explained by a retroaldol type of cleavage. Nevertheless, any mechanism must be only speculative at this time.

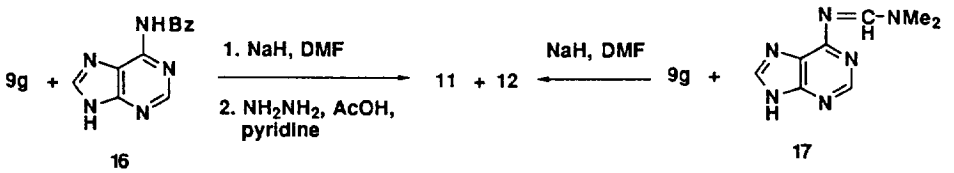
Quite surprisingly, **the rate of addition of carbonates 9f and 9g** into the reaction mixture **determines the success or failure of allene formation** at a scale larger than 0.2 mmol. Very slow introduction of carbonates **9f** and **9g** via a syringe pump is mandatory. Under such precautions, phenyl carbonate **9g**, which was the most successful reagent probably because methylation of adenine (**10**) was precluded, gave allene **11** and acetylene **12** in 8 and 5 % yield, respectively. Deprotection with BCl_3 in CH_2Cl_2 and subsequent methanolysis[10,14] afforded allenediol **4a** (80 %) and acetylene **15** (65 %). The UV and NMR spectra of **4a** were very similar to those of adenallene[3] (**1a**). As expected, the resonance of $C_{3'}$ was shifted upfield relative to that in **1a**.

Use of the sodium salt of adenine (**10**) favors the formation of N^9-allene **11**, since only 7 % of N^9-acetylene **12** and no allene **11** was isolated when K_2CO_3 was used as a base. The nature of the solvent

is also critical. In THF, no reaction took place; in DMSO and HMPA, only decomposition of carbonates **9f** or **9g** occurred. DMF was found to be the solvent of choice for the reaction. At temperatures lower than 40°C, no reaction took place. An increase to 80°C caused substantial decomposition of the carbonates **9f** and **9g**. The optimum temperature appears to be 60°C. Catalysts such as $Pd(PPh_3)_4$ and dibenzylideneacetone palladium /$Pd(dba)_2$/ did not improve the yields of allene **11** and acetylene **12**.

In order to improve the yield of allene **11**, the N^6-protected adenines **16** and **17** were employed in alkylations with phenyl carbonate **9g**. Thus, the sodium salt of N^6-benzoyladenine (**16**, 0.4 mmol), prepared from 2 equivalents of NaH, was allowed to react with 2 equivalents of methyl or phenyl carbonate **9f** and **9g**, which were slowly added to the reaction mixture (Scheme 3). The crude product

Scheme 3



was debenzoylated with buffered hydrazine[15] to furnish N^9-allene **11** in 7 % and 20 %, respectively. No N^9-acetylene **12** was observed. No reaction between N^6-benzoyladenine (**16**) and methyl carbonate **9f** occurred when only 1 equivalent NaH was used. When the reaction with phenyl carbonate **9g** was scaled up to ca. 2 mmol of **16**, both N^9-allene **11** and N^9-acetylene **12** were formed in 6 and 9 % yield after debenzoylation. The sodium salt of N^6-dimethylaminomethyleneadenine[16] (**17**) and phenyl carbonate **9g** gave a 1 : 1 mixture of acetylene **12** and allene **11** in 24 % yield. Because a clean resolution of intermediates **11** and **12** by column chromatography is difficult, it is advantageous to debenzylate a mixture of **11** and **12** and separate products **4a** and **15** (4 and 9 % yield, respectively). Despite lower yields, the procedure is simple and ample amounts of allenediol **4a** can be easily generated.

Another special feature of these transformations deserves mention. In model experiments[8] employing the 1,1-dialkylpropargyl chlorides and adenine (**10**) the N^7-acetylenes always accompanied the respective N^9-isomers whereas the formation of N^9-allenes was regioselective. No N^7-isomers of either acetylene **12** or allene **11** were observed in alkylations with carbonates **9f** or **9g** under any conditions. It has to be emphasized that no N^7-isomer was obtained even in the case of N^6-dimethylaminomethyleneadenine (**17**), although some previous findings indicated that the N^6-dimethylaminomethylene group of **17** was capable of directing alkylation to the N^7 position[16]. Similarly, N^7-dimethylaminomethyleneformycin was methylated exclusively at the N^1 position[17]. These results indicate that the S_N1 mechanism is of limited importance in the case of leaving groups of carbonate type, and that acetylene **12** is formed by an S_N2-like process.

