Decarboxylation of some Carboxymethyladenines

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We wish to report the decarboxylation reactions of 3- and 9-carboxymethyladenines (I and II, respectively). We have prepared 3-carbethoxymethyladenine (III) and 9-carbethoxymethyladenine (IV) by known procedures (1a-e). Esters III and IV were acid hydrolyzed to yield I (88%, m.p. 330-333°, dec.) and II (85%, m.p. 350°, dec.), respectively.

When acid I was heated at 300-305° (0.4 mm) in a microsublimation apparatus, 3-methyladenine (V) (2), 75%, was collected as the sole product. Acid II under similar conditions did not undergo decarboxylation and was recovered in high yield (85%) as the sublimate. These reactions were studied when the temperature was more rigorously controlled. Under these conditions, acid I slowly decomposed without sublimation to yield V while a majority (75%) of acid II sublimed before reaching the maximum temperature. However, a sufficient quantity of acid II was still present at the maximum temperature to confirm its lack of reactivity under these conditions.

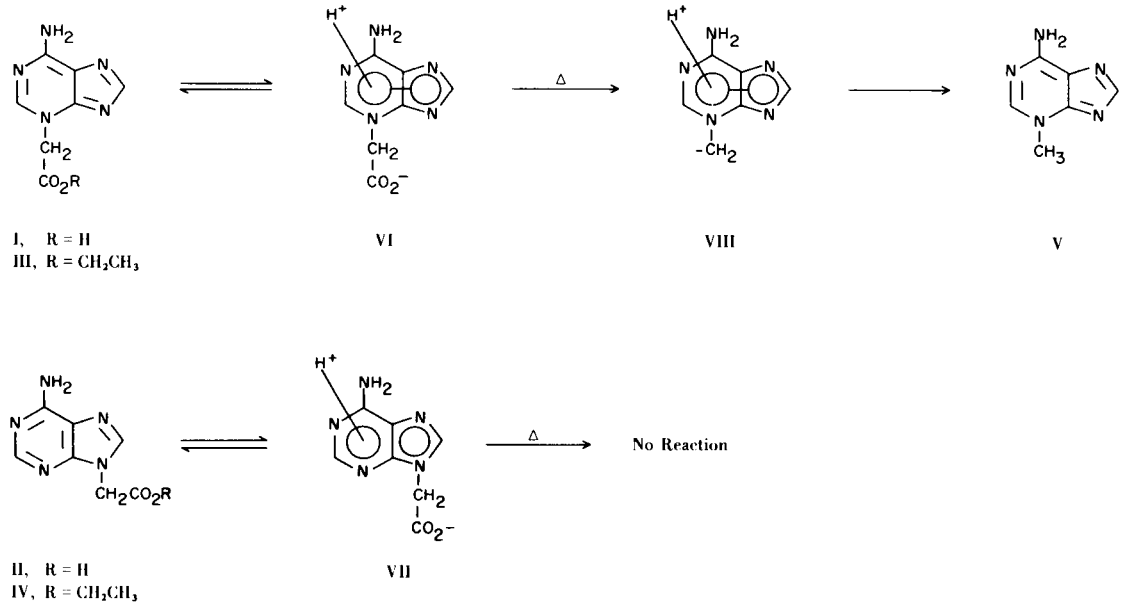
This startling difference in reactivity can be attributed to the much greater basicity of 3-substituted adenines if one assumes the *p*Ka's are relatively the same at 300° as at room temperature. In the present case the *p*Ka's of esters III and IV were 6.4 and 3.7, respectively. Therefore, acid I should exist predominantly as zwitterion VI while acid II would be much less dissociated. Since nitrogen-containing acids decarboxylate primarily through a zwitterion intermediate (3), acid I would undergo decarboxylation more readily than II. Acid II is removed from the reaction zone by sublimation (a fact in agreement with the undissociated form). However, this is not the primary reason for its lack of reactivity since even at 305-310° only II was recovered uncontaminated by 9-methyladenine (2).

EXPERIMENTAL (4)

3-Carbethoxymethyladenine (III).

