Short Syntheses of 1,2,3,5-Tetrahydro-5-oxopyrrolo-[1,2-*a*]quinoline-4-carboxylic Acid and 1,2,3,4-Tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic Acid Derivatives

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Short and efficient syntheses of 7-fluoro-8-(4-methylpiperazin-1-yl)-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]-quinoline-4-carboxylic acid and 8-fluoro-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]-quinoline-5-carboxylic acid are described. Both basic heterocycles were synthesized in two steps by the condensation of a benzoylacetate with an imino ether followed by an intramolecular nucleophilic displacement cyclization reaction.

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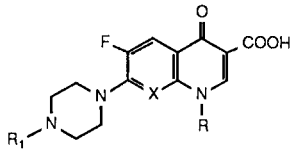
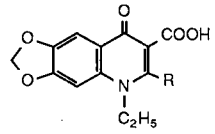
Recently, many potent clinically important antibacterials having a 1-substituted-1,4-dihydro-4-oxopyridine-3-carboxylic moiety, collectively known as quinolone, have been discovered. These agents include Norfloxacin **1** [1], Pefloxacin **2** [2], Ofloxacin **3** [3], Ciprofloxacin **4** [4], Enoxacin **5** [5] and Difloxacin **6** [6]. The structure-activity relationship of quinolones has been reviewed [7].



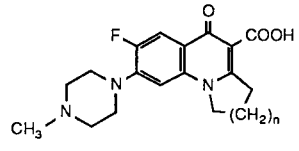
1 R = C_2H_5, R_1 = H, X = CH
2 R = C_2H_5, R_1 = CH_3, X = CH
3 X, R = $COCH_2CH(CH_3)$, R_1 = CH_3
4 R = C_3H_5, R_1 = H, X = CH
5 R = C_2H_5, R_1 = H, X = N
6 R = *p*-C_6H_4F, R_1 = H, X = CH

Structure-activity investigations have shown that substitution of the C-2 position lead to inactive compounds. For example, compounds **7** and **8** having a C-2 position substituted by a hydroxyl or methyl group respectively are inactive [8]. 5-Oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acid derivative **9**, however, has recently been reported to have good antibacterial activity [9]. Compound **9** has a thiazoline moiety which connects the C-2 substituent to the N-1 position. This led us to speculate that biological activity might also be retained if the C-2 and N-1 positions were bridged by an alkylene chain. In this paper, we would like to report our short and efficient syntheses and antimicrobial evaluations of 7-fluoro-8-(4-methylpiperazin-1-yl)-1,2,3,5-tetrahydro-5-oxopyrrolo-[1,2-*a*]quinoline-4-carboxylic acid (**10**) and 8-fluoro-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-6*H*-6-oxopyrido-[1,2-*a*]quinoline-5-carboxylic acid (**11**). Compound **10** is a carbabioisostere of **9** in which the sulfur atom is replaced by a carbon atom.