BIOLOGICAL ACTIVITY. Allenol **4a** and acetylene **15** were inactive in a number of antiviral and antitumor assays. Nevertheless, compound **4a** was deaminated by adenosine deaminase. As expected, acetylene **15** was totally inert.

EXPERIMENTAL

For general methods see[3,18]. A 60 % dispersion of NaH in mineral oil was used in all pertinent reactions.

N^6-Dimethylaminomethyleneadenine (17). A mixture of adenine (**10**, 0.675 g, 5 mmol) and dimethylformamide dimethyl acetal (2.5 mL, 18.8 mmol) was stirred at 60 - 70°C (bath temperature) until all the adenine (**10**) dissolved. The solution was then kept at room temperature for 16 h. Some product **17** precipitated but the whole reaction mixture was evaporated and the residue was triturated with ethanol and ether to give compound **17** (0.6 g, 63 %), mp. 262 - 264°C after recrystallization from DMF, lit.[16] 252 - 255°C. The UV and ^1H NMR spectra corresponded to those described[16]. The mother liquors were evaporated and the obtained product was washed with ether to afford additional **17** (0.28 g, 29 %).

1-Benzyloxy-2-benzyloxymethyl-3-butyn-2-ol (5). The crude 1,3-dibenzyloxyacetone[10] (**6**, 1.55 g, 5.73 mmol) was dissolved in THF (30 mL) under N_2 and the mixture was cooled in an ice bath. Ethynylmagnesium bromide (**7**, 0.5 M in THF, 17.2 mL, 8.6 mmol) was added dropwise over 15 min. The mixture was then stirred at room temperature for 1 h. The reaction was quenched by adding MeOH (10 mL) with stirring at 0°C during 30 min. The crude product obtained by evaporation was flash-chromatographed on a silica gel column in CH_2Cl_2 to give carbinol **5** (1.35 g, 79%) as a sirup. IR (NaCl) 3560 - 3420 cm^{-1} (s, OH), 3300 (vs, C≡CH), 2130 (w, C≡C); ^1H NMR ($CDCl_3$) ∂ 2.52 (s, 1, H_3), 3.68 (s, 4, 1-CH_2), 4.66 (s, 4, CH_2 of Bn), 7.37 (s, 10, Ph); ^{13}C NMR 69.67 (C_3), 73.09 (C_2), 73.13 (1-CH_2), 73.56 (CH_2 of Bn), 83.55 (C_1), 127.66, 128.31 and 137.62 (Ph); CI-MS 297 (M + 1, 4.5), 205 (M - Bn, 16.7), 181 (52.8), 91 (Bn, 100.0). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.79; H, 6.91.

2-Acetoxy-1-benzyloxy-2-benzyloxymethyl-3-butyne (9e). A. From Acetyl Chloride. A mixture of carbinol **5** (420 mg, 1.41 mmol) and acetyl chloride (6 mL) was stirred at room temperature for 2 h. The solution was evaporated and the residue was flash-chromatographed on a silica gel column with CH_2Cl_2 as the eluent to give acetate **9e** (410 mg, 86%) as a sirup. IR (NaCl) 3290 cm^{-1} (vs, C≡CH), 2130 (m, C≡C), 1750 (s, C=O); ^1H NMR ($CDCl_3$) ∂ 2.08 (s, 3, Me), 2.65 (s, 1, H_3), 3.89 and 3.98 (2d[19], 4, J = 9.6 Hz, 1-CH_2), 4.63 (s, 4, CH_2 of Bn), 7.34 (s, 10, Ph); ^{13}C NMR 21.83 (Me), 70.44 (1-CH_2), 73.82 (CH_2 of Bn), 75.90 (C_3), 77.20 (C_2, overlapped with $CDCl_3$), 79.97 (C_1), 127.80, 127.86, 128.51 and 138.01 (Ph), 169.32 (C=O). Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.30; H, 6.51.

