

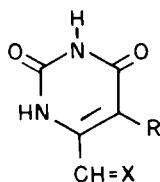
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## Pyrimidines. XX. A Convenient Preparation of Orotaldehyde and Thymine-6-carboxaldehyde (1)

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The only reported synthesis of orotaldehyde (Ia. uracil-6-carboxaldehyde, 6-formyluracil), a compound closely related to the biologically important orotic acid, involves the condensation of ethyl  $\gamma,\gamma$ -diethoxyacetoacetate with thiourea, followed by hydrolysis of the resulting diethylacetal in acid, and conversion of the thioxo function of 2-thiouracil-6-carboxaldehyde to an oxo function with hydrogen peroxide in alkali (2-6). The intermediate ethyl  $\gamma,\gamma$ -diethoxyacetoacetate, in turn, is prepared by the method of Johnson and Mikeska (7) from very pure (8) dichloroacetic acid *via* ethyl diethoxyacetate (2, 9).

It has now been found that compound Ia can be readily prepared by direct oxidation of 6-methyluracil (10) with selenium dioxide in refluxing acetic acid in good yield (11). The product as well as its two Cannizzaro derivatives--orotic acid and 6-hydroxymethyluracil--was found to be identical with that prepared by the known method (2-5).



I a. R = H, X = O

b. R = CH<sub>3</sub>, X = O

This facile oxidation can also be extended for the preparation of thymine-6-carboxaldehyde (Ib) from 6-methylthymine. Because of the ready availability of Ia and Ib, some hydrazone derivatives have been prepared and identified.

### EXPERIMENTAL (13)

#### Orotaldehyde (Ia).

A mixture of 63 g. (0.5 mole) of 6-methyluracil (10) 66.6 g. (0.6 mole) of selenium dioxide and 1500 ml. of glacial acetic acid was refluxed with mechanical stirring for 6 hours. During this time the

white suspension of selenium dioxide was gradually replaced by the gray selenium. The hot reaction mixture was filtered and the selenium cake was extracted with 2 x 250 ml. of boiling acetic acid. The combined yellow filtrate and extracts were evaporated to dryness under reduced pressure, giving 60 g. of a yellow solid, which gave a positive 2,4-dinitrophenylhydrazone test. The crude orotaldehyde, which still contained some selenium and excess selenium dioxide, was purified as follows: The solid was dissolved in 600 ml. of warm water, and an aqueous solution of sodium bisulfite (30 g. of sodium bisulfite in 60 ml. of water) was cautiously added in small portions to the stirred mixture. It was boiled with active charcoal and Celite for 10 minutes then filtered. The filtrate was acidified with concentrated hydrochloric acid to pH 1. On cooling, 25 g. of pure orotaldehyde was collected, m.p. 273-275° dec. (slower heating caused carbonization at 273-275° without melting). An additional 16 g. of product was obtained from the concentrated mother liquor which brought the total yield of Ia to 58%. An analytical sample was prepared by recrystallization from water and the off-white solid, m.p. 273-275° dec. (lit., (3) m.p. 273-275° dec.), was dried *in vacuo* at 120°.  $\lambda$  max (pH 1, 7), 261 m $\mu$  ( $\epsilon$ , 13,300);  $\lambda$  max (pH 11), 225 ( $\epsilon$ , 16,100), 291 m $\mu$  ( $\epsilon$ , 9,200). *Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 42.86; H, 2.88; N, 19.99. Found: C, 42.68; H, 3.05; N, 19.87.

#### Thymine-6-carboxaldehyde (Ib).

A mixture of 28 g. (0.20 mole) of 5,6-dimethyluracil (14) and 26.4 g. (0.24 mole) of selenium dioxide in 600 ml. of acetic acid was refluxed with stirring for 5 hours then filtered as previously described. A stream of sulfur dioxide was bubbled through the yellow filtrate for 10 minutes. The solvent was then removed under reduced pressure and the residue recrystallized from 200 ml. of water (with charcoal and Celite) to give 29 g. (94% yield) of product, m.p. 203-205°. An analytical sample was obtained by two recrystallizations from water, m.p. 209-211° (lit., (2) m.p. 212-213°), (60% recovery) as white needles.  $\lambda$  max (pH 1), 268 m $\mu$  ( $\epsilon$ , 7,800);  $\lambda$  max (pH 11), 223 ( $\epsilon$ , 11,200), 303 m $\mu$  ( $\epsilon$ , 8,900).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.99; H, 4.04; N, 18.50.

