Synthesis of 7-Ethyl-4,7-dihydro-4-oxo-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylic Acid

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7-Ethyl-4,7-dihydro-4-oxo-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylic acid (**4**), an analog of nalidixic acid, was synthesized in seven steps starting from commercially available 4-methylpyridine. Bacterial susceptibility to compound **4** was tested and the title compound was found to exhibit only weak antibacterial activity against a variety of pathogens including *S. Aureus, E. Coli* and *P. Aeruginosa.*

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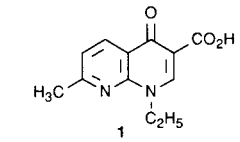
Introduction.

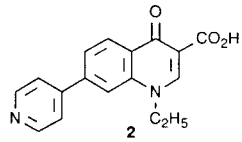
The quinolones have become one of the most promising group of antibacterial drugs in the history of antiinfective agents. Nalidixic acid (**1**) [1], the first prototypic "quinolone" [2] introduced into therapy in 1963 for the treatment of urinary infections, demonstrated activity against gram negative bacteria, but lacked substantial gram positive activity [1]. Since the introduction of **1**, numerous agents have emerged with potent broad spectrum activity and oral efficacy [3a,b]. Many of these newer agents are derived from either a quinolone or 1,8-naphthyridine nucleus.

With the objective of identifying a compound possessing a broader spectrum of activity than nalidixic acid, we synthesized the title compound **4**, which was veiwed as an analog of **1** and a related compound, rosoxacin **2**. Rosoxacin, the first quinolone proposed for the treatment of systemic infections, demonstrated activity against both gram negative and gram positive bacteria and is marketed for the treatment of gonorrhea [4]. Compound **4** is structurally related to the known antimicrobial thiophene **3**, an analog of nalidixic acid reported to have a similar antibacterial profile of activity [5].



1

Nalidixic Acid



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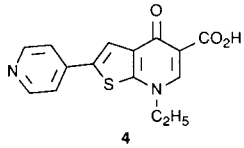
Rosoxacin



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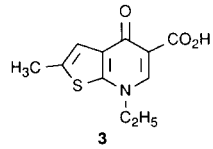

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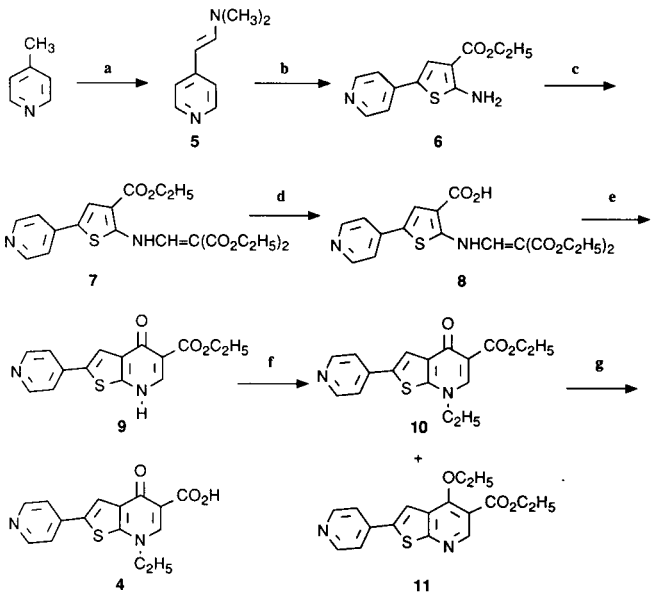
Chemistry.

The synthesis of compound **4** was accomplished by the seven step sequence depicted in Scheme 1. Treatment of 4-methylpyridine with Brederick's reagent (bis-dimethylamino-*tert*-butyloxymethane) [6] in refluxing dimethylformamide gave 4-(2-dimethylaminovinyl)pyridine (**5**) in 98% yield. Compound **5**, a surrogate for the unstable and very reactive 4-pyridylacetaldehyde, was cleanly converted to the desired thiophene **6** in 82% yield using the procedure developed by Gewald [7]. This versatile procedure provides ready access to alkyl and aryl substituted 2-aminothiophenes by the base catalyzed condensation of the appropriate aldehyde or ketone with ethyl cyanoacetate and elemental sulfur. Condensation of thiophene **6** with diethylethoxymethylenemalonate (EMME) at 140-160° afforded the aminomethylenemalonate derivative **7** in 58% yield. Thiophenecarboxylic acid **8** was obtained in 37% yield by selective saponification of triester **7** following the procedure reported by Kuwada and co-workers [8]. Synthesis of the thieno[2,3-*b*]pyridine nucleus was accomplished

SCHEME 1



Reagents:

a) $((CH_3)_2N)_2CHOC(CH_3)_3$, Δ (98%) b) S_8, ethyl cyanoacetate, morpholine, Δ (82%)

c) diethylethoxymethylenemalonate, Δ (58%) d) i. 10% KOH-EtOH; ii. aq. HCl (37%)

e) Dowtherm, Δ (65%) f) ethyl tosylate, K_2CO_3, DMF, Δ (46%) g) i. aq. NaOH, Δ; ii. HOAc (89%)

by the Gould-Jacobs reaction [9]; *i.e.* thermal cyclization of **8** in Dowtherm A at 250° gave thienopyridonecarboxylate **9** in 65% yield. Treatment of **9** with ethyl tosylate and potassium carbonate in dimethylformamide afforded the *N*-ethyl derivative **10** in 46% yield accompanied by the corresponding *O*-alkylated isomer **11**. Subsequent saponification of ethyl ester **10** gave the title compound **4** in 89% yield.

