*Jun-ichi Matsumoto,* Shinsaku Mishio and Shinsaku Minami*

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki-cho 33-94, Suita, Osaka 564, Japan

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8-Substituted 5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (**3**) rearranged to 8-substituted 7,8-dihydro-5-hydroxy-7-oxopyrido[2,3-*d*]pyrimidine-6-carboxaldehydes (**5**) when treated with sodium ethoxide in an aprotic polar solvent at room temperature. The 6-cyano analogue (**18**) also underwent ring transformation under the same mild conditions giving 7-amino-8-ethyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**21**). However, the ring transformations of the pyrido[2,3-*d*]pyrimidine bearing no $N_8$-substituent (**12**), ethyl 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine- (**14**) and -quinoline-3-carboxylates (**16**) failed to occur. A mechanism is discussed.

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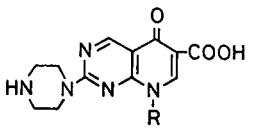
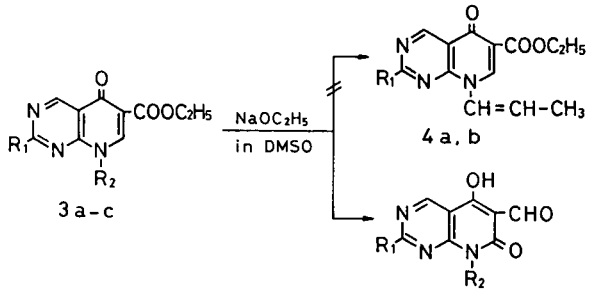
As part of our research program on pyrido[2,3-*d*]pyrimidine antibacterial agents (1), we became interested in preparing 5,8-dihydro-5-oxo-2-(1-piperazinyl)-8-(1-propenyl)-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**2**) for biological evaluation; the 8-vinyl derivative (**1**), among the compounds previously studied, has proved to be the most active *in vitro* and *in vivo* against gram-negative bacteria including *Pseudomonas aeruginaosa* (1). In an effort to convert 8-allyl-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (**3**) into the 8-(1-propenyl) isomers (**4**), a base-induced ring transformation has been found, which is the subject of this paper.

Scheme I



1 R = -CH=CH$_2$

2 R = -CH=CH-CH$_3$

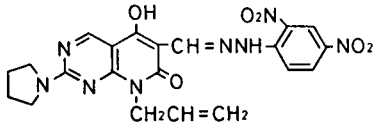


3 a-c

a: $R_1$ = $CH_3S$-, $R_2$ = -$CH_2$-CH=$CH_2$

b: $R_1$ =  , $R_2$ = -$CH_2$-CH=$CH_2$

c: $R_1$ =  , $R_2$ = -$C_2H_5$



6

It is well known that an alkoxide anion in dimethyl sulfoxide facilitates a prototropic rearrangement of an allyl to a 1-propenyl group (2). The allyl derivatives (**3a** and **3b**) when treated with sodium ethoxide in dimethyl sulfoxide at room temperature gave unexpected products $C_{12}H_{11}N_3O_3S$ (**5a**) and $C_{15}H_{16}N_4O_3$ (**5b**) in 40 and 66% yields, respectively. The infrared (ir) spectra of **5a** and **5b** showed a carbonyl absorption band at 1650 and 1665 $cm^{-1}$, respectively, but no absorption due to the ester carbonyl which appeared at 1680 $cm^{-1}$ in the starting materials **3a** and **3b**. The nuclear magnetic resonance (nmr) spectrum of **5a** (Table 2) revealed the presence of an allyl group in the molecule, indicating that no isomerization of the double bond had occurred in this reaction. In the same spectrum, signals due to the ethoxycarbonyl and pyridone C-7 protons disappeared. However a singlet signal at $\delta$ 10.14 and a very broad signal at $\delta$ 14.5 appeared, and were assigned to the aldehyde and hydroxyl protons, respectively. Similarly, the nmr spectrum of **5b** exhibited signals ascribed to the respective protons of allyl, pyrimidine C-4, hydroxyl, and aldehyde groups. The presence of an aldehyde group was further confirmed by conversion of **5b** into its 2,4-dinitrophenylhydrazone (**6**). These facts permit assignment of the products to structures **5a** and **5b**.

