Synthesis of 5-Oxo and 7-Oxopyrido[2,3-*d*]pyrimidines

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The synthesis of 4-amino-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine **4** and its isomer, 4-amino-2-methylthio-7-oxopyrido[2,3-*d*]pyrimidine **6** is described. The regiochemistry of the reaction of 4,6-diamino-2-methylthiopyrimidine **9** and diethyl ethoxymethylene malonate **12** is discussed.

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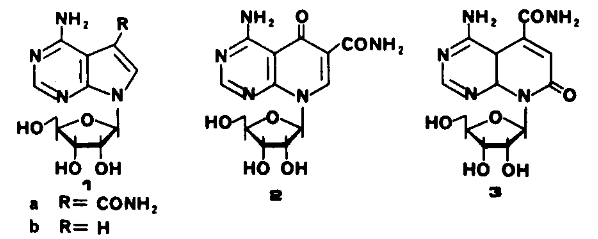
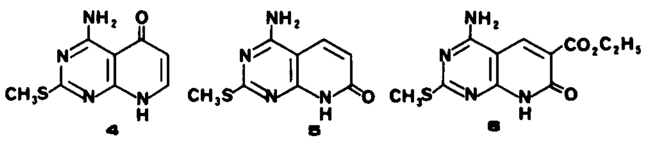
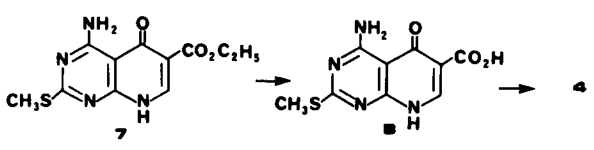
Sangivamycin **1a** and tubercidin **1b** are pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics which possess antitumor activity [1]. The pyrido[2,3-*d*]pyrimidine ring system is contained in a number of biologically active compounds including antitumor [2], antibacterial [3], and anticonvulsive agents [4]. Some antitumor activity was retained in the nucleoside 4-amino-6-carbamoyl-5-oxo-8-β-D-ribofuranosylpyrido[2,3-*d*]pyrimidine **2** [2], which is the 5-oxo homolog of sangivamycin. However, 4-amino-5-carbamoyl-7-oxo-8-β-D-ribofuranosylpyrido[2,3-*d*]pyrimidine **3** was devoid of antitumor activity [5]. This marked difference in activity between **2** and **3** could be due to either the position of the carboxamide or oxo group on the pyridine ring.



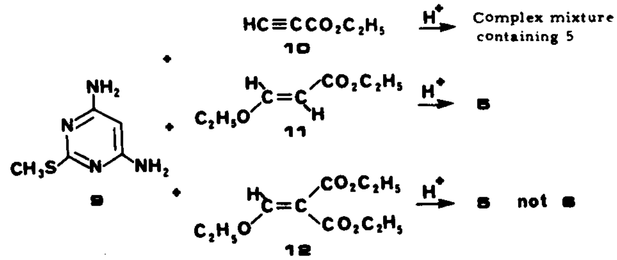


As part of a program directed toward the synthesis of additional homologs of sangivamycin and tubercidin, the synthesis of the pyrido[2,3-*d*]pyrimidines bases **4-6** was undertaken. This report gives the results of those synthetic efforts.

The ready availability of the ester **7** [2] suggested that conversion to the acid followed by decarboxylation should



Scheme 1



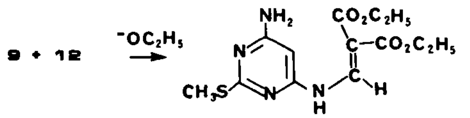
Scheme 2

give **4** (Scheme 1). Both sublimation and the use of copper/quinoline have found widespread use in the decarboxylation of aromatic acids [6]. Saponification of the ester **7** afforded an excellent yield of the carboxylic acid **8**. Vacuum sublimation of **8** did give a good yield of **4**. However, the product was always contaminated with modest amounts (≅20%) of the starting acid which proved to be difficult to remove by crystallization. Refluxing of **8** in phenyl ether under a nitrogen atmosphere gave **4** in excellent yield with no trace of starting acid. Structural assignment was readily confirmed using pmr spectroscopy by the appearance of two doublets in the aromatic region for H-6 and H-7 as well as two deuterium oxide exchangeable doublets. The latter signals are characteristic for the amino protons in 4-amino-5-oxopyrido[2,3-*d*]pyrimidines [2]. The amino hydrogens are non-equivalent due to intramolecular hydrogen bonding to the adjacent 5-oxo group.

