A Regiospecific Synthesis of 1-Methylamino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid

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An efficient and regiospecific synthesis of 1-methylamino-6-fluoro-7-(4-methylpiperizin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (3) *via* an intramolecular nucleophilic displacement cyclization reaction is reported.

The recent discoveries of the potent clinically important antibacterials Norfloxacin **1** [1] and Pefloxacin **2** [2], members of the quinolone-3-carboxylic acid group of antibacterial agents [3], have stimulated considerable interest in the synthesis of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives. During our research on the synthesis of novel 1-amino substituted quinolone derivatives, we discovered an efficient and regiospecific synthesis of a highly potent quinolone antibacterial, namely, 1-methylamino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**3**). An independent alternate synthesis of **3**, designated as WIN 49,375 and later named as Amifloxacin by Sterling-Winthrop research group is recently disclosed [4]. This prompts us to communicate our chemical investigation.

1, R = H,   R₁ = C₂H₅
2, R = CH₃, R₁ = C₂H₅
3, R = CH₃, R₁ = NHCH₃
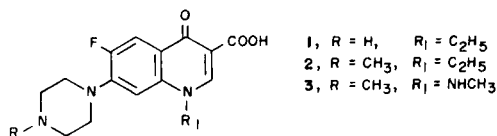
Amifloxacin is currently under development as potential clinically useful antibacterial agent [5]. The Sterling-Winthrop's synthetic route for the antibacterial **3** parallels the general synthetic approach for the synthesis fo 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic derivatives [3,4] involving the thermal cyclization of the anilinomethylene malonate **4** to yield the key intermediate, 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester (**5**). However, this cyclization reaction is not regiospecific and generates a minor undesired position isomer [6] making purification of the desired produce difficult. We now wish to report our regiospecific and efficient synthesis of **3** (Scheme I). This synthesis requires no column chromatographic purification making the process attractive in preparation of the compound in production scale.

4   5
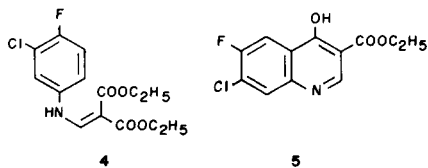
Condensation of 2,4-dichloro-5-fluoroacetophenone (**6**) [7] with two molar equivalents of sodium hydride in diethylcarbonate yielded the ethyl 2,4-dichloro-5-fluorobenzoyl acetate (**7**) (which existed in both keto and enol forms in approximately 2:1 ratio). Its nmr spectrum showed the presence of a singlet at δ 5.65 (corresponding to the enol olefinic proton) and another singlet at δ 4.07 (corresponding to the two keto methylene protons). The intensities of these two signals were about 1:4. Reaction of this ester with triethylorthoformate in acetic anhydride gave the one carbon homolog enol ether intermediate which upon evaporation of solvent to dryness was allowed to react with a slight excess of N-formyl-N-methyl hydrazine in methylene chloride at room temperature to give **8** (mp 115-116°, 86%). This enaminoketo ester exists in both *trans* and *cis* forms in solution with one of the isomers being predominant (more than 90%).

Scheme I
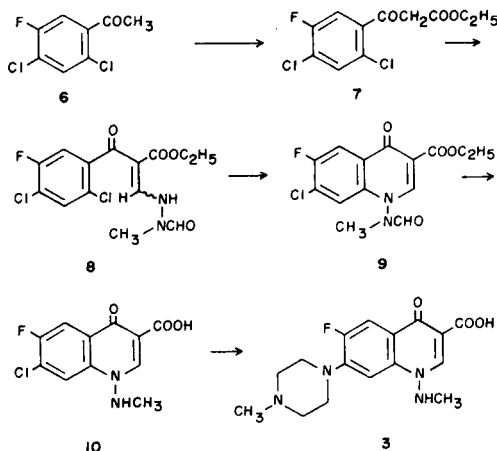
Regiospecific cyclization of **8** with 1 molar equivalent of sodium hydride in dimethylformamide at 140° yielded 1,4-dihydro-4-oxoquinoline-3-carboxylate **9** (mp 209-211°, 82%). Hydrolysis of **9** with 0.35 N hydrochloric acid in acetonitrile afforded the acid **10** (mp 272-273°, 94%).

