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Synthesis of Carboxylic Acid Derivatives of Adenine and Theophylline

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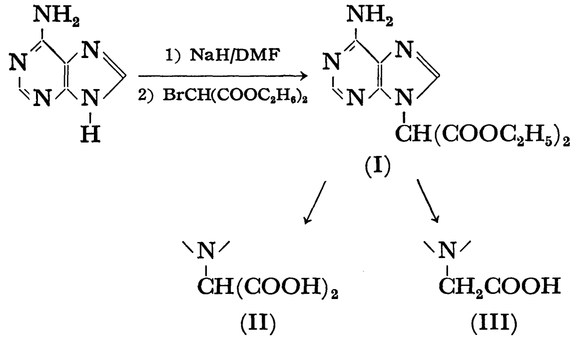
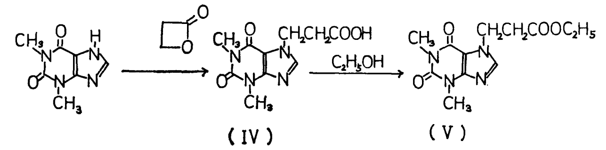
Michael-type addition reaction of purine with ethyl acrylate gives the corresponding *N*-*β*-carboxyethyl derivatives,[1] which are also obtained by the reaction of purine with *β*-halopropionate under base-catalyzed conditions.[2]

In this communication, we report new syntheses of carboxylic acid derivatives of adenine and theophylline.

When sodium salt of adenine[3] was treated with diethyl bromomalonate in dimethylformamide (DMF), diethyl adenyl-9-malonate (I) was easily obtained. It was hydrolyzed in alkaline solution to give its carboxylic acid derivatives (II and III).

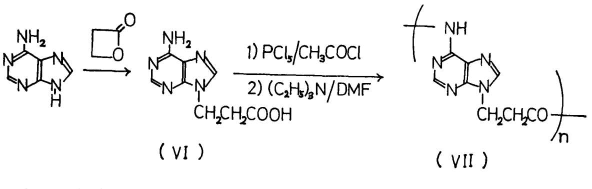


7-(*β*-carboxyethyl)theophylline (IV) was prepared when theophylline was allowed to react with *β*-propiolactone in DMF under base-catalyzed conditions. Its ethyl ester (V) was prepared from IV in ethanol in the presence of acetyl chloride.



Adenine was also converted into 9-(*β*-carboxyethyl)-adenine (VI) under the same reaction conditions. A similar result concerning the reaction of adenine with *γ*-butyrolactone has also been reported.[4]

The reaction of VI with phosphorus pentachloride gave the hydrochloride salt of acid chloride derivative, which was treated with triethylamine in DMF to afford a substance assumed to be a polymer containing adenine nuclei in the main chain (VII). The infrared spectrum of VII showed a new C=O stretching band corresponding to amide structure at 1630 cm^{-1}. The molecular weight of VII was not determined because of its insolubility in common solvents.



Ultraviolet spectra of I and VI showed λ_{max} near 260 nm, which suggests that the derivatives in question correspond to adenine substituted in 9-position. In the case of IV and V, λ_{max} appeared at 274 nm, which shows that the substituent was introduced into 7-position.

Carboxylic acid derivatives II and III as well as polymer VII thus obtained showed no melting points below 300°C, and were insoluble in common organic solvents.

Experimental

Diethyl-9-Adenylmalonate (I). A suspension of 1.35 g (10 mmol) of adenine and 0.52 g of 54% oily sodium hydride in 50 m*l* of DMF was stirred at ambient temperature for 1.5 hr. To the solution was added 3.5 g (14.7 mmol) of diethyl bromomalonate. After stirring for 6.5 hr, the reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from aqueous ethanol; yield 1.43 g (38%). Colorless needles, mp 172—173°C. IR (KBr): 3270, 3100 (ν_{N-H}), 1770, 1745 ($\nu_{C=O}$), 1670 ($\nu_{C=N}$), 1600 (δ_{N-H}), 1215 (ν_{C-O}), 2950 (ν_{C-H}), cm^{-1}. UV (C_2H_5OH): λ_{max} 259 (ε=11300), 209 (ε=14000).

Found: C, 49.18; H, 5.31; N, 24.10%. Calcd for $C_{12}H_{15}N_5O_4$: C, 49.15; H, 5.12; N, 23.89%.