The same ring transformation of the $N_8$-ethyl derivative (**3c**) was successful in forming the aldehyde (**5c**) in 62% yield. The assigned structure **5c** was supported again by ir and nmr spectral data and elemental analysis.

Further evidence of the structural assignment of **5** was provided by the following chemical transformations of the representative **5c**. Thus, oxidation of **5c** with hydrogen peroxide in aqueous alkaline solution gave 4-ethylamino-2-(1-pyrrolidinyl)pyrimidine-5-carboxylic acid (**7**); this apparently indicates that the pyrimidine moiety has not changed in structure during the conversion of **3c** into **5c**. The reaction of **5c** with hydroxylamine led to the oxime (**8**) which, on treatment with acetic anhydride, was converted

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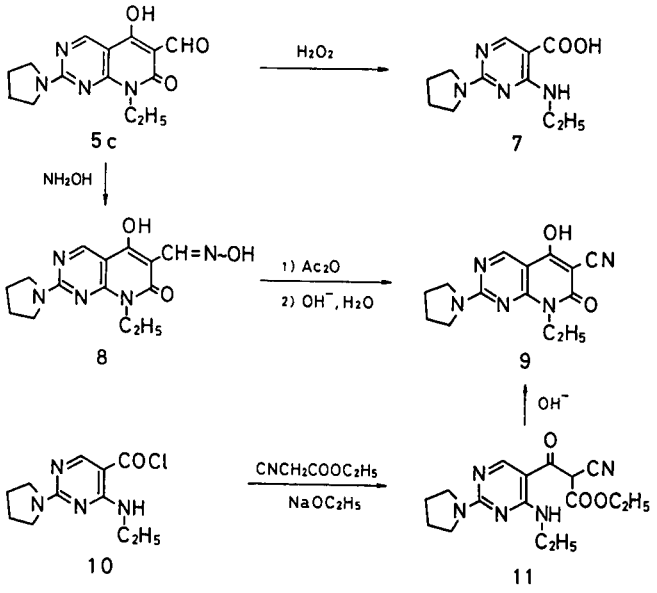
Scheme II



into the nitrile (**9**), showing a C≡N absorption at 2200 $cm^{-1}$ in its ir spectrum. The nitrile (**9**) proved to be identical with an authentic sample which was unequivocally prepared by treatment of 4-ethylamino-2-(1-pyrrolidinyl)-pyrimidine-5-carbonyl chloride (**10**) with ethyl cyanoacetate, followed by cyclization of ethyl 2-cyano-3-[4-ethylamino-2-(1-pyrrolidinyl)-5-pyrimidinyl]-3-oxopropionate (**11**) under alkaline conditions.