A solution of 70 g. (0.52 mole) of adenine, 65 g. (0.53 mole) of ethyl chloroacetate and 140 ml. of dimethylformamide was heated with stirring at 135-140° for 2 hours. The violet solution was cooled and 150 ml. ether and 150 ml. chloroform were added. The precipitated solids were isolated and dissolved in water. The aqueous solution was treated with charcoal and neutralized to *p*H 9 with ammonium hydroxide. The mixture was cooled and the resulting solids isolated. The solids were crystallized from water to yield 33 g. (37%) of pure III, m.p. 237.5-240.5°; λ max (water) *p*H 1, 274.0 (log ε 4.37), *p*H 7, 275.0 (log ε 4.17), *p*H 10, 273.0 mμ (log ε 4.13); *p*Ka 6.4; IR (potassium bromide) 3225, 1725 (C = O), 1665 (C = N) and 1235 cm^{-1}; NMR ($DMSOd_6$) δ 1.27

SCHEME I



I, R = H
III, R = CH_2CH_3

VI

VIII

V

II, R = H
IV, R = CH_2CH_3

VII

(t, J = 7.0 cps, 3 methyl protons), 4.23 (q, J = 7.0 cps, 2 methylene protons), 5.23 (s, 2 methylene protons), 7.78 (s, 1 purine proton), 8.09 (broad, 2 amino protons), and 8.31 (s, 1 purine proton). Paper chromatography of III in solvent systems A, B, C and D indicated it was homogeneous. The analytical sample, m.p. 237.5-240.5°, was obtained by recrystallization from water.

Anal. Calcd. for $C_9H_{11}N_5O_2$: C, 48.9; H, 5.0; N, 31.7. Found: C, 49.1; H, 5.00; N, 31.6.

9-Carbethoxymethyladenine (IV).

A solution of 148 g. (1.1 mole) of adenine, 3.5 l. of absolute ethanol and 500 ml. of benzene was dried by azeotropic distillation. Approximately 1 l. of distillate was collected. The sodium salt of adenine was prepared by adding over 2.5 hours 27 g. (1.16 mole) of sodium to the dried solution. Then 162 g. (1.3 mole) of ethyl chloroacetate was added to the alkaline solution. The stirred solution was heated at reflux overnight and then the majority of the solvent was removed by distillation. The residue was treated with 400 ml. of water and the resulting solids isolated. The solids were extracted with hot water and the combined extracts treated with charcoal and cooled. The isolated solids gave 56.1 g. (25.5%) of pure IV, m.p. 228-231°; λ max (water) *p*H 1, 256.5 (log ε 4.16), *p*H 7, 260.0 (log ε 4.17), *p*H 10, 259.0 mμ (log ε 4.16); *p*Ka 3.7; IR (potassium bromide) 3225, 1725 (C = O), 1665 (C = N) and 1250 cm^{-1}; NMR ($DMSOd_6$) δ 1.22 (t, J = 7.0 cps, 3 methyl protons), 4.18 (q, J = 7.0 cps, 2 methylene protons), 5.08 (s, 2 methylene protons), 7.22 (s, 2 amino protons), 8.13 (s, 1 purine proton) and 8.16 (s, 1 purine proton). Paper chromatography of IV in solvent systems A, B, C and D indicated it was homogeneous. The analytical sample, m.p. 233-235°, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.65. Found: C, 49.14; H, 5.01; N, 31.50.

3-Carboxymethyladenine (I).

A mixture of 15 g. (0.067 mole) of 3-carbethoxymethyladenine and 70 ml. of 2*N* hydrochloric acid was prepared and heated at reflux for 3 hours. The solution was cooled and the precipitated solid collected. The solids were dissolved in excess 2*N* sodium hydroxide and the resulting solution neutralized to *p*H 5.3 with 6*N* hydrochloride acid. The precipitated solid, m.p. 322° dec., was isolated (a small quantity of brown solid which floated on the acidified solution was previously removed and discarded) and dried. The base-acid treatment was repeated to yield 12.7 g. (88% as hydrate) of I, m.p. 322° dec. A thoroughly dried analytical sample, m.p. 330-333°, was prepared by the base-acid treatment (2X); λ max (water) *p*H 1, 274.5 (log ε 4.25) and *p*H 10, 274.0 mμ (log ε 4.11); IR (potassium bromide) 1680, 1640, 1590 cm^{-1}; NMR (trifluoroacetic acid) δ 5.58 (s, 2 methylene protons), 8.29 (diffuse s, 1 proton), 8.79 (diffuse s, 2 protons), 9.27 (diffuse s, 1 proton) and 11.2 (very broad). Paper chromatography of I in solvent systems B and C indicated it was homogeneous.

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.52; H, 3.62; N, 36.21. Found: C, 43.34; H, 3.70; N, 35.93.