The condensation of 6-aminopyrimidines with β-keto esters [7] and acetylenic esters [8] has been shown to yield 7-oxopyrido[2,3-*d*]pyrimidines. We have recently shown that the reaction of 1,3-dimethyl-6-aminouracil with diethyl ethoxymethylenemalonate, a chemical equivalent of a β-carbonyl ester, is regioselective forming the 7-oxopyrido[2,3-*d*]pyrimidine under acidic conditions. However, under basic conditions followed by thermal cyclization the 5-oxo isomer is formed [9]. Attempts to react 4,6-diamino-2-methylthiopyrimidine **9** with ethyl propiolate **10** directly in acetic acid gave a complex reaction mixture from which only small amounts of **5** could be isolated (Scheme 2). The β-aldehyde ester requisite for the synthesis of **5** from **9** is ethyl formylacetate. The ethyl acetal of this latter compound, 2-carbethoxyethenyl ethyl ether **11**, was prepared from ethyl propiolate using the procedure of Winterfeldt [10]. Reaction of **9** and **11** in acetic acid afforded a good yield of **5**. The lack of an aromatic singlet in the pmr spectrum indicates that cyclization must involve C-5 of the starting pyrimidine **9**. The appearance of two aromatic doublets and a deuterium oxide exchangeable 2 proton broad singlet is consistent with the assigned structure. The reaction likely proceeds through the aldehyde of **11**. The nmr experiments in which first **9** and **11** were reacted in trifluoroacetic acid and then only **11** was treated with trifluoroacetic acid showed that the rate of formation of **5** in the first experiment coincided with the rate of disappearance of **11** in the second experiment under identical reaction conditions.

The reaction of **9** and diethyl ethoxymethylenemalonate **12** in acetic acid did not afford the expected product **6**. The isolated product **5** was identical in all respects to the product obtained from **9** and **11**. This was somewhat surprising since 1,3-dimethyl-6-aminouracil and **12** gave the 6-carbethoxy-7-oxopyrido[2,3-*d*]pyrimidine in good yield under identical conditions [9]. This suggests that the decarbethoxylation occurs after formation of the adduct of **9** and **12** from reaction at C-5 of **9** but before cyclization of the amino group to one of the ester functionalities.

The reversal in regioselectivity shown by the reaction of **9** with **12** is striking. Under neutral [2] or basic conditions the product arises from attack of the amino group of **9** on **12** to form **13** (Scheme 3), while under acidic conditions initial attack must be from C-5 of **9** to give ultimately **5**. Using chromatography, there is no indication of the formation of **13** in the acid catalyzed reaction. An alternate synthesis of **6** is currently being investigated.



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Scheme 3

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The pmr spectra were recorded on a Varian EM-360 spectrometer in DMSO-d_6 with DSS as the internal standard. Chemical shifts are reported as δ values in parts per million (ppm). The uv absorption spectral data were obtained on a Cary Model 15 spectrometer. Microanalyses were performed by Baron Consulting Co. Analytical samples were dried *in vacuo* over toluene in the presence of phosphorus pentoxide.

4-Amino-6-carboxy-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**8**).

Compound **7** (2.98 g, 10 mmoles) [2] was refluxed in 50 ml of 1*N* sodium hydroxide until all solid had dissolved. The solution was adjusted to *p*H 5 with acetic acid, cooled, filtered to give 2.54 g (91%) of **8**, which was sufficiently pure to be used directly in the synthesis of **4**. For analysis, a small sample was recrystallized from hot DMF with addition of ethanol to the cloud point, cooling and filtering the white solid, slowly decomposes >300°, effervesces at 322°; uv (*p*H 1): λ max 298 nm (ε 22,200), 273 (49,800); (*p*H 7): 271 (46,000); (*p*H 11): 314 (14,800), 270 (43,800); ^{1}H nmr: δ 2.50 (s, 3H, SCH_3), 7.97 (s, 1, CH), 7.97 (br s, 1, NH), 9.00 (br s, 1, NH).