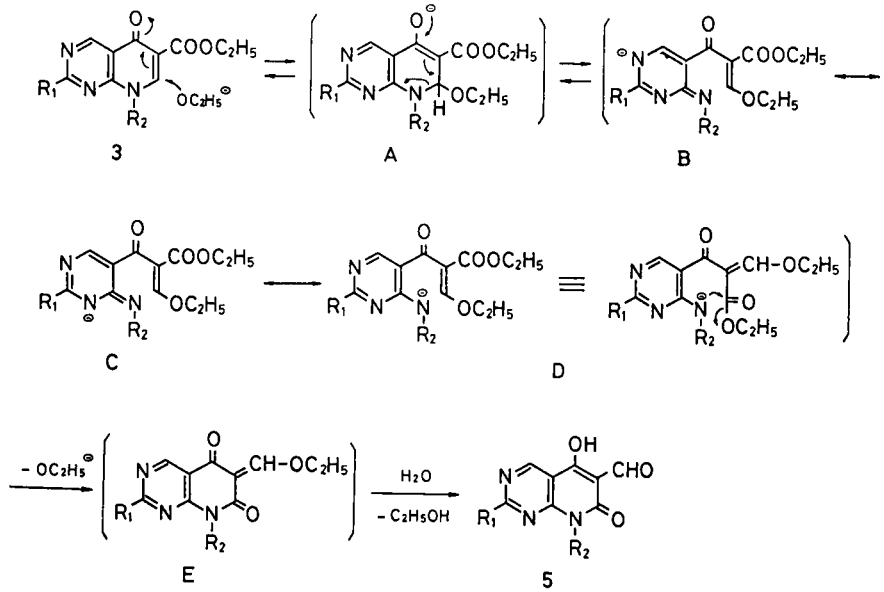
The ring transformation of **3c** to **5c** was effected also by the use of dimethylformamide as the solvent, though not satisfactory in yield. The use of ethanol, however, resulted in failure of the rearrangement.

A possible mechanism which accounts for the formation of the aldehyde (**5**) involves an initial nucleophilic attack of the ethoxide anion on C-7 of the pyrido[2,3-*d*]pyrimidine ring of **3**. An aprotic polar solvent such as dimethyl sulfoxide and dimethylformamide causes an increase in the nucleophilicity of the ethoxide anion because of decreased solvation, allowing the ethoxide to attack easily at C-7. The resulting anion (A) undergoes ring cleavage at the 7,8-bond to give the anion (B) which may be stabilized by delocalization of the negative charge through the nitrogen atoms of the pyrimidine ring as shown in B, C, and D. The negatively charged amino-nitrogen atom in D susbequently attacks the carbon atom of the ester carbonyl followed by re-cyclization with elimination of ethoxide, giving the ethoxymethylene derivative (E), which may be hydrolyzed during the work-up to result in the formation of the aldehyde (**5**).

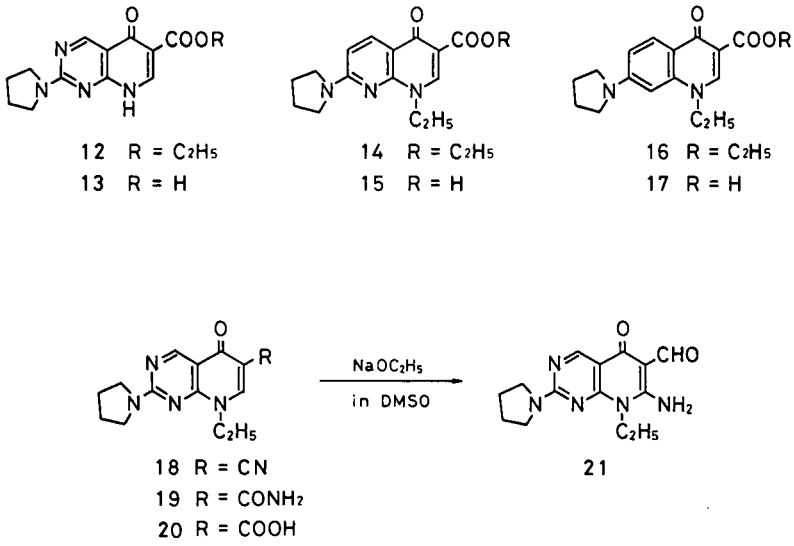
An attempt to convert the pyrido[2,3-*d*]pyrimidine derivative (**12**) bearing no $N_8$-substituent into the corresponding aldehyde under the same reaction conditions was unsuccessful, resulting merely in hydrolysis of the ester (**12**) to give the carboxylic acid (**13**). Failure of the rearrangement of **12** is probably due to the decreased positive character of C-7, which arises from pyridone-pyridinol tautomerization.

Ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)-1,8-naphthyridine- (**14**) and -quinoline-3-carboxylates (**16**), in which the same pyridone ring system as **3** was present, also failed to undergo the ring transformation; the isolated products were the corresponding carboxylic acids **15** and **17**, respectively. This fact is likely explained by assuming that the resonance stabilization of the ring-opened anion may

Scheme III



Scheme IV




12 R = $C_2H_5$
13 R = H
14 R = $C_2H_5$
15 R = H
16 R = $C_2H_5$
17 R = H
18 R = CN
19 R = $CONH_2$
20 R = COOH
21

not be enough to compensate for the lack of either one or two nitrogen atom(s) in their ring systems.

On the other hand, the mechanistic pathway discussed above allowed us to expect that 8-ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**18**) may undergo rearrangement into 7-amino-8-ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**21**). In fact, treatment of **18**, which was derived from the carboxylic acid (**20**) *via* the amide (**19**), with sodium ethoxide in dimethyl sulfoxide gave **21** successfully in 83% yield. Assignment of the structure **21** was based on spectral data and elemental analysis.

The transformations discussed above represent a new type of the base-induced rearrangement of the pyrido-[2,3-*d*]pyrimidine ring system.

## EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded in potassium bromide discs on a Hitachi model 215 spectrometer and uv spectra were taken with a Shimazu MPS-5000 spectrometer. Nmr spectra were determined on a Varian HA-100D spectrometer with tetramethylsilane as an internal standard.

Ethyl 8-Allyl-5,8-dihydro-2-methylthio- and -(1-pyrrolidinyl)-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylates (**3a** and **3b**).

Ethyl 5,8-dihydro-2-methylthio- and -(1-pyrrolidinyl)-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylates (3,4), respectively, were allowed to react with allyl bromide in the presence of sodium hydride in dimethylformamide according to the procedure described previously (1). The corresponding 8-allyl derivatives (**3a** and **3b**) were obtained. Compound **3a** had m.p. 113-114° (recrystallized from ethanol); 57% yield; ir: 1720, 1685, 1625 (C=O) $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 9.34 (1H, s, $C_4$-H), 8.46 (1H, s, $C_7$-H), 2.61 (3H, s, $SCH_3$), *ca.* 4.9 (2H, m, =CH-$CH_2$-N), 5.30 (2H, m, $CH_2$=CH-$CH_2$), *ca.* 6.0 (1H, m, $CH_2$=CH-$CH_2$), 1.40 (3H, t, J = 7 Hz, $CH_2CH_3$), 4.39 (2H, q, J = 7 Hz, $CH_2CH_3$).

*Anal.* Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 55.36; H, 4.66; N, 13.59; S, 10.37.

Compound **3b** had m.p. 170-173° (recrystallized from ethanol); 72% yield; ir: 1720, 1680, 1635 (C=O) $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 9.20 (1H, s, $C_4$-H), 8.33 (1H, s, $C_7$-H), 3.64 (4H, m, $CH_2NCH_2$), 2.02 (4H, m, $CH_2CH_2$), 4.80 (2H, m, =CH-$CH_2$-N), 5.27 (2H, m, $CH_2$=CH-$CH_2$), 6.0 (1H, m, $CH_2$=CH-$CH_2$), 4.36 (2H, q, J = 7 Hz, $OCH_2CH_3$), 1.38 (3H, t, J = 7 Hz, $OCH_2CH_3$).

*Anal.* Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.13; H, 6.14; N, 17.07. Found: C, 61.94; H, 5.81; N, 16.96.

8-Allyl-7,8-dihydro-5-hydroxy-2-methylthio- and -(1-pyrrolidinyl)-7-oxo-pyrido[2,3-*d*]pyrimidine-6-carboxaldehydes (**5a** and **5b**).

