

## A Convenient Route to 1-Substituted Adenines

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The need for a readily available intermediate suitable for preparing a variety of 1-substituted adenines became apparent in the course of our work in this area. A number of synthetic routes (1,2,3,4,5) are available but each has inherent limitations which affect its general applicability. The key intermediates in these procedures are certain specific 9-substituted adenines whose availability depends either on a multistep synthesis or on alkylation of adenine followed by purification of the resulting isomeric mixture.

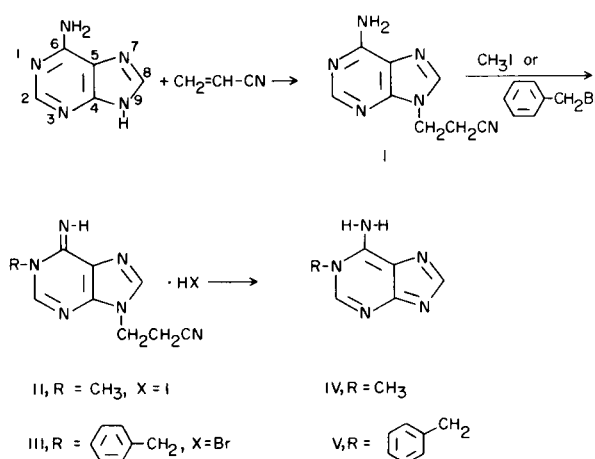
The naturally occurring ribonucleoside adenosine eliminates these above considerations and is sometimes used (3,4). Alkylation of these 9-substituted adenines afford 1,9-disubstituted adenines (1,2,3,4,5) which yield 1-substituted adenines by appropriate treatment. The functionality of the  $N_1$  group is limited by the method used to remove the blocking group. Thus, catalytic hydrogenolysis (2) of the  $N_9$ -benzyl group cannot be used if the  $N_1$ -substituent is also susceptible to hydrogenolysis or reduction, and alkaline oxidative cleavage (1) of the propenyl group limits the scope of that method. Acid cleavage (3,4) of the adenosine derivative is accompanied by purification problems (1). In addition, these sequences generally give low overall yield of  $N_1$  product.

Our study of Michael reactions with adenine (6) led to the development of a method which appears to be general for preparing 1-substituted adenines. As reported earlier (6), the base-catalyzed reaction of adenine with acrylonitrile afforded 9- $\beta$ -cyanoethyladenine (I) in excellent yield (90%). In the work reported here, compound I was alkylated with methyl iodide or with benzyl bromide to yield the corresponding 1,9-disubstituted adenines, II and III, respectively.

The facile reversal of the Michael reaction when compound I was treated with one equivalent of base (6) encouraged us to try the same general technique on products II and III. Treatment of either II or III with two equivalents of potassium *t*-butoxide in anhydrous methanol gave 1-methyladenine (IV) (7) and 1-benzyladenine (V), respectively, in nearly quantitative crude yield. Pure IV (70%) and pure V (80%) were obtained by crystallization of the crude products. Paper chromatography of crude and purified samples revealed only one ultraviolet-absorb-

ing spot. Authentic IV (7) was identical with our material. The absence of  $N_6$ -substituted adenines was confirmed by direct comparison with authentic  $N_6$ -methyladenine (7) and  $N_6$ -benzyladenine (8).

SCHEME I



## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or a Fisher-Johns melting point apparatus and are corrected. The ultraviolet spectra were determined in aqueous solution on a Beckman DK-2A ratio recording spectrophotometer. The infrared spectra were determined on a Beckman Model IR5A spectrophotometer. Chromatograms were developed on Whatman No. 2 paper by the ascending technique. The solvent systems employed were A, *n*-butyl alcohol-acetic acid-water (4:1:1) and B, 5% aqueous ammonium sulfate-isopropyl alcohol (95:5). The microanalyses were performed by our analytical department.

9- $\beta$ -Cyanoethyl-1-methyladenine Hydroiodide (II).

