Synthesis of 5,8-Dihydro-5-oxo-2-(3- or 4-pyridinyl)-pyrido[2,3-*d*]pyrimidine-6-carboxylic Acids and the Reinvestigation of the Thermal Cyclization of Diethyl (2-Hydroxy-4-pyrimidinyl)amino-methylenemalonate

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Diethyl [2-(3- or 4-pyridinyl)-4-pyrimidinyl]aminomethylenemalonates **5** prepared by the reaction between 2-(3- or 4-pyridinyl)-4-pyrimidinamines **3** and diethyl ethoxymethylenemalonate (**4**) were thermally cyclized to afford ethyl 5,8-dihydro-5-oxo-2-(3- or 4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylates **6**. The later were alkylated with ethyl iodide and then saponified to give 5,8-dihydro-8-ethyl-5-oxo-2-(3- or 4-pyridinyl)pyrido-[2,3-*d*]pyrimidine-6-carboxylic acids **2**. Thermal cyclization of diethyl (2-hydroxy-4-pyrimidinyl)amino-methylenemalonate (**8**) gave ethyl 1,6-dihydro-4,6-dioxo-4*H*-pyrimido[1,6-*a*]pyrimidine-3-carboxylate (**10**) instead of ethyl 5,8-dihydro-2-hydroxy-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylate (**9**) as previously claimed.

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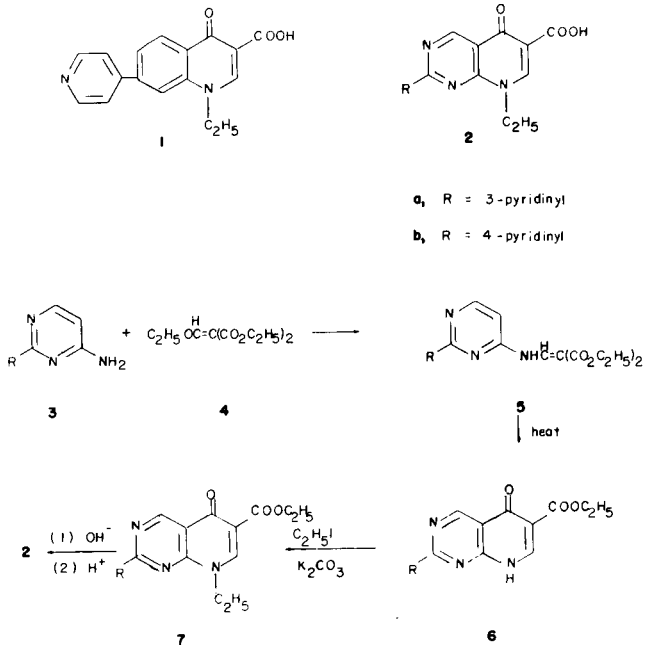
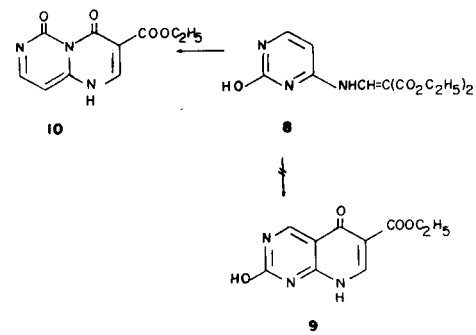
Rosaxacin (**1**) (1) which was developed in our laboratories has recently been marketed as an antigonorrhea agent (1). Our continuing efforts on the structural modification of **1** has led us to the synthesis of 5,8-dihydro-8-ethyl-5-oxo-2-(3- or 4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acids **2** which bear a close structural resemblance to **1**. This, probably, represents the first application of Gould-Jacobs synthesis of pyrido[2,3-*d*]pyrimidines bearing a heteroaryl substituent in the 2-position.

