Notes

New Quinolones(I); Synthesis of New Pyrido [3, 2-h] quinoline Derivatives and Their Antibacterial Activities

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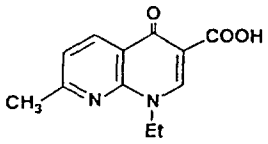
Since nalidixic acid(1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid) (**1**)[1] was developed as an antibacterial, for the treatment of urinary tract infections, many quinolones have been developed and reviewed[2-4].

Summarizing these known quinolone antibacterials, nalidixic acid[1], oxolinic acid[5], ciprofloxacin[6], and norfloxacin[7] are naphthyridine derivatives, pipemidic acid[8] and piromidic acid[9,10] are pyrimidopyridine derivatives, and cinoxacin[11] is cinnoline derivative. The "fluoro quinolones" so called "the third generation" are mostly naphthyridine or quinoline derivatives.

Considering that the benzopurine nucleoside, which has a benzene moiety between A ring and B ring of purine base, showed no difference in biological activities from purine nucleoside[13,14], it would be interesting to see whether or not pyridoquinoline derivatives, which can be formed *via* the insertion of benzene between A ring and B ring of naphthyridine, would show the same biological activities as nalidixic acid if the proper functional groups are chosen. Here we would like to report the results of our preliminary model study.



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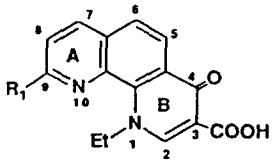
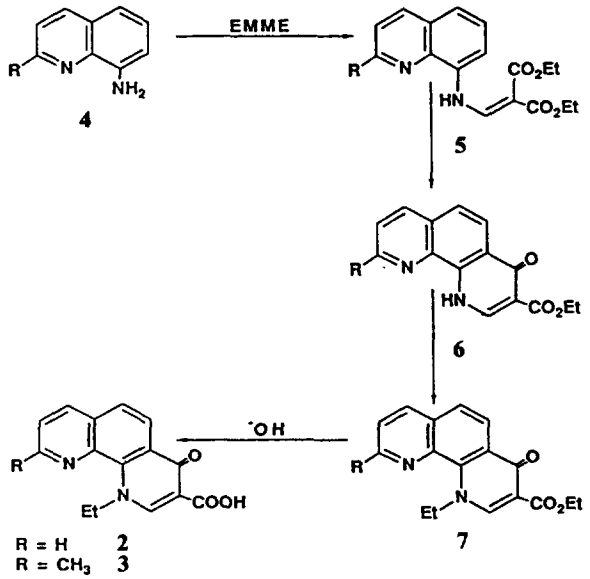


R_1 = H **2**
R_1 = CH_3 **3**

1-Ethyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylic acid (**2**), and 1-ethyl-9-methyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylic acid (**3**), were chosen as model compounds, since they are considered to have the same aromatic molecular flatness, and the same essential moieties of 4-oxo-3-carboxylic acid and 1-ethyl groups as nalidixic acid. If these model compounds show the similar biological activities to nalidixic acid, new various potential quinolone antibacterial compounds can be designed and tested their biological activities *in vitro*. The model compounds **2** and **3** were synthesized by the similar method to the synthesis of nalidixic acid (**1**) (Scheme 1).

This method is one of the known general methods to prepare the quinolone antibacterials[1,5-10].



R = H **2**
R = CH_3 **3**

Scheme 1.

Table 1. MIC Test (μg/ml)

	Strains	ATCC	Control Compd. (Nal. A)	Compd. (2)	Compd. (3)
Gram (+)	*Bacillus subtilis*	6633	128	64	16
	Staphylococcus aureus	65389	32	8	64
	Micrococcus luteus	9341	8	32	16
Gram (−)	*Klebsiella pneumonia*	10031	256	512	512
	Salmonella typhimurium	14028	4	8	512
	Pseudomonas aeruginosa	27853	4	4	16
	Enterobacter aerogenes	29751	2	16	512
	Escherichia coli	31030	4	8	512

8-Aminoquinoline (**4**, R=H) and 2-methyl-8-aminoquinoline (**4**, R=CH_3) were purchased from Aldrich Chemical Co. The 8-aminoquinoline was reacted with diethyl ethoxymethylenemalonate (EMME) to give diethyl N-(8-quinolinyl)-aminomethylenemalonate (**5**, R=H) without any difficulties. Compound **5** (R=H) was cyclized thermally to ethyl pyrido [3,2-h]-4-quinolone-3-carboxylate (**6**, R=H).