Anal. Calcd. for $C_9H_8N_4O_3S \cdot 1.5H_2O$: C, 38.71; H, 3.97; N, 20.06. Found: C, 39.10; H, 4.05; N, 19.73.

4-Amino-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**4**).

Compound **8** (2.0 g, 7.94 mmoles) was heated under vigorous reflux in 70 ml of diphenyl ether in a nitrogen atmosphere for 17 hours, cooled, filtered, and the solid washed with chloroform to give 1.65 g (100%) of crude product. Recrystallization from DMF-water afforded 1.23 g (75%) of pure **4** as white crystals, mp >360°; uv (*p*H 1): λ max 267 nm (ε 34,500); (*p*H 7): 292 (13,000), 264 (31,700), 256 (31,000); (*p*H 11): 305 br sh (7,480), 265 (31,500); ^{1}H nmr: δ 2.50 (s, 3H, SCH_3), 6.07 (s, 1, C_6H) (J = 7.4 Hz), 7.73 (d, 1, C_7H) (J = 7.4 Hz), 7.97 (br d, 1, NH) (J = 4 Hz), 9.62 (br d, 1, NH) (J = 4 Hz).

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.90. Found: C, 45.96; H, 4.03; N, 27.12.

4-Amino-2-methylthio-7-oxopyrido[2,3-*d*]pyrimidine (**5**).

Method A.

4,6-Diamino-2-methylthiopyrimidine **9** (15.7 g, 100 mmoles) and 2-carbethoxyethenyl ethyl ether **11** (16.0 g, 110 mmoles) were refluxed overnight in 150 ml of acetic acid, cooled to room temperature, filtered and the solid recrystallized from DMF-water to give 13.5 g (65%) of **5** as pale yellow crystals, mp 333° dec; uv (*p*H 1): λ max 320 nm (ε 45,200), 308 (45,200); (*p*H 7): 326 (44,700); (*p*H 11): 333 (37,300), 320 (38,000); ^{1}H nmr: δ 2.50 (s, 3H, SCH_3), 6.27 (d, 1, C_6H) (J = 10 Hz), 7.67 (br s, 2, NH_2), 8.08 (d, 1, C_5H) (J = 10 Hz).

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.90. Found: C, 45.97; H, 4.17; N, 26.75.

Method B.

Compound **9** (1.57 g, 10 mmoles) and **12** (2.18 g, 11 mmoles) were refluxed overnight in 15 ml of acetic acid, cooled, filtered and the solid recrystallized from DMF-water to give 749 mg (36%) of **5**, which was identical in all respects to **5** obtained by Method A.

2-Carbethoxyethenyl Ether Ether (**11**).

This compound was reported by Subramanyam [11]. We found it more convenient to prepare it according to method of Winterfeldt [10]. Ethyl propiolate (100 mmoles), ethanol (100 mmoles), and *N*-methylmorpholine (100 mmoles) were dissolved in 150 ml of diethyl ether, stirred at room temperature for 24 hours, evaporated with water aspiration and the residual oil distilled *in vacuo* to give 12.3 g (85%) of **11**, bp 0.6 mm 63° (lit [11] 61° at 0.5 mm); ^{1}H nmr: δ 1.23 (t, 3, CH_3), 1.30 (t, 3, CH_3), 4.03 (q, 2, OCH_2), 4.13 (q, 2, OCH_2), 5.27 (d, 1, CH) (J = 13 Hz), 7.66 (d, 1, CH) (J = 13 Hz).

Diethyl *N*-(2-Methylthio-4-amino-6-pyrimidinyl)aminomethylenemalonate **13**.

4,6-Diamino-2-methylthiopyrimidine **9** (15. 7 g, 10 mmoles) and **12** (23.5 g, 11 mmoles) were refluxed overnight in 100 ml of ethanol. The solution was cooled and filtered to give 27.6 g (85%) of **13** identical in all respects to **13** prepared by the method of Rizkalla and Broom [2].

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