#### General Preparation of Hydrazone Derivatives.

To 300 ml. of an aqueous (or ethanolic, or a mixture of both, depending on the solubility characteristics of different hydrazines) solution of substituted hydrazine (0.05 mole) was added dropwise, with stirring, 180 ml. of warm (60-70°) water containing 5.6 g. (0.04 mole) of orotaldehyde and 1 ml. of acetic acid. After addition was complete, the mixture was heated on a steam bath for 1 hour with stirring, then cooled. The resulting solid was collected by filtration, washed with cold water, and purified either by recrystallization from appropriate solvents (see Table I) or by reprecipitation from a basic solution with dilute hydrochloric acid.

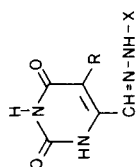
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TABLE I  
Hydrazones of Orotaldehyde and Thymine-6-carboxaldehyde



X	Empirical Formula	Recrystallization Solvents	Yield %	M. P. (°C)	Analyses			Found		pH 1		pH 11		Ethanol		
					Calcd. C	Calcd. H	Calcd. N	C	H	N	λ max	ε	λ max	ε	λ max	ε
CH <sub>3</sub>	C <sub>6</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	Water	58	274-275	42.86	4.79	33.32	42.75	4.75	33.22	322	30,100	231	6,900		
CHO	C <sub>8</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> · 1/2H <sub>2</sub> O	DMF + water	78	>360 darken 345	37.70	3.69	29.31	38.08	3.49	29.54	302	21,800	222	8,800		
C <sub>6</sub> H <sub>5</sub>	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	ethanol	74	354-356 (a)	57.39	4.38	24.34	57.44	4.17	24.50			316	20,300	241	10,600
p-C <sub>6</sub> H <sub>4</sub> -COOH	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> · 1/2H <sub>2</sub> O	DMF + water	81	>360	50.88	3.91	19.78	50.92	3.93	19.70	270	9,900	225	12,700	290	5,600
p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub>	C <sub>11</sub> H <sub>9</sub> N <sub>2</sub> O <sub>4</sub> · 1/2H <sub>2</sub> O	DMF + water	73	>360	46.48	3.55	24.64	46.68	3.24	24.92	360	42,500	268	10,700	298	5,300
CO	C <sub>11</sub> H <sub>9</sub> N <sub>2</sub> O <sub>3</sub> · 1/2H <sub>2</sub> O	pyridine	71	>360	49.25	3.76	26.11	48.96	3.51	26.25	405	21,400	362	36,800	372	27,400
CO-C <sub>6</sub> H <sub>5</sub>	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	-----	74	>360	55.81	3.90	21.70	55.56	3.67	21.87	268	15,000	223	11,800	228	9,800
CO-NH <sub>2</sub>	C <sub>9</sub> H <sub>7</sub> N <sub>2</sub> O <sub>3</sub> · 1/2H <sub>2</sub> O	DMF + water	75	>360 darken 340	34.95	3.91	33.97	34.85	3.76	33.65	316	23,100	335	26,800	312	35,200
CS-NH <sub>2</sub>	C <sub>8</sub> H <sub>7</sub> N <sub>2</sub> O <sub>2</sub> · 1/2H <sub>2</sub> O	repphn.	74	>360 (b)	32.43	3.63	31.52	32.60	3.30	31.45	303	26,700	228	9,800	276	17,300
CH <sub>3</sub>	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	ethanol + water	67	261-262	46.15	5.53	30.76	46.18	5.56	30.99			230	7,300	315	13,500
C <sub>6</sub> H <sub>5</sub>	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	ethanol	73	320-321	59.01	4.95	22.94	59.38	5.08	23.23	325	28,000	312	22,000	238	13,000
CS-NH <sub>2</sub>	C <sub>7</sub> H <sub>9</sub> N <sub>2</sub> O <sub>2</sub> S	DMF	69	>360 darken 360	37.00	3.97	30.82	37.36	3.88	30.57	268	15,000	238	13,000	292	6,200
											316	23,100	335	26,800	375	38,000
											405	21,400	405	28,000	245	8,300
											270	9,900	225	12,700	358	28,600
											360	42,500	268	10,700		
											405	21,400	405	28,000		
											268	15,000	223	11,800		
											316	23,100	335	26,800		
											303	26,700	228	9,800		
													276	17,300		
													315	13,500		
													230	10,200		
													348	24,000		
													230	7,300		
													312	22,000		
													238	13,000		
													292	6,200		
													375	38,000		
													245	8,300		
													358	28,600		

Lit. (4) m.p. 330°. (b) Lit., (5) m.p. 320°.

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