Diethyl [2-(3- or 4-pyridinyl)-4-pyrimidinyl]aminomethylenemalonates **5** were prepared either by reacting 2-(3- or 4-pyridinyl)-4-pyrimidinamines **3** (2) with diethylethoxymethylenemalonate (**4**) at high temperature or by reacting the sodium salt of **3** with **4** in dimethylformamide at low temperature. The cyclization of **5** to ethyl 5,8-dihydro-5-oxo-2-(3- or 4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylates (**6**) was accomplished in boiling Dowtherm in moderate yields. Alkylation of **6** with ethyl iodide in dimethylformamide in the presence of potassium carbonate followed by saponification gave **2** in high yield.

While our work was in progress in this area, Japanese workers claimed in a patent (3) to have prepared **9** by the thermal cyclization of diethyl (2-hydroxy-4-pyrimidinyl)-aminomethylenemalonate (**8**). Whereas, from the same reaction we obtained a compound melting at 268-270° which was higher than their reported melting point of 258-261°. The nmr spectrum of our compound displayed a pair of doublets at δ 6.41 (H-9, J = 7.8) and 8.4 (H-8, J = 7.8) which is consistent with isomeric structure **10** which has *ortho*-coupled protons.





EXPERIMENTAL

The nmr spectra were obtained on a Varian HA-100 spectrometer in deuterated trifluoroacetic acid using tetramethylsilane as the internal standard. Melting points were determined in open capillaries in an oil bath and are uncorrected. Yields reported are of purified compounds and are not optimized.

Diethyl [2-(3-Pyridinyl)-4-pyrimidinyl]aminomethylenemalonate (**5a**).

A mixture of 34.0 g (0.197 mole) of 2-(3-pyridinyl)-4-pyrimidinamine (**3a**) (2) and 43.0 g (0.2 mole) of diethyl ethoxymethylenemalonate (**4**) was

heated in an oil bath at 160-170° for 5 hours, cooled to room temperature and then crystallized from isopropanol-ether to give 56.0 g (82%) of **5a** as yellow prisms, mp 115-117°.

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.51; H, 5.30; N, 16.06.

Diethyl [2-(4-Pyridinyl)-4-pyrimidinyl]aminomethylenemalonate (**5b**).

To the ice cold stirred mixture of 86.0 g (0.5 mole) of 2-(4-pyridinyl)-4-pyrimidinamine (**3b**) (2) and 140.0 g (0.65 mole) of diethyl ethoxymethylenemalonate (**4**) and 500 ml of dimethylformamide was added 26.0 g (0.54 mole) of 50% sodium hydride over 40 minutes. The resulting mixture was further stirred in an ice bath for 30 minutes and at room temperature for 1 hour and then poured into 1 ℓ of water containing 60 ml of acetic acid. The precipitate was filtered, air dried, washed with hexane to remove oil (from sodium hydride) and then recrystallized from ethanol-ether to afford 139.5 g (81%) of pale yellow needles of **5b**, mp 142-144°.

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.76; H, 5.22; N, 16.53.

Ethyl 5,8-Dihydro-5-oxo-2-(3-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (**6a**).

The malonate **5a** (64.0 g, 0.19 mole) was added to 1.3 ℓ of boiling Dowtherm. The resulting solution was boiled while being stirred for 30 minutes and then cooled to room temperature. The dark crystalline solid that separated was collected (36.0 g). The filtrate was again boiled with stirring for 1 hour. On cooling to room temperature, there was obtained a second crop of 16.0 g of a dark solid. The two solids thus obtained were combined and recrystallized from dimethylformamide to afford 29.0 g (52%) of **6a** as a fluffy yellow solid, mp 280-282°, nmr δ 9.70 (*s*, H-7) and 10.28 (*s*, H-4).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.57; H, 3.99; N, 19.19.

Ethyl 5,8-Dihydro-5-oxo-2-(4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (**6b**).

The malonate **5b** (110.0 g, 0.32 mole) was added to 1.2 ℓ of boiling Dowtherm and the resulting mixture was boiled with vigorous stirring for 20 minutes. After cooling to room temperature, a dark solid was obtained in a crude yield of 20.0 g. The mother liquor was boiled with stirring again for 30 minutes, cooled to room temperature and the resulting dark solid was collected (12.0 g). The two fractions were combined and recrystallized from dimethylformamide to yield 22.0 g (23%) of tan crystals of **6b**, mp 278-280°; nmr δ 9.83 (*s*, H-7) and 10.46 (*s*, H-4).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.43; H, 4.01; N, 19.00.

