The Synthesis of a Pyrido[2,3-*c*]pyridazine: A Cinnoline Related to 6-Fluoronalidixic Acid

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An analog of the pyrido[2,3-*c*]pyridazine ring system, 1-ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxopyrido-[2,3-*c*]pyridazine-3-carboxylic acid (**13**), related to both cinoxacin (**1**) and nalidixic acid (**2**), has been synthesized. The reductive ring closure of 2-chloro-α-diazo-6-methyl-5-nitro-β-oxo-3-pyridinepropanoic acid, ethyl ester (**7**), proved to be the key reaction providing entry into the ring system.

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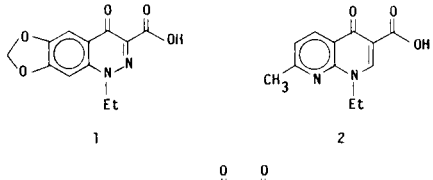
As part of our program to produce totally synthetic antibacterial agents, we have investigated the broad area of 4-oxoquinoline-3-carboxylic acids [1]. Within this framework, the recently synthesized pyrido[2,3-*c*]pyridazine ring system [2] was explored. It contains elements of both the cinnoline ring system characteristic of cinoxacin (**1**) and the 1,8-naphthyridine ring system common to both nalidixic acid (**2**) and enoxacin (**3**).

Chart I



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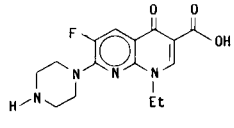

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An initial attempt to prepare an optimally substituted pyrido[2,3-*c*]pyridazine failed. The hydrazone **4**, which can be synthesized by the sequence of reactions outlines in Scheme I [3], could not be ring closed using several of the usual thermal and acid catalyzed conditions [4].

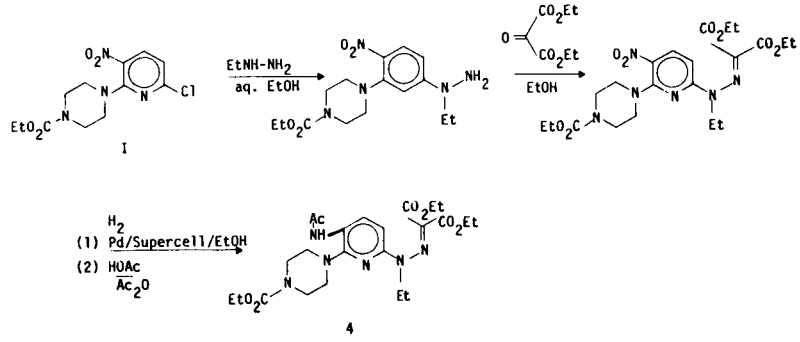
An alternate synthesis (Scheme II), beginning with 2-chloro-6-methyl-5-nitropyridine-3-carboxylic acid (**5**) [5], proceeded with a greater degree of success.

Since a ring closure at the C-3 position of the pyridine ring could not be effected using compound **4** (Scheme I), an alternate route for the formation of the pyridazine ring might be the nucleophilic displacement of the C-2 chlorine from the pyridine precursor, **7** (Scheme II).

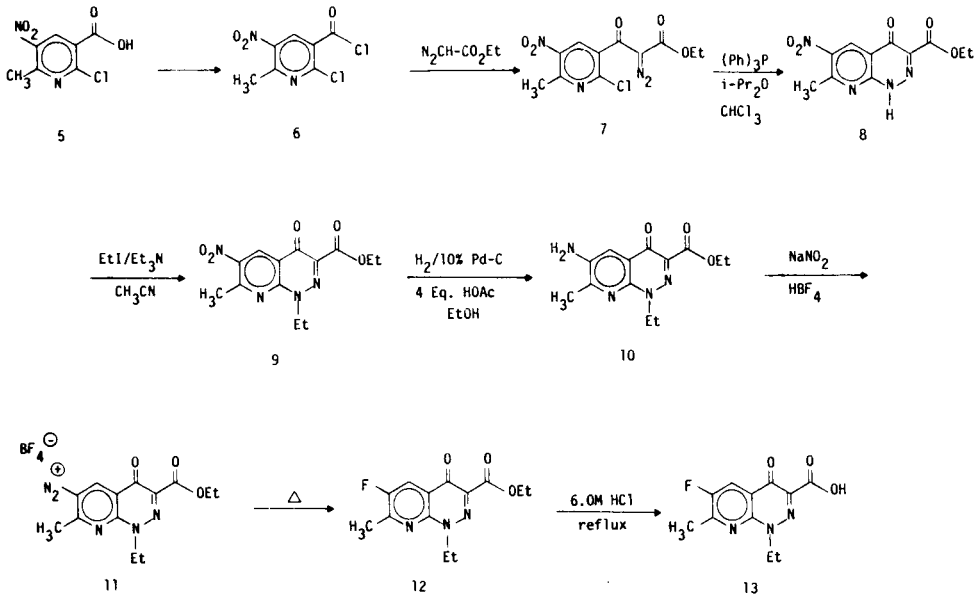
After converting **5** to the acid chloride **6**, reaction with ethyl diazoacetate afforded 60% of chromatographically pure α-diazo-β-keto ester **7**. The key reductive cyclization of **7** was effected using triphenyl phosphine in isopropyl ether-chloroform which produced the desired azacinnoline ring system **8** in a one pot reaction. The reaction of **7** involves the formation of the phosphazine **II** (Scheme III), which is then hydrolyzed to the hydrazone **III** [6]. The nucleophilic displacement of the 2-chloro substituent leads directly to the formation of **8**.