B. From Acetic Anhydride. Carbinol **5** (100 mg, 0.33 mmol) was refluxed in acetic anhydride (4 mL) with stirring for 4 h. The excess of acetic anhydride was removed in vacuo and the crude product was chromatographed on a silica gel column using hexane - acetone (4 : 1) as the eluent to give acetate **9e** (95 mg, 83 %), identical with a sample prepared by Method A.

2-(Methoxycarbonyl)oxy-1-benzyloxy-2-benzyloxymethyl-3-butyne (9f). A. From Carbinol 5. Sodium hydride (121 mg, 3.05 mmol) was added to a stirred solution of compound **5** (900 mg, 3.03 mmol) in THF (30 mL) at 0°C. The stirring at 0°C was continued for 6 h. Methyl chloroformate (0.35 mL, 4.5 mmol) was then added and the resulting mixture was stirred at 0°C for 1.5 h. The crude product obtained by evaporation was flash-chromatographed on a silica gel column using CH_2Cl_2 to give methyl carbonate **9f** (900 mg, 84 %) as a sirup. IR (NaCl) 3290 cm^{-1} (vs, C≡CH), 2135 (m, C≡C), 1760 (C=O); ^1H NMR ($CDCl_3$) ∂ 2.61 (s, 1, H_3), 3.71 (s, 3, MeO), 3.82 and 3.94 (2d[19], 4, J = 9.9 Hz, 1-CH_2), 4.58 (s, 4, CH_2 of Bn), 7.26 (s, 10, Ph); ^{13}C NMR 54.58 (MeO), 69.95 (1-CH_2), 73.58 (CH_2

of Bn), 76.22 (C_3), 77.55 (C_1), 79.20 (C_2), 127.60, 127.63, 128.29 and 137.68 (Ph), 153.18 (C=O). Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.32; H, 6.40.

B. From 1,3-Dibenzyloxyacetone (6). The experiment was performed as described for compound **5** but methyl chloroformate (1.3 mL, 16.8 mmol) was added instead of methanol. The stirring was continued at room temperature for 24 h. The mixture was evaporated and the residue was flash-chromatographed as described above to give methyl carbonate **9f** (1.34g, 68 %) which was identical with the product prepared by Method A.

2-(Phenoxycarbonyl)oxy-1-benzyloxy-2-benzyloxymethyl-3-butyne (9g). A. From Carbinol 5. The reaction was carried out as described for methyl carbonate **9f**, Method A. Phenyl chloroformate (0.17 mL, 1.36 mmol) was added to a suspension of sodium salt prepared from compound **5** (260 mg, 0.88 mmol) and NaH (36 mg, 0.9 mmol) in THF (12 mL). The reaction mixture was poured on ice (50 g) and ether (50 mL). The organic layer was separated and it was washed successively with HCl (5 %) (2 x 20 mL), water (20 mL) and then it was dried (Na_2SO_4). Evaporation of the solvent followed by flash-chromatography of the crude product on a silica gel column using CH_2Cl_2 - petroleum ether (3 : 1) gave phenyl carbonate **9g** (297 mg, 81 %) as a sirup. IR (NaCl) 3300 cm^{-1} (vs, C≡CH), 2140 (m, C≡C), 1760 (vs, C=O); ^1H NMR ($CDCl_3$) ∂ 2.70 (s, 1, H_3), 3.93 and 4.07 (2d^{19}, 4, J = 10.1 Hz, 1-CH_2), 4.64 (s, 4, CH_2 of Bn), 7.16-7.38 (apparent m, 15, Ph); ^{13}C NMR 69.95 (1-CH_2), 73.58 (CH_2 of Bn), 76.74 (C_3), 78.30 and 78.69 (C_1, C_2), 120.94, 125.92, 129.29, 150.75 (PhO), 127.56, 127.65, 128.28, 137.55 (Ph), 150.92 (C=O). Anal. Calcd for $C_{26}H_{24}O_5$: C, 74.98; H, 5.81. Found: C, 74.84; H, 5.82.

B. From 1,3-Dibenzyloxyacetone (6). The reaction was carried out as described for the preparation of the corresponding methyl carbonate **9f** (Method B). From 1,3-dibenzyloxyacetone (**6**, 3.05 g, 11.3 mmol), ethynylmagnesium bromide (**7**) in THF (0.5 M, 35 mL, 17.5 mmol) and phenyl chloroformate (1.9 mL, 15 mmol) in THF (50 mL), 4.01 g (85 %) of compound **9g** was obtained after a work up described above which was identical with an authentic sample prepared by Method A.