Microbiology Results.

Compound **4** displayed weak antibacterial activity compared to nalidixic acid (**1**), rosoxacin (**2**) and the related thienopyridine **3** when tested both *in vitro* and *in vivo* against a variety of gram negative and gram positive organisms.

EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The ^{1}H-nmr spectra were determined on a Varian HA-100 spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane as the internal standard. Infrared spectra (ir) were obtained on a Perkin-Elmer 457 spectrophotometer. Mass spectra (ms) were determined with a JEOL 01SC mass spectrometer.

4-(2-Dimethylaminovinyl)pyridine (**5**).

A solution of 4-methylpyridine (10.0 ml, 0.1 mole) and bis-dimethylamino-*tert*-butyloxymethane (25 ml, 0.12 mole) in dimethylformamide (25 ml) was heated at reflux for 12 hours under a nitrogen atmosphere and then concentrated under vacuum to give a tan solid. The product was recrystallized from cyclohexane to give 14.4 g (98%) of light yellow crystals: mp 101-102.5° (literature mp 100-102° [6]); ms: m/z 148 (M^+); ^{1}H nmr (deuteriochloroform): δ 2.83 (s, 6H, $N(CH_3)_2$), 4.99 (d, J = 13 Hz, 1H, $=CHN(CH_3)_2$), 7.0 (m, 3H, pyridine A_2B_2 + CH=C-N), 8.24 (d, J = 6 Hz, 2H, pyridine A_2B_2).

Ethyl 2-Amino-5-(4-pyridinyl)thiophene-3-carboxylate (**6**).

A solution of enamine **5** (28.19 g, 0.19 mole), ethyl cyanoacetate (21.55 g, 0.19 mole), sulfur (32.06 g, 0.19 mole) and morpholine (5 ml) in absolute ethanol (250 ml) was heated at 80-85° under a nitrogen atmosphere for 3 hours and then chilled in ice. The resulting crystals were collected, washed with hexane, and dried to give 38.55 g (82%) of **6**, mp 171.5-173°; ms: m/z 248 (M^+); ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 1.38 (t, 3H, CH_3), 4.31 (q, 2H, OCH_2), 7.28 (d, J = 6 Hz, 2H, pyridine A_2B_2), 7.5 (br s, 3H, NH_2 + thiophene-H), 8.44 (d, J = 6 Hz, 2H, pyridine A_2B_2).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 57.98; H, 4.92; N, 11.11; S, 12.94.

Diethyl [[[3-(Ethoxycarbonyl)-5-(4-pyridinyl)-2-thienyl]amino]methylene]propanedioate (**7**).

A mixture of aminothiophene **6** (3.0 g, 0.012 mole) and diethyl ethoxymethylenemalonate (2.62 g, 0.012 mole) was heated in an oil bath at 140-160° for 2 hours at atmospheric pressure and then under water aspirator pressure for 1 hour. After cooling, the resulting solid was recrystallized from hexane to give 2.9 g (58%) of **7**, mp 131-133°; ms: m/z 418 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.42 (m, 9H, CH_3 x 3), 4.40 (m, 6H, OCH_2 x 3), 7.34 (d, J = 6 Hz, 2H, pyridine A_2B_2), 7.58 (s, 1H, thiophene-H), 8.08 (d, J = 12 Hz, 1H, -CH=C), 8.56 (d, J = 6 Hz, 2H, A_2B_2), 12.57 (d, J = 12 Hz, 1H, NH).

Anal. Calcd. for $C_{20}H_{22}N_2O_6S$: C, 57.41; H, 5.30; N, 6.69; S, 7.66. Found: C, 57.41; H, 5.31; N, 6.78; S, 7.82.

Diethyl [[[3-Carboxy-5-(4-pyridinyl)-2-thienyl]amino]methylene]-propanedioate (**8**).

To a stirred refluxing solution of triester **7** (4.9 g, 0.012 mole) in ethanol (150 ml), was added hot 10% ethanolic potassium hydroxide (150 ml), and the reaction mixture was refluxed for 30 minutes. The resulting precipitated solid changed color from red-violet to orange. The mixture was then stirred at room temperature for 4 hours and the precipitate was collected by filtration. The solid was taken up in dilute aqueous hydrochloric acid, followed by addtion of concentrated aqueous ammonium hydroxide. Crude **8** was then precipitated from the aqueous solution by the addition of acetic acid and recrystallized from ethanol to give 1.68 g (37%) of product, mp 250-255°. The analytical sample melted at 254-256° (ethanol); ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.50 (t, 6H, CH_3), 4.56 (m, 4H, OCH_2), 8.15 (d, J = 6 Hz, 2H, pyridine A_2B_2), 8.34 (s, 1H, CH=C), 8.46 (s, 1H, thiophene-H), 8.74 (d, J = 6 Hz, 2H, pyridine A_2B_2), 11.90 (s, 2H, exchangeable H).