Compound **6** (R=H) was ethylated with ethyliodide in DMF under the base of K_2CO_3 to be ethyl 1-ethyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylate (**7**, R=H). Compound **7** (R=H) was sucessfully hydrolyzed with 1 N aqueous NaOH solution to be 1-ethyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylic acid (**2**). The other compound **3**, **5** (R=CH_3), **6** (R=CH_3) and **7** (R=CH_3) were synthesized similarly.

As shown in Table 1, the biological test results[15,16] showed comparable activities to nalidixic acid (control test) for both gram positive and gram negatives, which necessitate further synthesis of various related compounds, and evaluation of their biological activities.

Experimental

Pmr and mass spectra were measured by Varian EM-360, General Electric QE 300 and Shimadzu GC MS-QP1000A respectively. IR Spectra were measured by JASCO-810. Elemental analysis was done by Carlo Erba Strumetazione MOD-1106.

Diethyl N-(8-quinolinyl)-amino methylenemalonate (5: R=H). A mixture of 8-aminoquinoline (1 g, 0.007 mol) and diethyl ethoxy methylenemalonate (EMME) (1.5 m*l*, 0.007 mol) was heated at 70℃ for 2 hrs while stirring, to yield pale yellow crystal product. This product was recrystalized from ethanol, yielding 2.02 g of pure product **5** (R=H) (yield: 92%, mp. 98-99℃). Its IR(KBr) spectrum showed 1705 cm^{-1} for ester peak; ^{1}H-NMR ($CDCl_3$) δ 12.0 (d, 1H, NH), 8.7-7.5 (m, 6H, Ar-H), 8.6 (d, 1H, CH), 4.3-4.1 (m, 4H, $2CH_2$), 1.4-1.2 (m, 6H, $2CH_3$); ms: *m/e*(relative intensity) 314 (M^+, 22). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.91. Found: S, 64.59; H, 5.74; N, 8.75.

Ethyl 4-oxo-pyrido [3,2-h] quinoline-3-carboxylate (6: R=H). Compound **5** (R=H) (2 g, 0.0064 mol) was suspended in 10 m*l* of diphenylether and refluxed at 250℃ for 2 hrs. After finishing the reaction, the reaction mixture was cooled to room temperature and the product was crystallized out. After filtering, the crystal product was washed two~three times with pet. ether (low boiling) and recrystallized from DMF, yielding 1.4 g of pure product **6** (R=H) (yield: 80%, mp. 278-280℃). IR (KBr) showed 1620 cm^{-1} for ester absorption; ^{1}H-NMR (DMSO-d_6) δ 12.5 (d, 1H, NH), 9.1-7.8 (m, 5H, Ar-H), 8.6 (d, 1H, CH), 4.2 (q, 2H, CH_2), 1.2 (t, 3H, CH_3); ms: *m/e* (relative intensity) 268 (m^+, 26). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.48; N, 10.45. Found: C, 67.13; H, 4.55; N, 10.49.

Ethyl 1-ethyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylate (7: R=H). The mixture of 270 mg (0.001 mol) of compound **6** (R=H), 0.4 m*l* (0.005 mol) of ethyl iodide and 0.41 g (0.003 mol) of anhydrous K_2CO_3 in 30 m*l* of DMF was heated at 100℃ while stirring. After finishing the reaction, DMF solvent was evaporated under rotary evaporator. The residue was dissolved in water and extracted $CHCl_3$. The $CHCl_3$ solution was dried with anhydrous $MgSO_4$ and evaporated to dryness under rotary evaporator after filtering the $MgSO_4$. The product was purified by silicagel column chromatography with eluent of ethyl acetate and ethanol. (yield: 42%, mp. 189-190℃); ^{1}H-NMR ($CDCl_3$) δ 9.1-7.5 (m, 5H, Ar-H), 8.6 (s, 1H, CH), 5.5 (q, 2H, N-CH_2), 4.5 (q, 2H, CO_2CH_2), 1.5-1.2 (m, 6H, $2CH_3$); ms: *m/e* (relative intensity) 296 (M^+, 19) Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 68.85; H, 5.42; N, 9.42.

1-Ethyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylic acid (2). Compound **7** (R=H) (0.296 g, 0.001 mol) was dissolved in 30 m*l* of 10% NaOH solution and heated under steam bath for 1 hr. When reaction mixture was cooled to room temperature and neutralized with acetic acid, white crystal was obtained. The product was reacrystallized from ethanol, yielding 0.215 g (0.0008 mol) of pure product. (yield: 80%, mp. 226-228℃). IR (KBr) have 1715 cm^{-1} and 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 9.1-7.6 (m, 6H, Ar-H), 5.5 (q, 2H, CH_2), 1.7 (t, 3H, CH_3); ms: *m/e* (relative intensity) 268 (M^+, 0.8). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.48; N, 10.45. Found: C, 67.34; N, 4.46; N, 10.12.

