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Note

Synthesis of 8-(hydroxyalkyl)adenines*†

HASSAN S. EL KHADEM AND RONALD SINDRIC

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U. S. A.)

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We are involved in a program aimed at the synthesis of *C*-analogs of adenine nucleosides for screening against malaria. The present work deals with the synthesis of 8-(hydroxyalkyl)adenines, the *C*-analogs of adenine nucleosides of acyclic sugars. 8-(Hydroxymethyl)purine[1] and 8-(D-*gluco*-pentitol-1-yl)purine[2] have been prepared by treating the appropriate hydroxy acids with 4,5-diaminopyrimidine, and thermally cyclizing the amides formed. 8-(Hydroxymethyl)adenine was prepared[3] by heating ethyl glycolate with 4,5,6-triaminopyrimidine.

The synthesis of 8-(hydroxyalkyl)adenines described here (see Tables I and II) was performed by condensing 4,5,6-triaminopyrimidine (**1**) with aldonic acids (**2**) of various chain-lengths to give the amides (**3**) which, upon pyrolysis, afforded the desired 8-(hydroxyalkyl)adenines (**4**). Crystalline amides were obtained from glycolic, DL-glyceric, D-ribonic, D-xylonic, and D-allonic acids.

4,5,6-Triaminopyrimidine can yield two isomeric amides, one having the carbonyl group attached to the amino group on C-4 or C-6, and the other to the amino group attached to C-5. Unlike 2,4,5,6-tetraaminopyrimidine, which, with the ethyl hemiacetal of ethyl glyoxylate, gives 4-substituted derivatives in weak acids, and 5-substituted ones in stronger acids[4], only one amide was obtained when glycolic acid was treated with 4,5,6-triaminopyrimidine either in the absence of an acid, with *N,N'*-dicyclohexylcarbodiimide to react with the water formed, or in the presence of two molecular proportions of hydrochloric acid. In the absence of an acid, the 5-amino group of compound **1** would be the most basic group, owing to the inductive effect of the two ring-nitrogen atoms, which would cause a lowering of the electron density on the adjacent atoms C-4 and C-6, thus rendering the amino groups attached to these atoms less nucleophilic. The positively charged, imino resonance-forms would also lead to substitution on N-5 by lessening the nucleophilicity of the imino-nitrogen atoms (N-4 and N-6) more than for N-5 (which contributes less to the resonance

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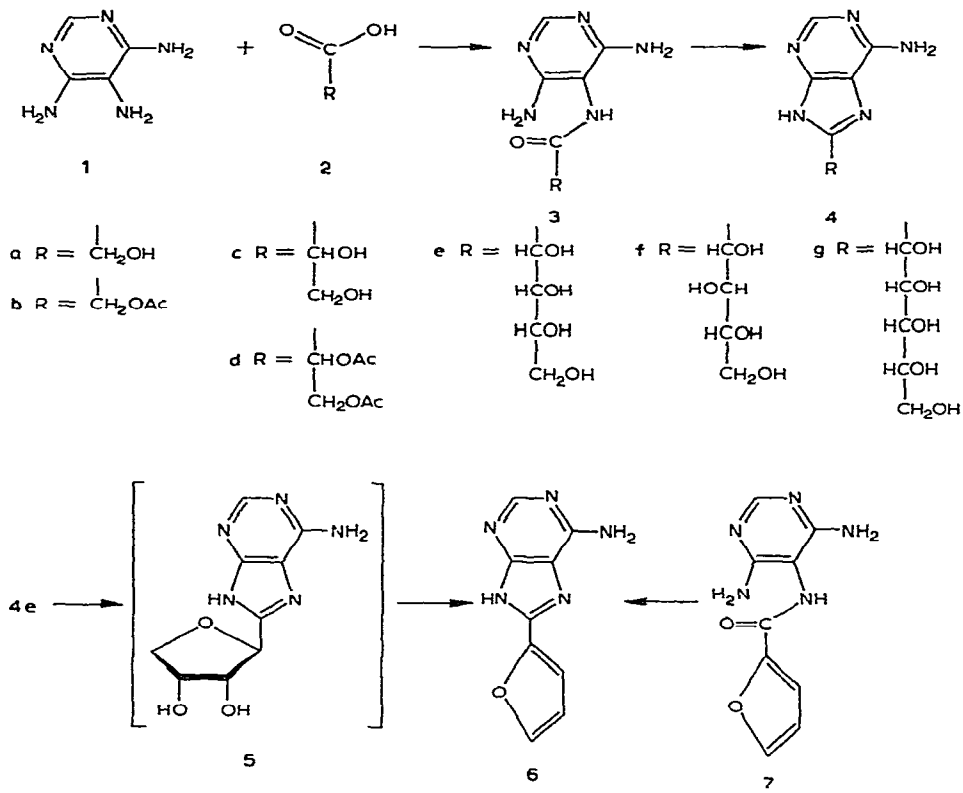
hybrid). The combined inductive and resonance effects would thus lead to the preponderance of one product; this was formulated as 3. It seems that, in our second experiment, the acid is not sufficiently strong to protonate the 5-amino group; with stronger acids, hydrolysis takes place, and a 4-amide is not obtained.