9-Carboxymethyladenine (II).

A mixture of 3.0 g. (0.0135 mole) of 9-carbethoxymethyladenine and 20 ml. of 2*N* hydrochloric acid was prepared and heated at reflux for 3 hours. The solution was neutralized to *p*H 4 with 2*N* sodium hydroxide and then cooled overnight. The precipitated solid was base-acid cyclized to yield after thorough drying 2.2 g. (85%) of II, m.p. 350° dec.; λ max (water) *p*H 1, 256.5 (log ε 4.15) and *p*H 10, 260.0 mμ (log ε 4.16); IR (potassium bromide) 1695 and 1615 cm^{-1}; NMR (trifluoroacetic acid) δ 5.60 (s, 2 methylene protons), 8.30 (diffuse s, 1 proton), 8.50 (diffuse d, 3 protons) and 11.0 (very broad). Paper chromatography of II in solvent systems B and C indicated it was homogeneous.

Anal. Calcd. for $C_7H_7N_5O_2$: C, 43.52; H, 3.62; N, 36.21. Found: C, 43.15; H, 3.77; N, 36.00.

Decarboxylation Procedures.

A.

A Wood's metal bath was heated to 109° and then a microsublimator containing 300 mg. (1.55 mmoles) of powdered 3-carboxymethyladenine (I) was immersed in the bath. The pressure was reduced to 0.4 mm and the temperature of the bath elevated to 300-305°. After 3 hours, 90 mg. (39%) of crude 3-methyladenine (V), m.p. 248-256°, was removed from the cold finger. Continued heating (3 hours) afforded an additional 80 mg. (35%) crude V, m.p. 248-254°. A portion of Crude V was purified (2X) by dissolving in hot water, adjusting the *p*H to 10 and cooling. The precipitated solid was isolated, m.p. 294-296° (lit. (5) m.p. 300-302°); λ max (water) *p*H 1, 273.5 (log ε 4.22), *p*H 7, 273.0 (log ε 4.18) and *p*H 10, 272.5 mμ (log ε 4.11). The ultraviolet spectra agree with the literature values (5) and with those obtained from an authentic sample (2). Paper chromatography of both crude and purified V in solvent systems B and C showed only one ultraviolet-absorbing spot which co-chromatographed with authentic 3-methyladenine (2).

B.

The above procedure was repeated on 200 mg. (1.04 mmoles) of acid I. At 280° (p.025 mm) after two hours 10 mg. of V was isolated. The temperature was elevated to 295° (0.025 mm) and after one hour an additional 25 mg. of V was collected. A final fraction, 95 mg. of V, was recovered after six hours at 305-310°.

C.

The above procedure was repeated on 200 mg. (1.04 mmoles) of 9-carboxymethyladenine (II). After two hours at 280° (0.025 mm), 25 mg. (12.5%) of sublimate was collected from the cold finger. The temperature was then elevated to 295° (0.025 mm) and after one hour an additional 125 mg. (62.5%) of sublimate was isolated. Finally heating at 305-310° for six hours afforded 20 mg. product. Each of these fractions was shown to be acid II and free of any detectable 9-methyladenine (2) by ultraviolet, and infrared spectral examination and by paper chromatography in solvent systems B and C.

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generous supply of authentic 3- and 9-methyladenines. The samples were compared by direct physical and spectrographic measurements.

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(4) Melting points were taken in capillaries with a copper block and are uncorrected. The microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or by our analytical department. The infrared spectra were determined on either a Beckman Model IR5A or a Perkin-Elmer Model 521 spectrophotometer. The ultraviolet spectra were determined in aqueous solution using a Beckman DK-2A ratio recording spectrophotometer. The nuclear magnetic resonance spectra were determined in either deuterated DMSO or trifluoroacetic acid with tetramethylsilane as an internal standard at 60 Mc/sec on a Varian Associates A-60 spectrometer at Simon Research Laboratory, Elgin, Ill., by Dr. W. Simon. *p*Ka values were obtained spectroscopically by our analytical department. Chromatograms were developed by the ascending technique with Whatman No. 1 paper. The solvent systems employed were A, water-*n*-butanol-acetic acid (5:4:1); B, dimethylformamide-28% aqueous ammonia-isopropyl alcohol (25:10:65); C, isopropyl alcohol-5% aqueous ammonium sulfate (5:95); D, *n*-butanol-acetic acid-water (4:2:1).

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