Diethyl N-(2-methyl-8-quinolinyl)aminomethylenemalonate (5: R=CH_3). A mixture of 2-methyl-8-aminoquinoline (1 g, 0.006 mol) and diethyl ethoxymethylenemalonate(EMME) (1.3 m*l*, 0.006 mol) was heated at 80℃ for 2 hrs with stirring. After cooling, the resulting yellow solid was filtered and recrystallized from ethanol to give 1.77 g of pure product **5** (R=CH_3) (yield: 90%, mp. 152-154℃); ^{1}H-NMR ($CDCl_3$) δ 12.0 (d, 1H, NH), 8.7-7.5 (m, 5H, Ar-H), 8.6 (d, 1H, CH), 4.3-4.1 (m, 4H, $2CH_2$), 2.8 (s, 3H, CH_3), 1.4-1.2 (m, 6H, $2CH_3$); ms: *m/e* (relative intensity) 328 (M^+, 52). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.85; H, 6.10; N, 8.54. Found: C, 65.72; H, 6.30; N, 8.32.

Ethyl 9-methyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylate (6: R=CH_3). Compound **5** (R=CH_3) (1.5 g, 0.0046 mol) was suspended in 15 m*l* of diphenyl ether and refluxed at 250℃ for 2 hrs. Then the reaction mixture was cooled to room temperature, the resulting solid was filtered and washed two~three times with pet. ether (low boiling) and recrystallized from DMF to give 1.04 g of pure product **6** (R=CH_3) (yield: 80%, mp. 260-262℃). ^{1}H-NMR (DMSO-d_6) δ 12.5 (d, 1H, NH), 8.6 (d, 1H, CH), 8.5-7.6 (m, 4H, Ar-H), 4.3 (q, 2H, CH_2), 2.8 (s, 3H, CH_3), 1.3 (t, 3H, CH_3); ms: *m/e* (relative intensity) 282 (M^+, 18). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.09; H, 4.96; N, 9.93. Found: C, 68.82; H, 5.02; N, 10.06.

Ethyl 1-ethyl-9-methyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylate (7: R=CH_3). The mixture of 0.5 g (0.0018 mol) of compound **6** (R=CH_3), 0.72 m*l* (0.009 mol) of ethyl iodide and 0.74 g (0.0054 mol) of anhydrous K_2CO_3 in 30 m*l* of DMF was heated at 100℃ with stirring. After finishing the reaction, DMF solvent was evaporated under rotary evaporator. The residue was dissolved in water and extracted $CHCl_3$. The $CHCl_3$ solution was dried with anhydrous $MgSO_4$ and evaporated to dryness under rotary evaporator after filtering the $MgSO_4$. The product was purified by Silicagel-column chromatography with eluent of ethyl acetate and ethanol (yield: 48%, mp. 200-202℃). ^{1}H-NMR ($CDCl_3$) δ 8.7-7.5 (m, 4H, Ar-H), 8.6 (s, 1H, CH), 5.3 (q, 2H, N-CH_2), 4.3 (q, 2H, CO_2CH_2), 2.8 (s, 3H, CH_3), 1.5-1.2 (m, 6H, $2CH_3$); ms: *m/e* (relative intensity) 310 (M^+, 25). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.36; H, 5.83; N, 8.80.

1-Ethyl-9-methyl-4-oxo-pyrido [3,2-h] quinoline-3-carboxylic acid (3). Compound **7** (R=CH_3) (0.3 g, 0.001 mol) was dissolved in 30 m*l* of 10% NaOH solution and heated under steam bath for 1 hr. When reaction mixture was cooled to room temperature and neutralized with acetic acid, white crystal was obtained. The product was recrystallized from ethanol, yielding 0.2 g (0.0007 mol) of pure product. (yield: 70%, mp. 232-234℃). ^{1}H-NMR ($CDCl_3$) δ 9-7.7 (m, 5H, Ar-H), 5.5 (q, 2H, CH_2), 2.8 (s, 3H, CH_3), 1.5 (t, 3H, CH_3); ms: *m/e* (relative intensity) 282 (M^+, 18). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.09; H, 4.96; N, 9.93. Found: C, 68.53; H, 5.18; N, 9.91.

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