Pyrolysis of the amides prepared afforded the following 8-(hydroxyalkyl)-adenines: 8-(hydroxymethyl)adenine[3] (**4a**), 8-(DL-dihydroxyethyl)adenine (**4c**), 8-(D-*ribo*-tetritol-1-yl)adenine (**4e**), and 8-(D-*allo*-pentitol-1-yl)adenine (**4g**), all obtained in crystalline form.

8-(2-Furyl)adenine (**6**) was formed as a by-product of 8-(D-*ribo*-tetritol-1-yl)-adenine (**4e**) during the pyrolysis of the D-ribonic amide **3e**. Its structure was established by comparison with an authentic sample prepared by pyrolyzing the amide (**7**) obtained by the action of furoyl chloride on 4,5,6-triaminopyrimidine.

Mild acetylation[5] of the amides (**3a** and **3c**) and 8-(hydroxyalkyl)adenines (**4a** and **4c**) respectively afforded the acetoxyalkyl derivatives (**3b** and **3d**) and (**4b** and **4d**), needed for screening. However, the mild conditions used resulted in incomplete acetylation, and decreased the yield. A small amount of the *N,O*-per-acetylated product was nevertheless formed, as evidenced by the mass spectra of the crude reaction-mixtures. This by-product could be removed by recrystallization.

Owing to the facile cyclization of the amides (3) to 8-(hydroxyalkyl)adenines (4), the mass spectra of compounds 3 were quite similar to those of compounds 4 (see Table II), showing molecular peaks which were the base peaks for the lower members and of lower intensities for the higher analogs. These were followed by peaks corresponding to the loss of water, presumably in the formation of the 8-(hydroxy-

TABLE I

AMIDES (3) AND 8-(HYDROXYALKYL)ADENINES (4)

Compound	*M.p.* (°C)	*Yield* (%)	*Formulas*	*Carbon* (%)		*Hydrogen* (%)		*Nitrogen* (%)	
				Calc.	*Found*	*Calc.*	*Found*	*Calc.*	*Found*
Amides									
3a	240	42	$C_6H_9N_5O_2$	39.34	39.34	4.95	4.85	38.23	38.25
3c	235	31	$C_7H_{11}H_5O_3 \cdot 0.5H_2O$	37.84	37.81	5.44	5.41	31.52	31.57
3e	187	12	$C_9H_{15}N_5O_5$	39.58	39.48	5.53	5.49	25.63	25.66
3f	254	11	$C_9H_{15}N_5O_5$	39.58	39.08	5.53	5.37	25.63	25.48
3g	184	25	$C_{10}H_{17}N_5O_6$	38.46	38.74	5.81	5.89	22.43	22.69
8-(Hydroxyalkyl)adenines									
4a	320	55	$C_6H_7N_5O$	43.64	43.42	4.27	4.33	42.40	42.47
4c	295	24	$C_7H_9N_5O_2$	43.08	42.44	4.65	4.57	35.88	35.94
4f	185	10	$C_9H_{13}N_5O_4$	42.35	42.08	5.13	5.27	—	—
4h	238	15	$C_{10}H_{15}N_5O_5 \cdot 2H_2O$	37.38	37.67	5.96	5.61	21.80	21.71
Acetates									
3b	250	15	$C_8H_{11}N_5O_3$	42.67	42.59	4.92	4.98	31.10	31.07
3d	230	59	$C_{11}H_{15}N_5O_5$	44.44	44.54	5.09	5.13	23.56	23.47
4b	258	36	$C_8H_9N_5O_2$	46.38	46.20	4.38	4.35	33.80	33.86
4d	255	65	$C_{11}H_{13}N_5O_4$	47.31	47.21	4.69	4.53	25.08	25.03

TABLE II

MASS-SPECTRAL DATA

Compound	m/e (% *of base peak*)
3a	183(100), 165(13), 152(80), 135(14), 125(65), 94(24), 71(15)
3b	225(100), 194(12), 183(23), 152(62), 135(11), 125(80), 100(12), 96(18)
3c	213(55), 152(30), 135(14), 125(100), 98(16), 71(40)
3d	297(99), 225(12), 196(67), 177(77), 167(41), 152(100), 175(65)
3e	219(23), 201(52), 177(37), 175(26), 164(23), 148(61), 135(47), 125(100), 112(7), 98(8), 71(20)
4a	165(100), 148(7), 147(43), 136(16), 120(11), 108(10)
4b	207(50), 165(65), 164(100), 148(30), 136(80), 121(22)
4c	195(96), 171(52), 165(94), 164(100), 149(18), 136(28), 135(43), 119(32), 108(32)
4d	279(17), 236(11), 219(33), 194(25), 177(100), 164(5), 149(9)
4e	225(9), 237(58), 201(45), 177(64), 165(69), 164(100), 135(31)
4g	285(1), 267(4), 255(1), 242(7), 231(12), 220(13), 213(32), 201(17), 191(20), 190(25), 177(100), 163(11), 149(4), 136(6), 122(3)
6	201(100), 184(9), 174(19), 135(1)