Alkylation of **8** using either potassium carbonate in refluxing triethyl phosphate or ethyl iodide, potassium carbonate and *N,N*-dimethylformamide at 100° failed to produce the desired product **9** [1]. However, when triethylamine was used at the base with ethyl iodide in acetonitrile, the ethyl analog **9** [7] was obtained in 82% yield. A modified hydrogenation of the alkylated nitro compound **9** using hydrogen, 10% palladium on carbon in acetic acid-ethanol produced the desired 6-amino compound **10** [7]

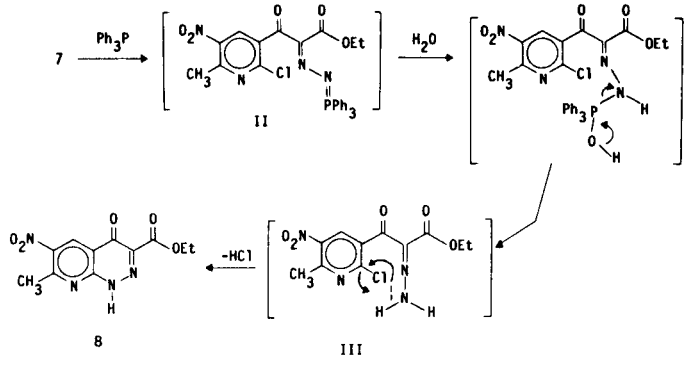
Scheme I



Scheme II



Scheme III



nearly quantitatively. Diazotization of this amine in 48% tetrafluoroboric acid produced the isolable diazonium salt **11**. Thermal decomposition of **11** in refluxing xylene followed by acid hydrolysis of the ester **12** afforded the title compound **13** in moderate yield. When this compound was tested along with its intermediates in our antibacterial screening, they did not have the anticipated activity.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm^{-1} resolution. Proton magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Column chromatography was performed using E. Merck "Silica Gel 60", 70-230 mesh ASTM. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 30-45° and pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry nitrogen atmosphere. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer.

2-Chloro-6-methyl-5-nitro-3-pyridinecarbonyl Chloride (**6**).

A solution of 8.6 g (39.7 mmoles) of 2-chloro-6-methyl-5-nitropyridine-3-carboxylic acid (**5**) [5] and 75 ml of thionyl chloride was refluxed for 2 hours. The solvent was removed *in vacuo* and replaced with 50 ml of toluene which was also removed *in vacuo*. The residue was used without further purification.

2-Chloro-α-diazo-6-methyl-5-nitro-β-oxo-3-pyridinepropanoic Acid, Ethyl Ester (**7**).

To 11.4 g (0.1 mole) of ethyl diazoacetate was added 8.6 g (36.6 mmoles) of 2-chloro-6-methyl-5-nitro-3-pyridinecarbonyl chloride (**6**), keeping the temperature below 5°. After the addition was complete, the

reaction was stirred at 5° for 1 hour and then heated at 50-60° for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel eluting with chloroform-ethyl acetate (9:1). The desired fractions were combined and concentrated *in vacuo* to give 7.0 g (61%) of **7**, mp 89-90°; ir: 2160 cm^{-1} (CN_2), 1724 cm^{-1} (C=O), 1706 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.22 (t, 3, CH_2CH_3), 2.90 (s, 3, CH_3), 4.19 (q, 2, CH_2CH_3), 8.26 (s, 1 , Ar).

Anal. Calcd. for $C_{11}H_9ClN_4O_5$: C, 42.25; H, 2.90; N, 17.92. Found: C, 42.49; H, 3.01; N, 18.03.

1,4-Dihydro-7-methyl-6-nitro-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid Ethyl Ester (**8**).