7 R = OH
8 R = CH_3

9

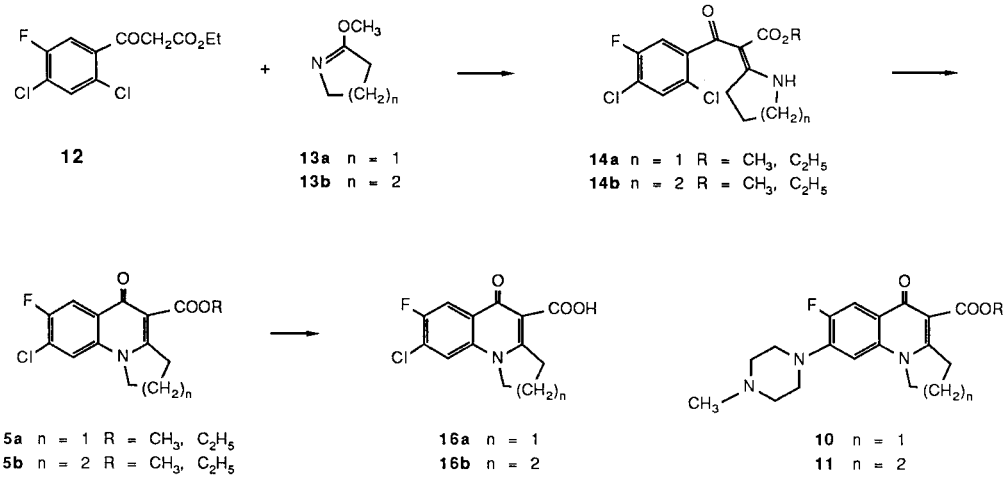


10 n = 1
11 n = 2

Compounds **10** and **11** represent new types of heterocyclic systems and were synthesized by an intramolecular nucleophilic displacement cyclization reaction (Scheme I), a process that had been successfully applied to the syntheses of Amifloxacin [10] and 1-arylquinolones [6]. The desired heterocyclic skeletons were synthesized in two synthetic steps.

Condensation of ethyl 2,4-dichloro-5-fluorobenzoylacetate (**12**) [10] with 2-methoxy-1-pyrroline (**13a**) in the presence of triethylamine at 65° yielded a mixture of ethyl and methyl 2-(2,4-dichloro-5-fluorobenzoyl)-2-(2-pyrrolidylidene)acetate (**14a**) in approximately 2:1 ratio. The nmr spectrum showed the presence of a triplet at δ 0.76 (corresponding to the ethyl-CH_3 protons) and a singlet at δ 3.37 (corresponding to the methyl protons). The ratio of the intensity of these two signals was about 2:1. Since the synthetic target compounds are the acids, the two esters were not separated and were used for further transformation. It is important to mention here that the reaction temperature is very critical. At higher reaction temperature, a substantial amount of compound **13a** rearranges to

Scheme I



N-methyl-2-pyrrolidinone. The use of sodium hydride to generate the enolate did not yield the desired product having methyl alkylation as the side reaction with 2-methoxy-1-pyrroline served as alkylating agent. Similar condensation of the acetate **12** with 2-methoxy-3,4,5,6-tetrahydropyridine (**13b**) at 80° yielded a mixture of ethyl and methyl 2-(2,4-dichloro-5-fluorobenzoyl)-2-(2-piperidylidene)acetate (**14b**) in approximately 2:1 ratio.

Regiospecific intramolecular cyclization of **14a** or **14b** with 1 molar equivalent of sodium hydride at 70° yielded a mixture of ethyl and methyl 7-fluoro-8-chloro-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylate (**15a**) or 8-fluoro-9-chloro-1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]-quinoline-5-carboxylate (**15b**). Hydrolysis of these mixtures with sodium hydroxide in tetrahydrofuran gave the 1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**16a**) and 1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic acid (**16b**) (mp 239°).

Displacement of **16a** or **16b** with an excess of 4-methylpiperazine in *N*-methylpyrrolidinone at 100° yielded 7-fluoro-8-(4-methylpiperazin-1-yl)-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**10**) and 8-fluoro-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic acid (**11**). These two compounds were converted to the hydrochloride salts upon treatment with dilute hydrochloric acid. These two compounds were tested for antibacterial activity and were found to be antibacterial agents. Compound **10** was found to have a MIC [11] of 0.78 μg/ml when tested against *Staphylococcus aureus* CMX686B and 1.56 μg/ml against *Escherichia coli* Juhl. Compound **11** was found to be substantially less active.

In summary, we have discovered an efficient synthetic route to 1,2,3,5-tetrahydro-5-oxopyrido[1,2-*a*]quinoline-4-carboxylic acid and 1,2,3,4-tetrahydro-6*H*-6-oxopyrido-[1,2-*a*]quinoline-5-carboxylic acid *via* an intramolecular nucleophilic displacement cyclization reaction. Both basic heterocycles were synthesized in two steps.