1-Benzyloxy-2-benzyloxymethyl-2-(3,5-dinitrobenzoyl)oxy-3-butyne (9d). The reaction was performed as described for the preparation of phenyl carbonate (**9g**, Method A). Thus, carbinol **5** (150 mg, 0.5 mmol), NaH (21 mg, 0.52 mmol) and of 3,5-dinitrobenzoyl chloride (175 mg, 0.76 mmol) in THF (10 mL) afforded 168 mg (69 %) of ester **9d** as a sirup. IR (NaCl) 3300 cm^{-1} (vs, C≡CH), 2135 (m, C≡C), 1750 (vs, C=O); ^1H NMR ($CDCl_3$) ∂ 2.75 (s, 1, H_3), 4.01 and 4.12 (2d^{19}, 4, J = 9.9 Hz, 1-CH_2), 4.64 (s, 4, CH_2 of Bn), 7.32 (s, 10, Ph), 9.06 (d, 2) and 9.19 (t, 1, DNBz); ^{13}C NMR 70.00 (1-CH_2), 73.67 (CH_2 of Bn), 77.10 (C_3), 78.14 (C_1), 78.45 (C_2), 122.41, 129.49, 133.88 and 148.45 (DNBz), 127.68, 127.84, 128.41 and 137.36 (Ph), 160.42 (C=O).

N^9-(4-Benzyloxy-3-benzyloxymethyl-1,2-butadien-1-yl)adenine (11) and N^9-(1-Benzyloxy-2-benzyloxymethyl-3-butyn-2-yl)adenine (12). Method A. From Sodium Salt of Adenine and Slow Addition of Phenyl Carbonate 9g. Sodium hydride (152 mg, 3.8 mmol) was added into a stirred suspension of adenine (**10**, 500 mg, 3.7 mmol) in DMF (15 mL) under N_2 at room temperature. The mixture was brought to 60°C and a solution of phenyl carbonate (**9g**, 1.71 g, 4.1 mmol) DMF (4 mL) was added dropwise over 6.5 h with the aid of a syringe pump. A clear solution was stirred

at the same temperature for a total of 23 h and then it was evaporated (oil pump). The residue was extracted with CH_2Cl_2 - MeOH (9 : 1, 50 mL). The combined extracts were washed successively with saturated aqueous $NaHCO_3$, H_2O, brine and then they were dried over Na_2SO_4. Chromatography on a silica gel column first with CH_2Cl_2 - AcOEt (2 : 1) and then with AcOEt - MeOH (95 : 5) gave acetylene **12** (82 mg, 5.4 %) and allene **11** (125 mg, 8.2 %) as sirups. Allene **11**: UV (EtOH) max 258 nm (ε 13,000), 216 (ε 27,900); IR (KBr) 3300 and 3180 cm^{-1} (s, NH_2), 1980 (w, C=C=C), 1680 - 1600 (broad s, adenine ring); ^1H NMR ($CDCl_3$) ∂ 4.20 (s, 4, 3'-CH_2), 4.52 (s, 4, CH_2 of Bn), 6.02 (s, 2, NH_2), 7.23 (s, 10, Ph), 7.35 (bs, 1, $H_{1'}$), 7.86 and 8.31 (2s, 2, H_2 and H_8); ^{13}C NMR 68.08 (3'-CH_2), 72.65 (CH_2 of Bn), 94.13 ($C_{1'}$), 113.23 ($C_{3'}$), 127.68, 127.80, 128.41 and 137.50 (Ph), 119.68, 138.25, 148.91, 153.34 and 155.62 (adenine), 194.73 ($C_{2'}$). Acetylene **12**: UV (EtOH) max 259 nm (ε 12,500), 209 (ε 23,400); IR (KBr) 3280 and 3140 cm^{-1} (s, NH_2 and C≡CH), 2140 (w, C≡C), 1680 and 1605 (s, adenine ring); ^1H NMR ($CDCl_3$) ∂ 2.77 (s, 1, $H_{3'}$), 4.05 and 4.30 (2d^{19}, 4, J = 9.6 Hz, 1'-CH_2), 4.42 and 4.47 (2d^{19}, 4, J = 12.3 Hz, CH_2 of Bn), 6.11 (s, 2, NH_2), 7.23 (s, 10, Ph), 8.09 and 8.20 (2s, 2, H_2 and H_8); ^{13}C NMR 61.60 ($C_{1'}$), 70.37 (1'-CH_2), 73.41 (CH_2 of Bn), 76.43 ($C_{3'}$), 79.61 ($C_{2'}$), 127.51, 127.73, 128.19 and 137.11 (Ph), 120.57, 141.12, 149.49, 151.92 and 155.60 (adenine); FAB-MS 414 (M + H, 39.3), 136 (adenine + H, 59.3), 91 (Bn, 100.0).