9-Adenylmalonic Acid (II). In 200 m*l* of aqueous solution of sodium hydroxide (1.6 g) was dissolved 3.0 g (10 mmol) of I. The mixture was stirred at ambient temperature for 16 hr and then was adjusted to pH 3 with concd. hydrochloric acid. The resulting precipitate was then filtered off and washed thoroughly with water; yield 1.85 g (76%). Colorless crystals. IR (KBr): 3380, 3100 (ν_{N-H}), 2800—2500 (ν_{OH}), 1705, ($\nu_{C=O}$), 1680 ($\nu_{C=N}$), 1605 (δ_{N-H}) cm^{-1}.

Found: C, 40.54; H, 2.95; N, 29.95%. Calcd for $C_8H_7N_5O_4$: C, 40.50; H, 2.95; N, 29.50%.

9-Carboxymethyladenine (III). To a solution of water-ethanol mixture (3:1) containing 0.4 g of sodium hydroxide was added 1.4 g of I, and stirred for 3 days at ambient temperature. The clear solution was then evaporated to dryness. The residue was dissolved in 10 m*l* of water and the solution was adjusted to pH 5 with concd. hydrochloric acid. The resulting precipitate was then filtered off and washed with water and ethanol; yield 0.15 g (16%). Colorless crystals. IR (KBr): 3400, 3150 (ν_{N-H}), 2800—2500 (ν_{OH}), 1705 ($\nu_{C=O}$),

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[2] R. Zelnik and M. Pesson, *Bull. Soc. Chim. France*, **1959**, 1667; *Chem. Abstr.*, **55**, 17641 (1960).

[3] N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).

[4] K. Okumura, T. Oine, Y. Yamada, M. Tomie, T. Nagura, M. Kawazu, T. Mizoguchi, and I. Inoue, *Chem. Commun.*, **1970**, 1045.

1605 (δ_{N-H}), 1680 ($\nu_{C=N}$) cm^{-1}.

Found: C, 43.37; H, 3.46; N, 36.35%. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.62; N, 36.27%.

7-(β-Carboxyethyl)theophylline (IV). 150 m*l* of DMF solution containing 16.2 g (90 mmol) of theophylline hydrate, 9.7 g (135 mmol) of β-propiolactone, and a trace of sodium hydroxide was refluxed for 4.5 hr. The solution was then concentrated under reduced pressure. The oily residue was crystallized with water. Recrystallization from water and ethanol gave a colorless crystal; yield 12.0 g (53%), mp 200—210°C (lit,[2] 204—205°C). (Found: C, 47.74; H, 4.86; N, 22.24%).

7-(β-Ethoxycarbonylethyl)theophylline (V). To an ethanol solution (15 m*l*) containing acetyl chloride (3.5 m*l*) was added 1.0 g of IV. The mixture was shaken vigorously for a few minutes until most of the solid dissolved and kept for 24 hr at ambient temperature. Pyridine (2 m*l*) was then added and after 48 hr at ambient temperature, the mixture was concentrated under reduced pressure. The oily residue was crystallized by trituration with water. Recrystallization from ethanol gave colorless crystals; yield 0.4 g (36%), mp 110°C (lit,[2] 105—106°C). (Found: C, 51.15; H, 5.93; N, 19.40%).

9-β-Carboxyethyladenine (VI). DMF solution (20 m*l*) containing 0.81 g (6.0 mmol) of adenine, 0.69 g (9.6 mmol) of β-propiolactone, and a trace of sodium hydroxide was refluxed for 2 hr. The solution was then evaporated to dryness *in vacuo*, the residue was recrystallized from water; yield 0.51 g (43%). Colorless needles, mp 272—278°C (dec.)(lit,[1] 284—228°C). IR (KBr): 3100, 3200 (ν_{N-H}), 3000—2600 (ν_{OH}) cm^{-1}. UV (H_2O): λ_{max} 260 (ε=10100), 206 (ε=14600). (Found: C, 46.25; H, 4.43; N, 33.69%).

Polymer derived from VI (VII). 0.5 g of 9-(β-carboxyethyl)adenine and 0.4 g of phosphorus pentachloride, protected carefully from moisture, was stirred in 3 m*l* of acetyl chloride at ambient temperature for 24 hr. The crude product was separated by filtration from the mixture and washed with petroleum ether. To this was rapidly added a solution of triethylamine (10 m*l*) in 100m*l* of DMF. After being stirred at ambient temperature for one week, the resulting precipitate was collected and recrystallized from hot water; yield 0.047 g (10%). IR (KBr): 1630 (amide $\nu_{C=O}$), 1680 ($\nu_{C=N}$) cm^{-1}.

Found: C, 50.60; H, 3.55; N, 36.72%. Calcd for $C_8H_7N_5O$: C, 50.52; H, 3.68; N, 36.84%.