EXPERIMENTAL

Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were obtained for all new compounds reported. Carbon, hydrogen, and nitrogen analyses (unless otherwise specified) were ±0.4% of the theoretical values. Microanalyses were performed by the Abbott analytical department. The nmr spectra were obtained on a Varian T-60 and a General Electric GN-300 spectrometers using tetramethylsilane as an internal standard. The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; b, broad. Mass spectra were recorded on a Hewlitt Packard 5985A mass spectrometer. The ir spectra were recorded on a Perkin-Elmer 683 infrared grating spectrometer or a Nicolet 605x FT-IR. The ir, nmr and ms data of all compounds were consistent with the assigned structures. Solutions were dried over magnesium sulphate.

Ethyl and Methyl 2-(2,4-Dichloro-5-fluorobenzoyl)-2-(2-pyrrolidylidene)-acetate (**14a**).

A solution of ethyl 2,4-dichloro-5-fluorobenzoylacetate (**12**) [10] (14 g, 50.2 mmoles) in triethylamine (7 ml, 50.3 mmoles) and 2-methoxy-1-pyrroline (**13a**) (8.5 g, 85.9 mmoles) was heated under nitrogen atmosphere at 65° for 48 hours. The mixture was evaporated under reduced pressure to give an oil. Purification on silica gel column using 1% ethyl acetate in methylene chloride as eluent yielded a mixture of ethyl and methyl acetate (**14a**) (14 g, 80%) in 2:1 ratio; ^{1}H nmr (deuteriochloroform): δ (2 sets of signals) 0.76 (t, J = 7.5 Hz, 3, ethyl CH_3), 2.03 (m, 2, CH_2), 3.22 (dd, J = 7 Hz, 2, N-CH_2), 3.37 (s, 3, CH_3), 3.68 (dd, J = 7 Hz, 2, vinyl CH_2), 3.87 (q, J = 7.5 Hz, 2, ethyl CH_2), 7.0 (d, $J_{H\text{-}F}$ = 9 Hz, 1, aromatic H), 7.40 (d, $J_{H\text{-}F}$ = 6 Hz, 1, aromatic H), 11.70 (bs, 1, NH).

By using the above procedure, using 2-methoxy-3,4,5,6-tetrahydropyridine instead of **13a** and heating the mixture at 80°, a mixture of ethyl and methyl 2-(2,4-dichloro-5-fluorobenzoyl)-2-(2-piperidylidine)-acetate (**14a**) was prepared in 2:1 ratio in 63% yield; ^{1}H nmr (deuteriochloroform): δ (2 sets of signals) 0.75 (t, J = 7.5 Hz, 3, ethyl CH_3), 1.80 (m, 4, CH_2CH_2), 2.93 (m, 2, NCH_2), 3.33 (s, 3, CH_3), 3.53 (m, 2, vinyl CH_2), 3.87 (q, J = 7.5 Hz, 2, ethyl CH_2), 7.05 (d, $J_{H\text{-}F}$ = 9 Hz, 1, aromatic H),

7.43 (d, J_{H-F} = 6 Hz, 1, aromatic H), 12.90 (bs, 1, NH).

Ethyl and Methyl 8-fluoro-9-chloro-1,2,3,4-tetrahydro-6*H*-6-oxopyrido-[1,2-*a*]quinoline-5-carboxylate (**15b**).