Ethyl 5,8-Dihydro-8-ethyl-5-oxo-2-(3-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (**7a**).

A slurry of 5.9 g (0.02 mole) of **6a**, 5.5 g (0.03 mole) of anhydrous potassium carbonate in 100 ml of dimethylformamide was stirred and heated on a steam bath for 30 minutes and then treated with 1.8 ml (0.022 mole) of ethyl iodide. The resulting mixture was further stirred and heated for 40 minutes and then concentrated to dryness. The residue was stirred in 25 ml of water and the insoluble solid was filtered and recrystallized from ethanol to give 4.8 g (67%) of off-white crystals of **7a**, mp 192-195°.

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.28. Found: C, 62.64; H, 4.81; N, 17.46.

Ethyl 5,8-Dihydro-8-ethyl-5-oxo-2-(4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (**7b**).

A mixture of 19.0 g (0.064 mole) of **6b**, 16.8 g (0.095 mole) of anhydrous potassium carbonate and 250 ml of dimethylformamide was heated on a steam bath with stirring for 30 minutes and then treated with 6.5 ml (0.08 mole) of ethyl iodide. The resulting mixture was continuously stirred and heated for 30 minutes and then concentrated. The residue was partitioned between chloroform and water. The organic phase was concentrated to give a solid residue which was recrystallized from isopropanol to afford 14.5 g (70%) of **7b** as yellow needles, mp 236-238°.

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.28. Found: C, 62.80; H, 4.92; N, 16.94.

5,8-Dihydro-8-ethyl-5-oxo-2-(3-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (**2a**).

A mixture of 13.0 g (0.04 mole) of **7a** and 100 ml of 2*N* aqueous potassium hydroxide was heated on a steam bath for 1 hour, cooled to room temperature and then neutralized by treating with concentrated hydrochloric acid. The resulting white crystalline solid was filtered, washed with water and dried to yield 10.0 g (93%) of **2a**, mp 278-280°; nmr: δ 9.71 (*s*, H-7) and 10.30 (*s*, H-4).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.81; H, 4.09; N, 18.87.

5,8-Dihydro-8-ethyl-5-oxo-2-(4-pyridinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic Acid (**2b**).

A mixture of 14.0 g (0.047 mole) of **7b**, 80 ml of methanol and 80 ml of 10% aqueous sodium hydroxide was refluxed for 1 hour. The methanol was removed under reduced pressure. The residual solution was treated with concentrated hydrochloric acid whereupon a tan solid was precipitated which was recrystallized from dimethylformamide to afford 12.5 g (98%) of tan crystals of **2b**, mp 275-277°; nmr δ 9.57 (*s*, H-7) and 10.22 (*s*, H-4).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.78; H, 4.07; N, 18.89.

Diethyl (2-Hydroxy-4-pyrimidinyl)aminomethylenemalonate (**8**).

A mixture of 99.0 g (0.9 mole) of cytosine (4) and 195.0 g (0.9 mole) of diethyl ethoxymethylenemalonate (**4**) was heated in an oil bath at 160° for 5 hours, cooled and the product was then crystallized from dimethylformamide to give 170.0 g (67%) of **8**, mp 195-197° (lit (3), mp 191-194°).

Ethyl 5,8-dihydro-4,6-dioxo-4*H*-pyrimido[1,6-*a*]pyrimidine-3-carboxylate (**10**).

Diethyl (2-hydroxy-4-pyrimidinyl)aminomethylenemalonate (**8**) (65.0 g, 0.23 mole) was added to 1 ℓ of vigorously stirred and boiling Dowtherm. After 10 minutes the reaction mixture was cooled to room temperature. The resulting yellow crystalline solid was collected, washed with ethanol and dried to yield 33 g (61%) of **10** as a yellow powder, mp 268-270° (lit (3), mp 258-261°).

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 50.79; H, 3.97; N, 18.23.

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