

SYNTHESIS OF SOME PYRIMIDO[4,5-b][1,4]OXAZINES

STARTING FROM 5-AMINOPYRIMIDINES

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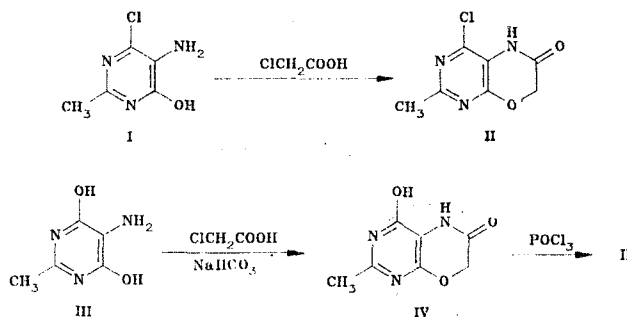
Derivatives of pyrimido[4,5-b][1,4]oxazine with hydroxy-, chloro-, and substituted amino groups at the 4-position were synthesized. The structures of the compounds were confirmed by mass-spectrometry and by alternate synthesis.

Until now, the pyrimido[4,5-b][1,4]oxazine system has received little attention. However, this system is interesting, since it is the oxygen analog of pteridine, which is a precursor of folic acid and its antagonists, and hence is a potential anticancer agent.

A method for the preparation of the pyrimido[4,5-b][1,4]oxazine derivatives has been developed, based on the reaction between a 5-aminopyrimidine with a hydroxyl group at the 4 or 6 position and an  $\alpha$ -halogen containing carbonyl compound [1-3].

In order to find out more about the chemistry of pyrimido[4,5-b][1,4]oxazine, we have studied the reaction of some 5-aminopyrimidines [4] with chloroacetic acid.

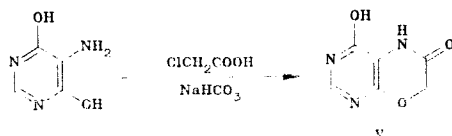
For example, the reaction of 5-amino-2-methyl-6-hydroxy-4-chloropyrimidine (I) with monochloroacetic acid, followed by treatment with sodium carbonate [1-3], gave 2-methyl-4-chloropyrimido[4,5-b][1,4]oxazine-6-one (II).



The structure of the ketone II was confirmed by an alternate synthesis: cyclization of 5-amino-4,5-dihydroxy-2-methylpyrimidine (III) with monochloroacetic acid yielded 2-methyl-4-hydroxypyrimidino[4,5-b][1,4]-oxazine-6-one (IV), which on chlorination with phosphorus oxychloride gave II.

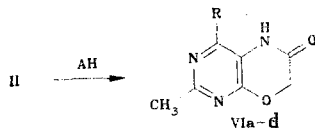
The physicochemical constants of compound II, obtained by both methods, are in good agreement, indicating that samples obtained by both routes are identical.

Using the same method, 5-amino-4,6-dihydroxypyrimidine and chloroacetic acid gave 4-hydroxypyrimido[4,5-b][1,4]oxazine-6-one (V).



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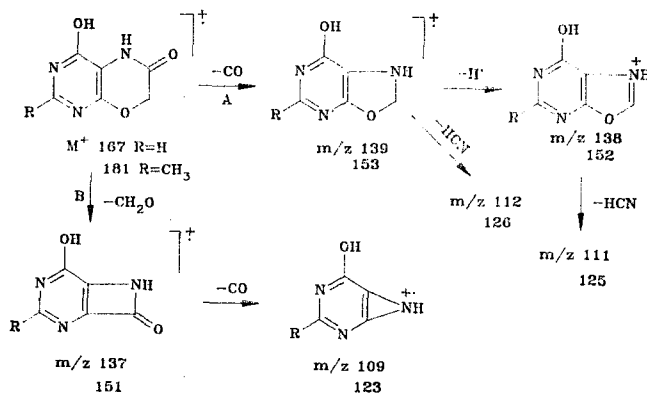
Because of the mobility of the chlorine atom in 4-chloropyrimido oxazine II, a nucleophilic substituent was introduced into the molecule; heating II with an amine in alcohol gave the corresponding 4-aminosubstituted pyrimidooxazine-6-one (VIa-d).



a A=N(CH<sub>3</sub>)<sub>2</sub>, b A=N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, c A = morpholyl, dA = piperidyl

The structures of compounds II and IV-VIa-d were confirmed by mass spectroscopy, their purity by TLC.

All the mass spectra contained peaks corresponding to the molecular ions. The fragmentation of compounds IV and V proceeds by two different paths, A and B, with destruction of the pyrimidinoxazine skeleton.



For compound II, the elimination of a chlorine atom from the  $[M - (CO - H)]^+$  ion gave rise to an ion with  $m/z = 145$ .

For compounds IVa-d, the pathway by which  $M^+$  disintegrates depends on the nature of the amino group, i.e., for all practical purposes, the pyrimidinoxazine ring is not affected.

The toxicity and antitumor activity of the compounds were studied on sarcoma 45, Walker's carcinoma, and Erlich's ascitic carcinoma using the method described in [5]. The absolute lethal dose of compounds II and IV-VIa-d for a single intraperitoneal injection into white mice was 1.25-1.5 g/kg; however, these substances did not possess any appreciable antitumor activity against the tumors listed above.