To a cold solution of ethyl and methyl 2-(2,4-dichloro-5-flurobenzoyl)-2-(2-piperidylidene)acetate (16 g, 44.4 mmoles) in tetrahydrofuran (350 ml) under nitrogen atmosphere was slowly added a 60% sodium hydride-in-oil suspension (3.52 g, 87.7 mmoles). The mixture was heated at 75° for 2.5 hours. The mixture was cooled and acetic acid (8 ml) was then added in slowly. The mixture was evaporated under reduced pressure to nearly dryness. The residue was dissolved in methylene chloride (600 ml). The solution was extracted with saturated sodium chloride solution (300 ml). The organic portion was separated and dried and evaporated to dryness. The residue was purified through dry silica gel column using 30% ethyl acetate in methylene chloride as eluent yielding 2.3 g of the ethyl ester of **15b** (A), mp 185°, 1.5 g of the methyl ester of **15b** (B), mp 158° and 5.2 g of ethyl and methyl mixture with a total yield of 64%.

Compound **A** had ^{1}H nmr (deuteriochloroform): δ 1.30 (t, J = 7 Hz, 3, ethyl CH_3), 1.97 (m, 4, CH_2CH_2), 2.95 (dd, J = 6 Hz, 2, N-CH_2), 4.04 (dd, J = 6 Hz, 2, vinyl CH_2), 4.38 (q, J = 7 Hz, 2, ethyl CH_2), 7.60 (d, J_{H-F} = 5 Hz, 1, aromatic H), 8.05 (d, H_{H-F} = 9 Hz, 1, aromatic H).

Anal. Calcd. for $C_{16}H_{15}ClFNO_3$: C, 59.35; H, 4.64; N, 4.33. Found C, 58.97; H, 4.74; N, 4.19.

Compound **B** had ^{1}H nmr (deuteriochloroform): δ 1.98 (m, 4, CH_2CH_2), 2.95 (dd, J = 6 Hz, 2, N-CH_2), 3.09 (s, 3, CH_2), 4.05 (dd, J = 6 Hz, 2, vinyl CH_2), 7.63 (d, J_{H-F} = 5 Hz, 1, aromatic H), 8.07 (d, J_{H-F} = 9 Hz, 1, aromatic H).

Anal. Calcd. for $C_{15}H_{13}ClFNO_3$: C, 58.16; H, 4.20; N, 4.52. Found: C, 57.90; H, 4.26; N, 4.34.

By using a similar procedure, a mixture of ethyl and methyl 7-fluoro-8-chloro-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylate (**15a**) was prepared in 2:1 ratio; ^{1}H nmr (deuteriochloroform): δ (2 sets of signals) 1.20 (t, J = 7 Hz, 3, ethyl CH_3), 2.37 (m, 2, CH_2), 3.57 (dd, J = 7.5 Hz, 2, N-CH_2), 3.90 (s, 3, CH_3), 4.18 (dd, J = 7.5 Hz, 2, vinyl CH_2), 4.36 (q, J = 7 Hz, 2, ethyl CH_2), 7.3 (d, J_{H-F} = 6 Hz, 1, aromatic H), 8.08 (d, J_{H-F} = 9 Hz, 1, aromatic H).

8-Fluoro-9-chloro-1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic Acid (**16b**).

To a solution of **15b** (4.4 g, 13.6 mmoles) in tetrahydrofuran (100 ml) at 75° was added a 1 *N* sodium hydroxide solution (34 ml, 34 mmoles). After heating at 75° for 16 hours the solution was evaporated under reduced pressure to dryness. The residue was dissolved in 350 ml of water. The solution was acidified with acetic acid (4 ml) yielding a precipitate. The solid was filtered and washed with water and dried yielding the carboxylic acid **16b** (3.2 g, 80%), mp 239° dec; ^{1}H nmr (DMSO-d_6): δ 2.25 (m, 2, CH_2), 3.65 (dd, J = 7.5 Hz, 2, N-CH_2), 4.48 (dd, J = 7.5 Hz, 2, vinyl CH_2), 8.02 (d, J_{H-F} = 9 Hz, 1, aromatic H), 8.15 (d, J_{H-F} = 6 Hz, 1, aromatic H).