A stirred mixture of 500 mg. (1.64 mmoles) of **3a**, 170 mg. (2.5 mmoles) of sodium ethoxide, and 5 ml. of dimethyl sulfoxide was allowed to stand overnight at room temperature. The mixture was diluted with *ca.* 40 ml. of water and extracted with chloroform to remove the neutral portion. The aqueous layer was acidified with acetic acid to *p*H 5.5 and extracted with chloroform. The extract was washed with water and dried. The chloroform was evaporated to leave the crude product which was collected and recrystallized from ethanol, giving 180 mg. (39.6%) of **5a** (Tables 1 and 2).

Similar treatment of 540 mg. (1.64 mmoles) of **3b** with 170 mg. (2.5 mmoles) of sodium ethoxide in 5 ml. of dimethyl sulfoxide afforded 197 mg. (65.6%) of **5b** (Tables 1 and 2).

8-Ethyl-7,8-dihydro-5-hydroxy-7-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**5c**).

a) In Dimethyl Sulfoxide.

A mixture of 500 mg. (1.58 mmoles) of ethyl 8-ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylate (**3c**) (4), 210 mg. (3.1 mmoles) of sodium ethoxide, and 5 ml. of dimethyl sulfoxide was allowed to stand at room temperature for 45 hours with stirring. The reaction mixture was worked up in the same manner as with **5a**, giving 280 mg. (61%) of **5c** (Tables 1 and 2).

b) In Dimethylformamide.

A stirred mixture of 500 mg. (1.58 mmoles) of **3c**, 130 mg. (1.9 mmoles) of sodium ethoxide, and 3 ml. of dimethylformamide was allowed to react at room temperature for 24 hours. The reaction mixture was worked up in the same manner as that described above, giving 150 mg. (33%) of **5c**.

Table 1

7,8-Dihydro-5-hydroxy-7-oxopyrido[2,3-*d*]pyrimidine Derivatives

| Compound No. | M.p. (°C) | Recrystallization Solvent | Yield (%) | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 111-113 | Ethanol | 39.6 | $C_{12}H_{11}N_3O_3S$ (a) | 51.97 | 4.01 | 15.16 | 51.96 | 3.87 | 14.99 |
| **5b** | 165-166 | Ethanol | 65.6 | $C_{15}H_{16}N_4O_3$ | 59.99 | 5.37 | 18.66 | 60.29 | 5.61 | 18.48 |
| **5c** | 214-215 | Ethanol | 62.0 | $C_{14}H_{16}N_4O_3$ | 58.32 | 5.59 | 19.44 | 58.36 | 5.64 | 19.37 |
| **6** | 287-289 | DMF | 75.0 | $C_{21}H_{20}N_8O_6$ | 52.50 | 4.20 | 23.34 | 52.49 | 4.01 | 23.22 |
| **8** | 236-238 | DMF | 60.0 | $C_{14}H_{17}N_5O_3$ | 55.43 | 5.65 | 23.09 | 55.60 | 5.73 | 22.88 |
| **9** | >300 | Ethanol | 36.4 | $C_{14}H_{15}N_5O_2$ | 58.93 | 5.30 | 24.55 | 59.18 | 5.35 | 24.28 |
| **21** | >300 | Ethanol | 82.5 | $C_{14}H_{17}N_5O_2$ | 58.52 | 5.96 | 24.38 | 58.70 | 6.03 | 24.28 |

(a) *Anal.* Calcd. for S, 11.57. Found: S, 11.57.