To a solution of 1.88 g. (0.01 mole) of 9- $\beta$ -cyanoethyladenine (I) in 150 ml. of *N,N*-dimethylformamide was added slowly 3.26 g. (0.23 mole) of methyl iodide. The solution was sealed and agitated at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue dissolved in 300

ml. water. The solution was brought to pH 10 with concentrated ammonium hydroxide and then reduced under high vacuum initially at ambient temperatures and finally at 30-35° to 80 ml. The solution was cooled at 0° for 36 hours and 1.8 g. (54%) crude product, m.p. 229-231°, was isolated. The solid was crystallized from water-ethanol to yield 1.35 g. (41%) of pure II, m.p. 252-254° dec.;  $\lambda$  max (water) pH 1, 258.0 (log  $\epsilon$  4.125), pH 7, 258.5 (log  $\epsilon$  4.116), pH 10, 258.5 (log  $\epsilon$  4.124) and shoulder 265.0 m $\mu$  (log  $\epsilon$  4.070); IR (Nujol) 2230 (CN), 1690, 1620, 1570 (C=N, C=C) cm<sup>-1</sup>. The analytical sample, m.p. 256-258° dec., was obtained by recrystallization from water-ethanol.

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>6</sub>·HI: C, 32.73; H, 3.36; N, 25.46. Found: C, 32.58; H, 3.42; N, 25.30.

#### 9- $\beta$ -Cyanoethyl-1-benzyladenine Hydrobromide (III).

The general procedure for preparing II was used. A mixture of 1.88 g. (0.01 mole) of I and 3.92 g. (0.023 mole) of benzyl bromide was prepared and allowed to react for 36 hours at room temperature. The solution was cooled at 0° for 3 days and 1.9 g. (53%) of crude product, m.p. 235-245°, was isolated and crystallized from 95% ethanol to yield 1.4 g. (39%) of pure III, m.p. 245-247°;  $\lambda$  max (water) pH 1, 259.0 (log  $\epsilon$  4.117), pH 7, 259.5 (log  $\epsilon$  4.117), pH 10, 260.0 (log  $\epsilon$  4.113) and shoulder 266.5 m $\mu$  (log  $\epsilon$  4.063).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>6</sub>·HBr: C, 50.15; H, 4.21; N, 23.40. Found: C, 50.40; H, 4.45; N, 23.69.

#### 1-Methyladenine (IV).

A solution of 330 mg. (0.01 mole) of 9- $\beta$ -cyanoethyl-1-methyladenine hydroiodide in 30 ml. of anhydrous methanol was treated with 224 mg. (0.02 mole) of potassium *t*-butoxide. The resulting alkaline solution was heated at reflux under nitrogen for 45 hours and then neutralized to pH 7.2 with 66 mg. of acetic acid in 10 ml. of methanol. Then 20 ml. of water was added and the methanol removed under reduced pressure. The mixture was cooled and 149 mg. (100%) of crude IV, m.p. 293-300°, was isolated by filtration. Crystallization from methanol-water afforded 104 mg. (70%) of pure IV, m.p. 302-304° [lit. (1,3) m.p. 296-299° dec., 310-312° dec.];  $\lambda$  max (water) pH 1, 258.5 (log  $\epsilon$  4.064), pH 7, 265.0 (log  $\epsilon$  4.033), pH 10, 269.5 (log  $\epsilon$  4.078) and 0.1 *N* sodium hydroxide, 270 m $\mu$  (log  $\epsilon$  4.157). The ultraviolet spectra agree with the literature values (1,3,4). Paper chromatography of both crude and purified IV in solvent systems A and B showed only one ultraviolet-absorbing spot which co-chromatographed with authentic 1-methyladenine (7). *N*<sub>6</sub>-Methyladenine (7), used as a standard in both systems, had a different R<sub>f</sub> value.

#### 1-Benzyladenine (V).

The general procedure followed in the preparation of IV was used. A solution of 359 mg. (0.01 mole) of 9- $\beta$ -cyanoethyl-1-benzyladenine hydrobromide in 30 ml. of anhydrous methanol was treated with 224 mg. (0.02 mole) potassium *t*-butoxide and heated at reflux for 45 hours. The mixture was cooled and 220 mg. (98%) of crude V, m.p. 241-246°, was isolated by filtration. Crystallization from methanol-water gave 176 mg. (80%) of pure V, m.p. 247-248° [lit. (2,9) m.p. 244-246°];  $\lambda$  max (water) pH 1, 260.5 (log  $\epsilon$  4.092), pH 7, 267.0 (log  $\epsilon$  4.07), pH 10, 271.0 (log  $\epsilon$  4.11) and 0.1 *N* sodium hydroxide, 271.5 m $\mu$  (log  $\epsilon$  4.155). The ultraviolet spectra agree with the literature values (2,9). Paper chromatography of crude V and purified V in solvents A and B showed only one ultraviolet-absorbing spot. It did not move at the same rate as authentic *N*<sub>6</sub>-benzyladenine (8).

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