Anal. Calcd. for $C_{14}H_{11}ClFNO_3 \cdot \frac{1}{4}H_2O$: C, 56.00; H, 3.83; N, 4.67. Found: C, 55.82; H, 3.71; N, 4.44.

Similarly, 7-fluoro-8-chloro-1,2,3,5-tetrahydro-5-oxo-pyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (**16a**) was prepared; ^{1}H nmr (DMSO-d_6): δ 1.78 (m, 4, CH_2CH_2), 3.70 (m, 2, N-CH_2), 4.37 (m, 2, vinyl CH_2), 8.18 (d, J_{H-F} = 9 Hz, 1, aromatic H), 8.45 (d, J_{H-F} = 6 Hz, 1, aromatic H).

7-Fluoro-8-(4-methylpiperazin-1-yl)-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]-quinoline-4-carboxylic Acid (**10**) Hydrochloride Salt.

To a solution of the chloro acid **16a** (700 mg, 2.49 mmoles) in *N*-methyl-2-pyrrolidinone (7 ml) at 100° was added in *N*-methylpiperazine (2 ml, 18.1 mmoles). After heating at 100° under nitrogen atmosphere for 48 hours, the mixture was cooled to room temperature and the solid was filtered. The residue was washed with cold water and ethanol. The solid was dissolved in 0.1 *N* hydrochloric acid solution (15 ml). The solution was evaporated to dryness yielding 7-fluoro-8-(4-methylpiperazin-1-yl)-1,2,3,5-tetrahydro-5-oxopyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**10**) hydrochloride salt (480 mg, 50%) mp >250°; ^{1}H nmr (trifluoroacetic acid): δ 2.67 (m, 2, CH_2), 3.17 (s, 3, N-CH_2), 3.83 (m, 10, N-CH_2), 4.95 (m, 2, vinyl CH_2), 7.42 (d, J_{H-F} = 6.5 Hz, 1, aromatic H), 8.25 (d, J_{H-F} = 12 Hz, 1, aromatic H).

Anal. Calcd. for $C_{18}H_{21}FClN_3O_2 \cdot \frac{1}{2}H_2O$: C, 55.31; H, 5.61; Cl, 9.09; N, 10.76. Found: C, 55.52; H, 5.50; Cl, 8.98; H, 10.76.

Similarly prepared was 8-fluoro-9-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-6*H*-6-oxopyrido[1,2-*a*]quinoline-5-carboxylic acid (**11**) hydrochloride salt, mp >250°; ^{1}H nmr (trifluoroacetic acid): δ 2.08 (m, 2, CH_2), 2.28 (m, 2, CH_2), 3.13 (s, 3, N-CH_3), 3.45 (m, 2, N-CH_2), 3.75 (m, 2, N-CH_2), 3.83 (m, 2, N-CH_2), 3.92 (m, 2, N-CH_2), 4.12 (m, 2, N-CH_2), 4.73 (m, 2, vinyl CH_2), 7.63 (d, J_{H-F} = 6 Hz, 1, aromatic H), 8.25 (d, J_{H-F} = 12 Hz, 1, aromatic H).

Anal. Calcd. for $C_{19}H_{22}FN_3O_3 \cdot 1\text{-}\frac{1}{3}HCl$: C, 55.95; H, 5.73; H, 10.31. Found: C, 55.60; H, 5.62; N, 10.23.

In Vitro Antibacterial Activity.

The *in vitro* antibacterial activity of the test compound was determined by conventional agar dilution procedures. The organisms were grown overnight in brain-heart infusion (BHI) broth (Difco 0037-01-6) at 36°. Two-fold dilutions of the stock solution (2,000 μg/ml) of the test compound were made in BHI agar to obtain a test concentration ranging from 200/μg/ml to 0.005 μg/ml. The plate was inoculated with approximately 10^4 organisms. It was then incubated at 36° for 18 hours. The minimal inhibitory concentration (MIC) was the lowest concentration of the test compound that yielded no visible growth on the plate.

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