alkyl)adenines in the case of the amides. Diagnostic peaks in the mass spectra of the amides (**3**) appeared at *m/e* 125 owing to the liberation of 4,5,6-triaminopyrimidine, and at *m/e* 152 for the loss of the saccharide chain. These peaks were insignificant in the spectra of 8-(hydroxyalkyl)adenines (**4**), and could be used to check the purity of the latter compounds. The amides and the 8-(hydroxyalkyl)adenines showed fragmentations characteristic of their hydroxyalkyl chain; thus, peaks were observed for adenine (*m/e* 135), 8-formyladenine (*m/e* 164), and, if the chain contained two or more carbon atoms, the 8-(oxirano)- and 8-(oxireno)-adenines (*m/e* 176, 178). For compounds having four carbon atoms, an important fragment corresponding to the formation of 8-(2-furyl)adenine (**6**) appears at *m/e* 201.

EXPERIMENTAL

General. — Infrared spectra were recorded with a Perkin–Elmer PE-700 infrared spectrometer. Mass spectra were recorded with a Varian M-66 mass spectrometer operated by M. P. Gilles. Melting points were determined on a Kofler melting-point apparatus and are uncorrected. Elemental analyses were made by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

4,5,6-Triaminopyrimidine (**1**). — The sulfate, hydrate (obtained from K and K Laboratories, Inc., Cleveland, Ohio) was dissolved in hot 2M sodium hydroxide, and the free amine that separated on cooling was recrystallized from hot water; m.p. 248°.

Amides (**3**). — *Method A.* A solution of 4,5,6-triaminopyrimidine (0.05M) and the required aldonic acid (0.05M) in 1M hydrochloric acid (100 ml) was boiled for 8 h under reflux. The mixture was cooled, passed through a column (2.2 × 24 cm) of Dowex-50 (H^+) cation-exchange resin, and the column eluted with water until the eluate showed a negative test for chloride ion with silver nitrate. The column was then eluted with aqueous ammonia (2%), and the first 500 ml of yellow eluate was collected, and concentrated under diminished pressure to a few ml; the product crystallized out as pale-yellow crystals (see Table I).

Method B. Equimolar amounts of the amine, the acid, and *N,N'*-dicyclohexylcarbodiimide in tetrahydrofuran were boiled for 12 h under reflux. The mixture was evaporated to dryness, the residue treated with water, and the substituted urea removed by filtration. The filtrate was processed as in method *A*, by using a cation-exchange resin to retain the amide and then eluting with ammonia; the yields were 20% lower than with method *A*.

8-(Hydroxyalkyl)adenines (**4**). — The amide **3** (1 g) was placed in a boiling tube, pyrolyzed for 8 h at 200–220°, and the mixture cooled. The brown solid was scraped out, placed in the thimble of a Soxhlet extractor, and extracted for 12 h with water. The resulting extract was treated with charcoal, the suspension filtered, and the filtrate concentrated to a few ml under diminished pressure, whereupon the product crystallized (see Table I).

Acetates (**3b**, **3d**, **4b**, *and* **4d**). — A suspension of the amide (**3a** or **3c**) or the 8-(hydroxyalkyl)adenine (**4a** or **4c**) (0.4 g) in pyridine (50 ml) and acetic anhydride

(0.8 ml) was stirred for 1 h at 0°, for 6 h at room temperature, and then for 16 h at 5–10°. Three 50-ml portions of methanol and then three 50-ml portions of toluene were added and evaporated under diminished pressure, and the resulting solid was recrystallized from hot ethanol (see Table I).

4,6-Diamino-5-(2-furoyl)aminopyrimidine (**7**). — Compound **1** (1.08 g) was stirred with anhydrous pyridine (50 ml), and 2-furoyl chloride (1.41 g) was added dropwise during 10 min; the mixture was stirred overnight, the suspension filtered, the filtrate evaporated under diminished pressure, the residue dissolved in water, and the solution passed through a column of Dowex-50 (H^+) ion-exchange resin. The aqueous eluate was discarded, and a colored fraction, collected by eluting the column with aqueous ammonia (2%), yielded compound **7** (0.69 g; 35%); m.p. 275–278°.

Anal. Calc. for $C_9H_9N_5O_2$: C, 49.31; H, 4.14; N, 31.95. Found: C, 49.31; H, 4.17; N, 31.92.

8-(2-Furyl)adenine (**6**). — Compound **7** (0.02 g) was placed in a vertical sublimator and kept for 1 h at 220°. The product (**6**), which was extremely insoluble in water, was purified by sublimation at 260°/0.01 torr. 8-(2-Furyl)adenine was also obtained as a by-product of the pyrolysis of amide **3e** by subliming the material that precipitated from the extract during Soxhlet extraction; it had m.p. 360°; mass spectral data: *m/e* 201(100), 184(9), 174(19), 135(1).

Anal. Calc. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.43; H, 3.53; N, 34.88.

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