#### EXPERIMENTAL

Mass spectra were taken on an MX-1303; the ionization energy was 30 eV and the temperature was 30-40°C lower than the melting point of the test compounds (see Table 1); samples were introduced directly into the ion source. TLC was carried out on Silufol UV-254 plates in methanol-water (1:1), and spots were visualized in UV light.

Physicochemical data are given in Table 1.

**5-Amino-2-methyl-6-hydroxy-4-chloropyrimidine (I).** A mixture of 1.95 g (10 mmoles) of 5-amino-2-methyl-6-hydroxypyrimidine hydrochloride [4] and 10 ml of water was refluxed until the solid had dissolved, and the solution then made alkaline (pH 8.5-9) by the addition of triethylamine. The crystals which separated on cooling were filtered off, carefully washed with cold water, and dried.

**5-Amino-4,6-dihydroxy-2-methylpyrimidine Hydrochloride.** A mixture of 1.83 g (10 mmoles) of 5-acetamido-4,6-dihydroxy-2-methylpyrimidine [6] and 3 ml of concentrated HCl in 25 ml of ethanol was refluxed for 5 h. The precipitated material was filtered off, washed with ethanol, and dried to give 1.42 g (80%), mp 273-274°C. Found, %: C 33.7, H 4.4, Cl 19.8, N 23.6. C<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>2</sub>. Calculated, %: C 33.8, H 4.5, Cl 20.0, N 23.7.  $M^+$  (mass-spectrometrically) 141.

TABLE 1. Properties of Compounds I-VIa-d

Compound	Mp, °C	$R_f$	Found, %			Empirical formula	Calculated, %			Yield, % (method)
			C	H	N (Cl)		C	H	N (Cl)	
I	233-234	—	37,4	4,0	26,4 (22,1)	C <sub>5</sub> H <sub>6</sub> ClN <sub>3</sub> O	37,6	3,8	26,3 (22,2)	73,8
II	235-236	0,77	41,8	3,3	20,6 (17,2)	C <sub>7</sub> H <sub>6</sub> ClN <sub>3</sub> O <sub>2</sub>	41,2	3,0	21,0 (17,8)	36,4 (A), 42,4 (B)
III	270	—	42,4	4,9	30,0	C <sub>5</sub> H <sub>7</sub> N <sub>3</sub> O <sub>2</sub>	42,6	5,0	29,8	87,3
IV	295-296	0,66	46,8	3,7	23,0	C <sub>7</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	46,4	3,9	23,2	46,7
V	>300	—	43,0	3,0	25,0	C <sub>6</sub> H <sub>5</sub> N <sub>3</sub> O <sub>3</sub>	43,1	3,0	25,1	33,0
VIa	195-196	—	51,9	5,8	26,6	C <sub>9</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub>	51,9	5,8	26,9	50,3
VIb	179-180	—	55,6	6,7	23,4	C <sub>11</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	55,9	6,8	23,7	52,9
VIc	238-239	0,70	52,9	5,6	22,4	C <sub>11</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>	52,9	5,6	22,9	72,0
VI d	187-189	0,66	58,4	6,8	22,2	C <sub>12</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	58,0	6,5	22,6	61,3

5-Amino-4,6-dihydroxy-2-methylpyrimidine (III) was obtained analogously from 1.78 g (10 mmoles) of 5-amino-4,6-dihydroxy-2-methylpyrimidine hydrochloride.

2-Methyl-4-hydroxypyrimido[4,5-b][1,4]oxazine-6-one (IV). A mixture of 4.2 g (30 mmoles) of III and 18.9 g (200 mmoles) of monochloroacetic acid was heated on a water bath at 70°C until the mixture dissolved; the water evolved in the reaction was removed by evacuating with a water pump for 3-4 h. After removal of most of the water, the mixture was cooled to room temperature and carefully washed with ether (2 × 30 ml). To the residue was added 3.4 g (25 mmoles) of sodium bicarbonate in 20 ml of water and the mixture heated on the water bath for 1-1.5 h; the resulting solution was then acidified to pH 5 with acetic acid. The crystals which separated on cooling were filtered off.

2-Methyl-4-chloropyrimido[4,5-b][1,4]oxazine-6-one (II). A. Compound IV was obtained from I by the same method.

B. A mixture of 3.6 g (20 mmoles) of IV, 18.0 ml of phosphorus oxychloride, and 10 ml of dimethylaniline was refluxed for 3-3.5 h. The excess phosphorus oxychloride was driven off on the vacuum pump, the residue dissolved in 50 ml of benzene, and the benzene solution carefully washed with 40 ml of cold water. After removal of the solvent, the residue was recrystallized from alcohol.

4-Hydroxypyrimido[4,5-b][1,4]oxazine-6-one (V) was obtained from 3.8 g (30 mmoles) of 5-amino-4,6-dihydroxypyrimidine [7] by the method used to prepare IV.

4-Dimethylamino-2-methylpyrimido[4,5-b][1,4]oxazine-6-one (VIa). A mixture of 1 g (5 mmoles) of II and 10 ml of saturated dimethylamine in methanol was refluxed for 6 h in an autoclave at 85-90°C. The solvent was removed and the residue recrystallized from alcohol.

4-Aminosubstituted-2-methylpyrimido[4,5-b][1,4]oxazine-6-one (VIb-d). A mixture of 1 g (5 mmoles) of II and a twofold excess of the corresponding amine was refluxed for 4-5 h in 20 ml of alcohol. The solvent was removed and the residue recrystallized from alcohol.

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