B. From N^6-Benzoyladenine (16). Sodium hydride (160 mg, 4.0 mmol) was added into a stirred solution of N^6-benzoyladenine (**16**, 470 mg, 2.0 mmol) in DMF (12 mL) at room temperature under N_2. After evolution of H_2 ceased, the mixture was heated at 60°C and phenyl carbonate **9g** (1.63 g, 3.9 mmol) in DMF (3 mL) was added dropwise over 1.5 h with the aid of a syringe pump. The resulting mixture was stirred at the same temperature for a total of 27 h and then it was evaporated in vacuo. The residue was dissolved in a mixture of pyridine (7.2 mL) and AcOH (2 mL), the solution was cooled to 0°C and hydrazine hydrate (2.8 mL) was added slowly. The mixture was stirred at room temperature overnight and then evaporated. The residue was dissolved in Et_2O (50 mL), and the solution was washed successively with saturated aqueous $NaHCO_3$, H_2O and brine, and then dried (Na_2SO_4). The crude product obtained by evaporation was chromatographed as described in Method A to give acetylene **12** (70 mg, 8.6 %) and allene **11** (45 mg, 5.6 %) which were identical with authentic samples prepared as described above.

A similar experiment performed on a 0.7 mmol scale of **16** and 1.4 mmol of **9g** or **9f** afforded only allene **11** (35 mg, 20 % and 12 mg, 7 %, respectively).

C. From N^6-Dimethylaminomethyleneadenine (17). Sodium hydride (21 mg, 0.51 mmol) was added at room temperature into a stirred solution of N^6-dimethylaminomethyleneadenine (**17**, 95 mg, 0.5 mmol) in DMF (5 mL). After evolution of H_2 ceased, the mixture was heated at 60°C under N_2 and phenyl carbonate **9g** (210 mg, 0.5 mmol) in DMF (1 mL) was added dropwise over 1 h with the aid of a syringe pump. The resulting mixture was stirred at the same temperature for 4 h. The reaction mixture was evaporated in vacuo and the residue was chromatographed on a silica gel column. Elution with AcOEt - MeOH (99 : 1) gave phenol (40 mg, 85 %). Elution with AcOEt - MeOH (95 : 5) gave a 1 : 1 mixture (determined by ^1H NMR, 50 mg, 24 %) of allene **11** and acetylene **12.**

N^9-(3-Hydroxymethyl-4-hydroxy-1,2-butadien-1-yl)adenine (4a). Boron trichloride in CH_2Cl_2 (1 M, 4.3 mL, 4.3 mmol) was added dropwise into a stirred solution of allene **11** (180 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) at -78°C under N_2. The mixture was stirred at -78°C for 3 h whereupon CH_2Cl_2 - MeOH (1 : 1, 8 mL) was added slowly. The clear solution was evaporated and MeOH (3 x 6 mL) was evaporated from the residue. The latter was dissolved in MeOH, solid $NaHCO_3$ was added and the solution was evaporated. The crude product was chromatographed on a silica gel column using CH_2Cl_2 - MeOH (85 : 15) to give allenediol **4a** (80 mg, 80 %), m.p. 165°C (decomp.) after recrystallization from AcOEt - MeOH (3 : 1). UV (EtOH) max 261 nm (ε 15,200), 215 (ε 31,900); (pH 7) max 260 (ε 13,700), 213 (ε 28,000); IR (KBr) 3400 - 3120 cm^{-1} (vs, NH_2 and OH), 1975 (w, C=C=C), 1660 and 1610 (s, adenine ring); ^1H NMR (DMSO-d_6) ∂ 4.11 (4, s, CH_2), 5.16 (2, broad s, OH), 7.34 (1, s, $H_{1'}$), 7.42 (2, s, NH_2), 8.19 and 8.21 (2, 2s, H_2 and H_8); + D_2O 4.06 (4, apparent t, $^5J_{CH2,1'}$ 2.4 - 2.7 Hz, CH_2), 7.30 (1, t, $^5J_{1',CH2}$ 2.4 Hz, $H_{1'}$), 8.11 and 8.17 (2, 2s, H_2 and H_8). ^{13}C NMR (DMSO-d_6) 59.54 (3'-CH_2), 94.57 ($C_{1'}$), 120.45 ($C_{3'}$), 118.89, 138.67, 148.27, 152,77 and 155.94 (adenine), 192.21 ($C_{2'}$); EI-MS 135 (100, adenine), 108 (33.3, adenine - HCN); FAB-MS 234 (100, M + H), 136 (44.9, adenine + H). Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.34; H, 5.00; N, 29.86.