Table 2

Spectral Data of 7,8-Dihydro-5-hydroxy-7-oxopyrido[2,3*d*]pyrimidine Derivatives

| Compound No. | Nmr δ (100 MHz) $C_4$-H | CHO | OH | $-CH_2CH=CH_2$ | Solvent | Ir (Potassium Bromide) $cm^{-1}$ | | Uv (Ethanol) Nm (Logε) |
|---|---|---|---|---|---|---|---|---|
| **5a** | 9.05 (s) | 10.14 (s) | 14.5 (br) | 5.95 (1H, m)<br>5.27 (2H, m)<br>4.98 (2H, m) | Deuteriochloroform | 1650, | 1590 | 238 (4.30), 274 (4.13), 328 sh (4.16), 346 (4.19), 366 (4.12). |
| **5b** | 8.91 (s) | 10.03 (s) | 14.5 (br) | 5.94 (1H, m)<br>5.23 (2H, m)<br>4.87 (2H, m) | Deuteriochloroform | 1665, | 1610 | 237 (4.31), 281 (4.07), 314 sh (3.96), 330 sh (4.07), 344 (4.11), 374 (4.16). |
| **5c** | 8.90 (s) | 10.03 (s) | 14.6 (br) | — | Deuteriochloroform | 1660, | 1610 | 238 (4.40), 281 (4.26), 314 sh (4.13), 330 sh (4.13), 348 sh (4.20), 374 (4.32). |
| **8** | 8.77 (s) | (a) | (b) | — | DMSO-$d_6$ | 1650,<br>1620, | 1630 sh,<br>1600 | c) |
| **9** | 8.74 (s) | — | (b) | — | DMSO-$d_6$ | 2200,<br>1630 | 1650, | 223 (4.42), 234 sh (4.37), 271 (4.31), 301 (4.01), 341 (4.19), 366 (4.11). |
| **21** | 8.82 (s) | 9.96 (s) | (b) | — | DMSO-$d_6$ | 3250,<br>1650, | 3100,<br>1630 | 223 (4.32), 237 (4.42), 283 (4.41), 296 sh (4.39), 315 (4.41). |

(a) The signal due to -CH=N- appears at δ 8.32 (1H, s). (b) Not observed. (c) Not measured.

The 2,4-dinitrophenylhydrazone (**6**) of **5b**.

A mixture of 100 mg. of **5b**, 70 mg. of 2,4-dinitrophenylhydrazine, 4 ml. of ethanol, and one drop of concentrated hydrochloric acid was heated on a steam bath for 5 minutes. The resulting precipitate was collected, washed with water, and recrystallized from dimethylformamide to give 120 mg. (75%) of **6** (Table 1); ir: 1655 (C=O), 1530, 1320 ($NO_2$) $cm^{-1}$.

4-Ethylamino-2-(1-pyrrolidinyl)pyrimidine-5-carboxylic acid (**7**) and its Ethyl Ester.

a)

To a stirred solution of 18.0 g. (70 mmoles) of ethyl 4-chloro-2-(1-pyrrolidinyl)pyrimidine-5-carboxylate in 100 ml. of ethanol was added 20 ml. of aqueous 70% ethylamine and the mixture was allowed to stand at room temperature overnight. The reaction mixture was concentrated to dryness *in vacuo* and the residue taken up in chloroform. The chloroform solution was washed successively with saturated aqueous sodium bicarbonate and water, and dried. Evaporation of the solvent gave the crude product which was recrystallized from *n*-hexane to afford 13.5 g. (72.5%) of ethyl 4-ethylamino-2-(1-pyrrolidinyl)pyrimidine-5-carboxylate; m.p. 82-83°; ir 1660 (C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.63; N, 21.20. Found: C, 58.56; H, 7.93; N, 21.41.

A mixture of 13.5 g. of the ester obtained above, 6.5 g. of potassium hydroxide, 80 ml. of ethanol, and 5 ml. of water was gently refluxed for 30 minutes. After evaporation of the solvent *in vacuo*, the residue was dissolved in water and the resulting solution was acidified with acetic acid to *p*H 5. The precipitate was collected and recrystallized from ethanol giving 10.8 g. (89.5%) of **7**, m.p. 203-205°.

*Anal.* Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 56.13; H, 6.70; N, 23.89.

b) Oxidation of **5c** with Hydrogen Peroxide.