Displacement of **10** with an excess of 4-methylpiperazine in N-methylpyrrolidinone at 100° yielded **3** which was

then converted to the hydrochloride salt. The antibacterial activity of **3** is disclosed [4].

In summary, we have discovered a regiospecific efficient synthesis of a clinically useful antibacterial agent, 1-methylamino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid *via* an intramolecular nucleophilic displacement cyclization reaction.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer Model 710 A infrared spectrophotometer. The nmr spectra were recorded on a Varian Associates T-60 spectrometer in deuterated solvents; resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. The high-resolution mass spectra were determined on an Associated Electrical Industries MS-902 double-focusing mass spectrometer and were processed on an IBM 1800 computer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Satisfactory spectral data have been obtained for all new compounds. Proton magnetic resonance data and elemental analysis data are given in individual experiments. Solutions were dried over magnesium sulphate.

Ethyl 2,4-Dichloro-5-fluorobenzoylacetate (**7**).

To a cold solution of 2,4-dichloro-5-fluoroacetophenone (20.5 g, 99.0 mmoles) in diethylcarbonate (300 ml) was added slowly at room temperature 60% sodium hydride-in-oil suspension (8.2 g, 205 mmoles). The mixture was then heated at 80° for 1.5 hours. It was then poured into ice cold water (700 ml) solution containing acetic acid (25 ml). The mixture was extracted with three portions of ether (400 ml). The organic phase is dried, evaporated and the obtained oil was distilled at 111° at 0.7 mm of Hg to give benzoylacetate **7** (22.2 g, 80%); ¹H nmr (deuteriochloroform): δ (2 sets of signals) 1.17 (t, J = 7 Hz, 3, ethyl CH₃), 1.27 (t, J = 7 Hz, 3, ethyl CH₃), 4.07 (s, 2, CH₂), 4.17 (q, J = 7 Hz, 2, ethyl CH₂), 4.27 (q, J = 7 Hz, 2, ethyl CH₂), 5.65 (s, 1, vinyl H), 7.47 (m, 2 sets of 2, aromatic H), 12.48 (s, 1, enol OH).

Ethyl 3-*N*-Formyl-*N*-methylhydrazyl-2-(2,4-dichloro-5-fluoro)benzoylacrylate (**8**).

To a solution of benzoylacetate **7** (30 g, 107.5 mmoles) in triethylorthoformate (27 ml, 162 mmoles) and acetic anhydride (61 ml, 434 mmoles) was heated at 130° for 1.5 hours with the removal of the ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to a mobile oil which was then dissolved in methylene chloride (250 ml). *N*-Formyl-*N*-methylhydrazine (8 ml, 108 mmoles) was then added into the solution. After 1.5 hours, the solution was evaporated to dryness and crystallized from 20% ether in hexane solution yielding 34 g of **8** **7** (86% yield), mp 115-116°; ¹H nmr (deuteriochloroform): (major isomer) δ 0.94 (t, J = 7 Hz, 3, ethyl CH₃), 3.23 (s, 3, NCH₃), 4.03 (q, J = 7 Hz, 2, ethyl CH₂), 7.05 (d, J_{H-F} = 9 Hz, 1, aromatic H), 7.04 (d, J_{H-F} = 6 Hz, 1, aromatic H), 8.16 (m, 2, CHO and vinyl H), 12.1 (d, J = 9 Hz, N-H).

Anal. Calcd. for $C_{14}H_{13}Cl_2FN_2O_4$: C, 46.28; H, 3.58; N, 7.71. Found: C, 46.14; H, 3.74; N, 7.72.

Ethyl 1-(*N*-Formyl-*N*-methyl)amino-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**9**).