N^9-(1-Hydroxy-2-hydroxymethyl-3-butyn-2-yl)adenine (15): The reaction was carried out under the same conditions used for preparation of allenediol **4a**. Thus, from intermediate **12** (207 mg, 0.5 mmol) and BCl_3 in CH_2Cl_2 (1 M, 5 mL, 5 mmol) diol **15** (76 mg, 65 %) was obtained by chromatography using CH_2Cl_2 - MeOH (9 : 1) as the eluent, m.p. 135°C (decomp.) after recrystallization from AcOEt - MeOH (3 : 1). UV (EtOH) max 260 nm (ε 15,000), 209 (ε 17,800); (pH 7) 260 (ε 13,800), 207 (ε 17,400); IR (KBr) 3440 - 3120 cm^{-1} (vs, NH_2, OH and C≡CH), 2130 (C≡CH), 1680 and 1610 (vs, adenine ring); ^1H NMR (DMSO-d_6) ∂ 3.70 (1, s, $H_{3'}$), 4.02 and 4.21 (4, 2m, after addition of D_2O 2d[19], J 11.0 Hz, 1'-CH_2), 5.47 (2, t, ^3J 5.9 Hz, OH), 7.28 (2, s, NH_2), 8.12 and 8.15 (H_2 and H_8); ^{13}C NMR[20] 62.97 ($^1J_{1'}$-CH2 145.8 Hz, 1'-CH_2), 64.18 ($^2J_{1',1'}$-CH2 27.9 Hz, $C_{1'}$), 78.36 ($^1J_{3',H-3'}$ 253.4 Hz, $C_{3'}$), 81.03 ($^2J_{2',H-3'}$ ca. 51 Hz, $C_{2'}$), 119.85, 140.64, 149.00, 151.77 and 156.23 (adenine); FAB-MS 234 (43.8, M + H). Anal. Calcd. for $C_{10}H_{11}N_5O_2$ x 0.3 H_2O: C, 50.33; H, 4.90; N, 29.34. Found: C, 50.68; H, 5.14; N, 28.91.

Synthesis of Allene 4a and Acetylene 15 by Deprotection of the Mixture of Intermediates 11 and 12. Phenyl carbonate **9g** (6.8 g, 16.4 mmol) in DMF (5 mL) was added dropwise over 17 h with the aid of a syringe pump into a stirred suspension of sodium salt of adenine at 60°C (bath temperature), which was prepared from adenine (**10**, 2 g, 14.8 mmol) and NaH (600 mg, 15 mmol) in DMF (60 mL). The mixture was stirred at the same temperature for additional 6 h and then it was evaporated in vacuo. The residue was flash-chromatographed on a silica gel column using CH_2Cl_2 - AcOEt (2 : 1) and CH_2Cl_2 - MeOH (9 : 1) to give a mixture of intermediates **11** and **12** (1.3 g, 21 %). The latter product was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to -78°C. Boron trichloride in CH_2Cl_2 (1 M, 30 mL, 30 mmol) was added dropwise over a period of 1 h. The resulting mixture was stirred at -78°C for 3 h. The work-up followed the preparation of **4a** from **11** and chromatography on a silica gel column using CH_2Cl_2 - MeOH (9 : 1) gave acetylene **15** (300 mg, 8.7 %), adenine (**10**, 50 mg, 2.5 %) and allene **4a** (150 mg, 4.3 %) all of which were identical with authentic samples.