A solution of 10.7 g (34.2 mmoles) of keto ester **7** in 200 ml of isopropyl ether-chloroform (1:1) was cooled to 20° and treated with a solution of 10.75 g (41.0 mmoles) of triphenylphosphine in 50 ml of isopropyl ether. The reaction was stirred at room temperature overnight, and the resulting precipitate was removed by filtration, washed with chloroform-isopropyl ether (1:1), and dried *in vacuo* to give 4.9 g (52%) of **8**, mp 264-266°; ir: 1723 (C=O); nmr (DMSO-d_6): δ 1.30 (t, 3, CH_2CH_3), 2.88 (s, 3, CH_3), 4.32 (q, 2, CH_2CH_3), 8.88 (s, 1, Ar), 14.48 (s, br, CO_2H).

Anal. Calcd. for $C_{11}H_{10}N_4O_5$: C, 47.48; H, 3.62; N, 20.14. Found: C, 47.14; H, 3.80; N, 19.85.

1-Ethyl-1,4-dihydro-7-methyl-6-nitro-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid Ethyl Ester (**9**).

A solution of 46.5 g (0.17 mole) of **8** and 17.3 g (0.17 mole) of triethylamine in 1 l of acetonitrile was treated with 266.8 g (1.71 moles) of ethyl iodide. The reaction mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform and water. The organic layer was washed with water (3 x 200 ml), dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with chloroform. The fractions containing the desired product were combined and evaporated *in vacuo* to give 41.9 g (81%) of **9**, mp 86-87°; ir: 1738 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.47 (m, 6, OCH_2CH_3, NCH_2CH_3), 2.96 (s, 3, CH_3), 4.41 (q, 2, OCH_2CH_3), 4.69 (q, 2, NCH_2CH_3), 9.07 (s, 1, Ar).

Anal. Calcd. for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 51.00; H, 4.68; N, 18.08.

6-Amino-1-ethyl-1,4-dihydro-7-methyl-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid Ethyl Ester (**10**).

A mixture of 6.3 g (20.6 mmoles) of nitro ester **9**, 0.5 g of 10% palladium on carbon, 5 ml of acetic acid and 100 ml of absolute ethanol was shaken in an atmosphere of hydrogen at 46.3-51.0 psi and temperatures of 21-28° for 24 hours. The catalyst was removed by filtering through Celite, the filtrate evaporated *in vacuo* and the residue triturated with ether to give 5.4 g (95%) of **10**, mp 173-175°; ir: 1739 cm^{-1} (C=O), 1724 cm^{-1} (C=O), 3335 and 3434 cm^{-1} (NH_2); nmr (deuteriochloroform): δ 1.47 (m, 6, OCH_2CH_3, NCH_2CH_3), 4.43 (q, 2, OCH_2CH_3), 4.98 (s, br, 2, NH_2), 4.73 (q, 2, NCH_2CH_3), 8.00 (s, 1, Ar).

Anal. Calcd. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.27; H, 5.60; N, 20.01.

3-(Ethoxycarbonyl)-1-ethyl-1,4-dihydro-7-methyl-4-oxopyrido[2,3-*c*]-pyridazine-6-diazonium, Tetrafluoroborate (**11**).

A solution of 2.0 g (7.2 mmoles) of amine **10** in 15 ml of 48% tetrafluoroboric acid was cooled to 0° and treated with a solution of 0.76 g (11 mmoles) of sodium nitrite in 2 ml of water keeping the temperature 0-5°. When the addition was complete the reaction was stirred at 0-5° for ½ hour and then allowed to come to room temperature over 1.5 hours. After cooling to 0°, the mixture was diluted with 50 ml of ether. The solid was removed by filtration, washed with ether (5 x 20 ml) and dried *in vacuo* to give 1.9 g (70%) of **11**, mp 132-134°.

1-Ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid, Ethyl Ester (**12**).

To 100 ml of refluxing xylene was added portionwise 1.6 g (4.27 mmoles) of diazonium tetrafluoroborate **11**. After the addition was complete, the reaction was refluxed for 10 minutes and the solvent removed *in vacuo*. The residue was triturated with chloroform, the insoluble material removed by filtration, and the filtrate evaporated *in vacuo*. Purification by column chromatography (chloroform 8:ethyl acetate 2) gave 0.25 g (21%) of **12** as the only isolable product, mp 68-72°; ir: 1738 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.49 (m, 6, OCH_2CH_3, NCH_2CH_3), 2.72 (d, 2, J = 4 Hz, CH_3), 4.44 (q, 2, OCH_2CH_3), 4.77 (q, 2, NCH_2CH_3), 8.21 (d, 1, J = 12 Hz, C_5H).