To a stirred solution of 200 mg. of **5c** in aqueous 10% sodium hydroxide was added 20 ml. of 3% hydrogen peroxide. The mixture was allowed to stand overnight at room temperature and then acidified with acetic acid to *p*H 5. The aqueous solution was extracted with chloroform and the extract was washed with water, and dried. Evaporation of the solvent left the crude product which was recrystallized from ethanol giving 70 mg. of **7**.

The Oxime (**8**) of **5c**.

A mixture of 400 mg. (1.39 mmoles) of **5c**, 200 mg. (2.88 mmoles) of

hydroxylamine hydrochloride, 2 ml. of aqueous 10% sodium hydroxide, and 5 ml. of ethanol was allowed to stand overnight at room temperature. After removal of the neutral material by extraction with chloroform, the aqueous mixture was acidified with acetic acid to *p*H 5. The pecipitate was collected and recrystallized from dimethylformamide to give 250 mg. (59.4%) of **8** (Tables 1 and 2).

8-Ethyl-7,8-dihydro-5-hydroxy-7-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (**9**).

a) From the Oxime (**8**).

A mixture of 350 mg. (1.16 mmoles) of **8** and 15 ml. of acetic anhydride was gently refluxed for 2.5 hours. After removal of an excess of acetic anhydride by distillation, the residual solid was washed with aqueous 5% sodium bicarbonate and recrystallized from ethanol to give 120 mg. (36.4%) of **9** (Tables 1 and 2).

b) From the Propionate (**11**).

A mixture of 1.8 g. of **11** and 30 ml. of aqueous 10% sodium hydroxide was heated at 80° for 20 minutes. The mixture was then acidified with aqueous 10% acetic acid to *p*H 5 to give the precipitate which was collected, washed with water, and recrystallized from ethanol giving 1.1 g. (73%) of **9**.

4-Ethylamino-2-(1-pyrrolidinyl)pyrimidine-5-carbonyl Chloride Hydrochloride (**10**).

A mixture of 10.0 g. (42.3 mmoles) of **7**, 10 ml. of thionyl chloride, and 10 ml. of chloroform was gently refluxed for 30 minutes. The mixture was concentrated to dryness *in vacuo*, and the residue washed with chloroform giving 12.0 g. of **10** as a pale brown powder; ir: 3280, ~2500, 1740, 1640, 1620 $cm^{-1}$. This product was used in the next step without further purification.

Ethyl 2-Cyano-3-[4-ethylamino-2-(1-pyrrolidinyl)-5-pyrimidinyl]-3-oxopropionate (**11**).

To a stirred solution of 16 g. of ethyl cyanoacetate in 180 ml. of toluene was added portionwise 4 g. of 50% sodium hydride. After a 20 minute period of stirring, 12.0 g. of **10** was added to the solution all at once. The resulting mixture was allowed to stand overnight at room temperature and then heated at 80° for one hour. After removal of the solvent followed by addition of water, the resulting aqueous solution was neutralized with acetic acid and extracted with chloroform. The extract was washed with water, dried, and the solvent distilled off to leave the crude product which was recrystallized from ethanol, giving 10.5 g. (74.9%) of **11**, m.p. 174-173°; ir: 3300 (NH), 2180 (C≡N), 1700, 1640 (C=O) $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 8.35 (1H, br s, OH or NH), 8.26 (1H, s, $C_4$-H), 4.20 (2H, q, J = 7 Hz, $NCH_2CH_3$), 3.65 (4H, m, $CH_2NCH_2$), 3.48 (2H, q, J = 7 Hz, $OCH_2CH_3$), 1.22, 1.28 (each 3H, t, J = 7 Hz, $NCH_2CH_3$, $OCH_2CH_3$).

*Anal.* Calcd. for $C_{16}H_{21}N_5O_3$: C, 57.99; H, 6.39; N, 21.14. Found: C, 58.10; H, 6.33; N, 20.95.