Anal. Calcd. for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.38; H, 4.74; N, 7.21.

Ethyl 4,7-Dihydro-4-oxo-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylate (**9**).

Compound **8** (6.0 g, 0.015 mole) was added to refluxing Dowtherm A (300 ml) and heating was continued for 30 minutes followed by cooling to room temperature. An insoluble residue was removed by filtration and *n*-hexane (3000 ml) was added to the filtrate to precipitate the crude product. The precipitate was collected to give 3.0 g (65%) of product which was recrystallized from ethyl acetate affording 2.5 g of pure **9**, mp 250-253° dec; ms: m/z 300 (M^+). A second crop of 0.4 g, mp 240-246° dec was also obtained. The analytical sample, prepared similarly, had mp 246-250° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, CH_3), 4.78 (q, 2H, OCH_2), 8.50 (d, J = 6 Hz, 2H, pyridine A_2B_2), 8.62 (s, 1H, thiophene-H), 8.98 (d, J = 6 Hz, 2H, pyridine A_2B_2), 9.28 (s, 1H, N=CH-), 12.02 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 59.97; H, 4.07; N, 9.39.

Ethyl 7-Ethyl-4,7-dihydro-4-oxo-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylate (**10**).

To a stirred solution of **9** (6.25 g, 0.021 mole) in dry dimethylformamide (61 ml) was added milled potassium carbonate (4.5 g, 0.033 mole). The mixture was heated at 75-80° and a solution of ethyl tosylate (5.7 g, 0.029 mole) in dimethylformamide (15 ml) was added over a period of 45 minutes. The mixture was heated at this temperature for 4 hours, cooled to room temperature and then filtered to remove insoluble salts. The filtrate was evaporated under vacuum leaving a residue which was then partitioned between water and chloroform. The chloroform layer was washed with brine, dried (anhydrous sodium sulfate) and evaporated leaving 6.4 g of crude product.

Thin layer chromatographic analysis (30% methanol in ethyl acetate, silica) indicated two components in approximately equal amounts.

The crude product was extracted with ethyl acetate affording 3.11 g (46%) of **10**, the more polar component. Recrystallization from ethyl acetate afforded 2.19 g of **10**, mp 262-267°; ms: m/z 328 (M^+); ^1H nmr (deuteriotrifluoroacetic acid): δ 1.55 (t, 3H, CH_3), 1.90 (t, 3H, CH_3), 4.80 (m, 4H, CH_2 x 2), 8.49 (d, J = 6 Hz, 2H, pyridine A_2B_2), 8.65 (s, 1H, thiophene-H), 8.98 (d, J = 2 Hz, 2H, pyridine A_2B_2), 9.28 (s, 1H, -N-CH=C). This material was directly converted to the title compound **4**, in the next experiment.

Crystallization (ether-cyclohexane) of the mother liquors containing the less polar component afforded ethyl 4-ethoxy-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylate (**11**), mp 116-119°; ms: m/z 328 (M^+); ^1H nmr (deuteriotrifluoroacetic acid): δ 1.58 (t, 3H, CH_3), 1.75 (t, 3H, CH_3), 4.67 (q, 2H, CH_2), 5.13 (q, 2H, CH_2), 8.49 (d, J = 6 Hz, 2H, pyridine A_2B_2), 8.72 (s, 1H, thiophene-H), 8.97 (d, J = 6 Hz, 2H, pyridine A_2B_2), 9.25 (s, 1H, N=CH); ir (potassium bromide): ν 1703 cm^{-1} ($CO_2C_2H_5$).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 62.17; H, 4.89; N, 8.48.

7-Ethyl-4,7-dihydro-4-oxo-2-(4-pyridinyl)thieno[2,3-*b*]pyridine-5-carboxylic Acid (**4**).

A suspension of **10** (3.0 g, 0.009 mole) in water (100 ml) was treated with sodium hydroxide (0.73 g, 0.0183 mole) and heated on a steam bath for 1 hour. The solution was cooled, treated with charcoal, and the filtrate was acidified with acetic acid to precipitate the crude carboxylic acid. Recrystallization from dimethylformamide gave 2.37 g (89%) of **4**, mp 315-316° dec; ^1H nmr (deuteriotrifluoroacetic acid): δ 1.92 (t, 3H, CH_3), 4.90 (q, 2H, CH_2), 8.50 (d, J = 6 Hz, 2H, pyridine A_2B_2), 8.68 (s, 1H, thiophene-H), 9.00 (d, J = 6 Hz, 2H, pyridine A_2B_2), 9.38 (s, 1H, N-CH=C), 12.2 (br s exchangeable H); ir (potassium bromide): ν 1600 cm^{-1} (C=O), 1720 cm^{-1} (COOH), 3440 cm^{-1} (COOH).

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33. Found: C, 60.00; H, 4.10; N, 9.37.

Acknowledgement.

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