To a cold solution of benzoylacrylate **8** (10.3 g, 28.3 mmoles) in dimethylformamide (50 ml) was slowly added a 60% sodium hydride-in-oil suspension (1.16 g, 29 mmoles). The mixture was heated at 140° for 3.5 hours under nitrogen atmosphere and was cooled and evaporated under reduced pressure to nearly dryness. Five ml of acetonitrile was added and followed by the addition of 1 liter of water and the mixture was filtered. The solid was recrystallized from hot acetonitrile (75 ml) yielding 7.65 g of **9** (82%) mp 209-211°; ¹H nmr (DMSO-d₆): δ 1.20 (t, J = 7 Hz, 3, ethyl

CH₃), 3.47 (s, 3, NCH₃), 4.23 (q, J = 7 Hz, 2, CH₂), 7.94 (d, J_{H-F} = 6 Hz, 1, aromatic H), 7.96 (d, J_{H-F} = 9 Hz, 1, aromatic H), 8.34 (s, 1, 2-H or CHO), 8.73 (s, 1, 2-H or CHO). Also present in the spectrum are low intensity signals for rotational isomer 7.69 (double d), 8.50 (s) and 8.90 (s).

Anal. Calcd. for $C_{14}H_{12}ClFN_2O_4$: C, 51.45; H, 3.68; N, 8.58. Found: C, 51.15; H, 3.73; N, 8.40.

1-Methylamino-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**10**).

To a solution of **9** (10.6 g, 32.5 mmoles) in acetonitrile (150 ml) at 90° was added a hydrochloric acid solution (7.5 ml of concentrated hydrochloric acid in 70 ml of water). After heating at 90° for 7 hours, the mixture was cooled. It was filtered and the residue was washed with acetonitrile/water mixture to give the 1-methylamino-6-fluoro-7-chloro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**10**) (8.26 g, 94% yield), mp 272-273°; ¹H nmr (deuteriotrifluoroacetic acid): δ 3.20 (s, 3, NCH₃), 8.36 (d, J_{H-F} = 8.5 Hz, 1, 5-H), 8.81 (d, J_{H-F} = 6 Hz, 1, 8-H), 9.64 (s, 1, 2-H).

Anal. Calcd. for $C_{11}H_8ClFN_2O_3$: C, 48.80; H, 3.00; N, 10.35. Found: C, 48.76; H, 2.96; N, 10.28.

1-Methylamino-6-fluoro-7-(4-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**3**) Hydrochloride Salt.

To a solution of the chloro acid **10** (9.69 g, 35.8 mmoles) in *N*-methyl-2-pyrrolidinone (70 ml) at 100° was added in *N*-methylpiperazine (19 ml, 171.5 mmoles). After heating at 100° under nitrogen atmosphere for 20 hours, the solution was evaporated to nearly dryness under reduced pressure. Ethanol (50 ml) was added and the mixture was boiled for 5 minutes and cooled. It was filtered and the residue was washed with ethanol yielding **3**. The solid was suspended in 300 ml of water. Hydrochloric acid (1N) (37 ml) was added and the mixture was warmed to form a solution. The insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The solid was suspended in *N*-methyl-2-pyrrolidinone (15 ml) and heated at 100° under nitrogen atmosphere for 10 minutes, cooled and filtered and washed with ether yielding the hydrochloride salt of **3** (9.7 g, 73%); ¹H nmr (deuteriotrifluoroacetic acid): δ 2.70 (s, 3, N-CH₃), 3.43 (m, 8, piperazine CH₂), 7.61 (d, J_{H-F} = 6 Hz, 1, 8-H), 7.83 (d, J_{H-F} = 12 Hz, 1, 5-H), 9.55 (s, 1, 2-H).

Anal. Calcd. for $C_{16}H_{19}FN_4O_3$·HCl: C, 51.82; H, 5.40; N, 15.11; F, 5.12; Cl, 9.58. Found: C, 51.62; H, 5.49; N, 15.21; F, 5.06; Cl, 9.60.

REFERENCES AND NOTES

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