Anal. Calcd. for $C_{13}H_{14}FN_3O_5$: C, 55.91; H, 5.05; N, 15.05. Found: C, 56.28; H, 4.84; N, 14.73.

1-Ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid (**13**).

A solution of 0.25 g (0.9 mmole) of ethyl ester **12** in 5 ml of ethanol and 5 ml of 6 *M* hydrochloric acid was heated at reflux for 18 hours. The solvent was removed *in vacuo*, the residue triturated with ether and the solid removed by filtration to give 0.2 g (88%) of **13**, mp 151-153°; ir: 1758 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.44 (t, 3, NCH_2CH_3), 2.69 (d, 3, J = 4 Hz, CH_3), 4.73 (q, 2, NCH_2CH_3), 8.34 (d, 1, J = 11 Hz, C_5H); ms: m/e (relative intensity) 252 (m^+ 1, 42.6), 234 (m^+ −OH, 21.4), 207 (m^+ $-CO_2$, 55.5) 179 (207 + H, −Et, 95.4), 151 (179 −CO, 100).

Anal. Calcd. for $C_{11}H_{10}FN_3O_3$: C, 52.59; H, 4.01; N, 16.73. Found: C, 52.90; H, 4.24; N, 16.45.

1-Ethyl-1,4-dihydro-7-methyl-6-nitro-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid (**14**).

A suspension of 0.33 g (1.07 mmoles) of ethyl ester **9** in 10 ml of 6.0 *M* hydrochloric acid was heated at 95° for 6 hours and then allowed to stand at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue recrystallized from 2-propanol to give 0.22 g (73%) of **14**, mp 133-134°; ir: 1763 cm^{-1} (C=O); nmr (DMSO-d_6): δ 1.44 (t, 3, NCH_2CH_3), 2.92 (s, 3, CH_3), 4.64 (q, 4, NCH_2CH_3), 8.94 (s, 1, Ar).

Anal. Calcd. for $C_{11}H_{10}N_4O_5$: C, 47.48; H, 3.62; N, 20.14. Found: C, 47.56; H, 3.38; N, 20.05.

6-Amino-1-ethyl-1,4-dihydro-7-methyl-4-oxopyrido[2,3-*c*]pyridazine-3-carboxylic Acid (**15**).

A solution of 1.0 g (3.62 mmoles) of ethyl ester **10** in 25 ml of 6.0 *M* hydrochloric acid was heated at 100° for 2.5 hours. The solvent was removed *in vacuo* and the residue triturated with 50 ml of ethanol/ether (1:1). The solid was removed by filtration, washed with ethanol/ether (2 x 10 ml, 1:1), and dried *in vacuo* to give 0.8 g (89%) of **15**, mp 287-289°; ir: 1748 cm^{-1} (C=O), 3343 and 3420 cm^{-1} (NH_2); nmr (DMSO-d_6): δ 1.45 (t, 3, NCH_2CH_3), 2.53 (s, 3, CH_3), 4.78 (q, 2, NCH_2CH_3), 7.48 (s, 1, Ar), 7.67 (s, br, 3, NH_2, CO_2H).

Anal. Calcd. for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.18; H, 4.77; N, 22.59.

REFERENCES AND NOTES

[1] R. Albrecht, *Prog. Drug Res.*, **21**, 9 (1977).

[2] P. Cregar-Čadež, A. Pollak, B. Stanovnik, M. Tišler and B. Wechtersbach-Lažetić, *J. Heterocyclic Chem.*, **9**, 351 (1972); I. Maeba and R. N. Castle, *J. Heterocyclic Chem.*, **16**, 249 (1979); I. Maeba, K. Mori and R. N. Castle, *J. Heterocyclic Chem.*, **16**, 1559 (1979).

[3] The starting material **I** for Scheme I can be found in; *J. Heterocyclic Chem.*, **21**, 673 (1984).

[4] Methods included: [a] Heating in Dowtherm-A at 250° for 2-3 hours; [b] Reaction in a mixture of sulfuric acid and acetic anhydride at reflux; [c] Heating at reflux in phosphorus oxychloride; [d] For a review of methods, see reference [1].

[5] R. P. Mariella and A. J. Havlick, *J. Am. Chem. Soc.*, **74**, 1915 (1952).

[6] A similar mechanism has been proposed for the formation of the pyrimido[4,5-*c*]pyridazine ring system. T. Mujamoto, Y. Koshitaka, J. Matsumoto and S. Minami, *Chem. Pharm. Bull.*, **26**, 14 (1978).

[7] The two esters **9** and **10** were hydrolyzed to their corresponding acids **14** and **15** for further confirmation of structure. The procedure along with physical and spectral characteristics are included in the experimental.