Reaction of Adenine (10) with Methyl Carbonate 9f. Sodium salt of adenine prepared from adenine (**10**, 126 mg, 0.93 mmol) and NaH (38 mg, 0.95 mmol) in DMF (20 mL) as described above, was stirred with methyl carbonate **9f** (330 mg, 0.93 mmol) at 60°C for 20 h. The mixture was evaporated and the residue was extracted with CH_2Cl_2 - MeOH (9 : 1), 50 mL). The crude product obtained by evaporation was chromatographed on a silica gel column using CH_2Cl_2 - AcOEt (95 : 5) to remove the unreacted carbonate **9f** and carbinol **5**. The elution was continued with AcOEt - MeOH (95 : 5) to give acetylene **12** (5 mg, 1 %), then with CH_2Cl_2 - MeOH (9 : 1) to furnish **13a** (7 mg, 3 %) as a sirup and, finally, N^9-methyladenine (**14**, 25 mg, 18 %), mp. 297 - 299°C, lit.[21] 300°C. UV (pH 2 and 12), ^1H and ^{13}NMR spectra were similar to those reported[22-24]. Exact mass calcd 149.0701, found 149.0695. Compound **13a**: UV (EtOH) max 261 nm (ε 13,000), 209 (ε 19,500); IR (KBr) 3280 and 3120 cm^{-1} (s, NH_2), 1950 (s, C=O), 1685, 1610 and 1585 (s, adenine ring), ^1H NMR (DMSO-d_6) ∂ 1.55 (2, qt, J 7.5 Hz), 1.85 (2, qt, J 7.5 Hz), 4.08 (2, t, J 6.6 Hz) and 4.16 (2, t, J 6.9 Hz, CH_2 groups), 3.67 (3, s, OMe), 7.20 (2, s, NH_2), 8.13 and 8.14 (2, 2s, H_2 and H_8); EI-MS 266 (3.5, M + H), 265 (19.5, M), 206 (21.4, M - CO_2Me), 191 (36.8, M - OCO_2Me + H), 190 (100, M - OCO_2Me), 176 (17.9, M - CH_2OCO_2Me), 163 (19.2, M - $(CH_2)_2OCO_2Me$ + H), 162 (12.2, M - $(CH_2)_2OCO_2Me$), 149 (22, M - $(CH_2)_3OCO_2Me$ + H), 148 (25.7, M - $(CH_2)_3OCO_2Me$), 136 (27.5, adenine + H), 135 (44.6, adenine), 108 (17, adenine - HCN).

Ammonolysis of **13a** with NH_3/MeOH (20 %) at room temperature overnight gave compound **13b**, m.p. 196 - 199°C identical with that of an authentic sample[3].

The experiment performed on a 0.12 mmol scale of adenine (**10**) and evaluated by TLC in CH_2Cl_2 - MeOH (9 : 1) and AcOEt - MeOH (95 : 5) indicated the presence of allene **11** and acetylene **12**, but neither N^9-methyladenine (**14**) nor carbonate **13a** could be detected.

Deamination of 3'-Hydroxymethyladenallene (4a) with Adenosine Deaminase. A. Assay by TLC and Paper Electrophoresis[25]. Compound **4a** (2.6 μmol) was incubated with adenosine deaminase from calf intestine (0.4 units) in Na_2HPO_4 (0.05 M, pH 7.5, 0.4 mL) at room temperature. Periodically, aliquots were examined by TLC (CH_2Cl_2 - MeOH, 4 : 1) and paper electrophoresis[18] (0.05 M sodium citrate, pH 3.5). After 19 h the deamination of **4a** was complete.

B. Spectrophotometric Assay. Adenosine deaminase (6.6 units, 0.105 mL, 0.05 M Na_2HPO_4, pH 7.5) was added to a solution of compound **4a** (95 μM, 3 mL) in the same buffer. UV spectrum after 3 min. showed a quantitative deamination of **4a** (disappearance of the maximum at 261 nm). The obtained spectrum was similar to that of hypoxallene[3] (UV max 221 nm).

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