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)-1,8-naphthyridine-3-carboxylate (**14**).

A mixture of 2.0 g. (7.13 mmoles) of ethyl 7-chloro-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**5**), 2.3 g. (32.3 mmoles) of pyrrolidine, and 30 ml. of ethanol was heated to reflux for 2 hours. The mixture was concentrated to dryness *in vacuo*, and the residual solid recrystallized from ethanol to give 1.68 g. (74.8%) of **14**, m.p. 196-198°.

*Anal.* Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.33. Found: C, 64.69; H, 6.57; N, 13.34.

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)quinoline-3-carboxylate (**16**).

To a stirred suspension of 5.0 g. (17.5 mmoles) of 1-ethyl-1,4-dihydro-4-oxo-7-(1-pyrrolidinyl)quinoline-3-carboxylic acid (**6**) in 70 ml. of chloroform was added successively 1.94 g. (19.2 mmoles) of triethylamine and 2.09 g. (19.2 mmoles) of ethyl chloroformate. The mixture was stirred for 30 minutes at room temperature and then 30 ml. of ethanol was added. After a one hour period of stirring, the reaction mixture was concentrated to dryness *in vacuo*. The residue was taken up in chloroform and the solution washed successively with aqueous 3% sodium hydroxide and water. Evaporation of the chloroform gave the crude product which was recrystallized from ethanol giving 4.56 g. (83%) of **16**, m.p. 207-208°.

*Anal.* Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.75; H, 7.02; N, 8.91.

Attempted Ring Transformations of **12**, **14**, and **16**.

According to the procedure described above, compounds **12** (4), **14**, and **16** (1.0 g.), respectively, were allowed to react with sodium ethoxide (1.2 equivalents) in 10 ml. of dimethyl sulfoxide at room temperature. The mixture was diluted with water, and neutralized with acetic acid to give the corresponding carboxylic acids **13** (650 mg.) (4), **15** (710 mg.) (5), and **17** (700 mg.) (6), respectively, which were identified by comparison with their authentic specimens.

8-Ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**18**).

A mixture of 500 mg. (1.74 mmoles) of **19** and 1.2 g. of tosyl chloride was kept at 130° for 15 minutes. While the mixture being hot, *ca.* 20 ml. of acetone was added to give the precipitate which was collected, washed successively with aqueous 3% sodium hydroxide and water, and recrystallized from dimethylformamide giving 420 mg. (89.5%) of **18**, m.p. >300°; ir: 2225 (C≡N), 1640 (C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.68; H, 5.62; N, 26.01.

8-Ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxamide (**19**).

To a suspension of 2.88 g. (10 mmoles) of 8-ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**20**) (4) in 30 ml. of dried chloroform was added successively 1.2 g. (12 mmoles) of triethylamine and 1.3 g. (12 mmoles) of ethyl chloroformate under ice cooling. The resulting clear solution was allowed to stand at room temperature for 30 minutes with stirring. Into the cold solution was introduced an excess of gaseous ammonia and then the mixture was stirred for 30 minutes. The resulting precipitate was collected and recrystallized from a mixture of chloroform and methanol to give 2.87 g. (96%) of **19**, m.p. 287-288°.

*Anal.* Calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.67; H, 5.63; N, 24.71.

7-Amino-8-ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-6-carboxaldehyde (**21**).

A stirred solution of 500 mg. (1.85 mmoles) of **18**, 238 mg. (3.5 mmoles) of sodium ethoxide, and 5 ml. of dimethyl sulfoxide was allowed to stand for 24 hours at room temperature. The resultant reddish brown mixture was diluted with water to give the precipitate which, after acidification of the mixture with acetic acid to *p*H 6.5, was collected, washed with water, and recrystallized from ethanol giving 440 mg. (82.5%) of **21** (Tables 1 and 2).

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