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A New Synthesis of 7*H*-Pyrido[1,2,3-*de*][1,4]benzoxazine Derivatives Including an Antibacterial Agent, Ofloxacin[1)]

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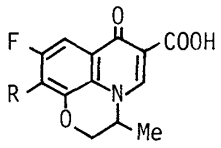
A new method for the synthesis of 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine derivatives was developed. The method is characterized by the intramolecular cyclization of 1-(1-hydroxyprop-2-yl)-8-fluoro-4-quinolones which are prepared in three or four steps from ethyl 2,3,4,5-tetrafluorobenzoylacetate. As an application of this method, ofloxacin, an antibacterial agent, was synthesized.

Keywords——7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine; ethyl 2,3,4,5-tetrafluorobenzoylacetate; intramolecular cyclization; antibacterial agent; ofloxacin

Ofloxacin (**1**),[2)] a member of the pyridonecarboxylic acid antibacterial agents, has recently been introduced into chemotherapy. It is characterized chemically by a 1,4-oxazine ring fused to a quinoline nucleus, *i.e.*, a 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine structure.



1 : R = MeN N

2 : R = F

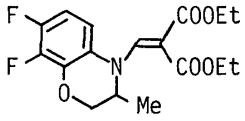


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Chart 1

The reported synthesis[3)] of **1** involves the displacement reaction of *N*-methylpiperazine with 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid (**2**), which is available by the well-known cyclization of the precursor **3** with polyphosphoric ester followed by hydrolysis. Our interest in the ring system led us to investigate an alternative route for the synthesis of 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine derivatives. An intramolecular cyclization involving a nucleophilic attack of the hydroxyl group of the N-1 appendage on C-8 of the 8-fluoro-4-quinolone derivatives (**6** and **10**) was found to provide the desired compounds. This paper deals with a new and efficient route for the synthesis of 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine derivatives including ofloxacin (**1**).

The requisite compound **4** was prepared, according to the known method,[4)] by the condensation of ethyl ethoxymagnesium malonate with 2,3,4,5-tetrafluorobenzoyl chloride (accessible from the corresponding carboxylic acid), followed by hydrolysis of the condensate. The ketoester **4** was treated with ethyl orthoformate in acetic anhydride and the product, without isolation, was allowed to react with 2-amino-1-propanol in a mixture of isopropyl ether and ethanol to give the enaminoketoester **5**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5** shows that **5** is an approximately 1 : 4 or 4 : 1 mixture of (*E*)- and

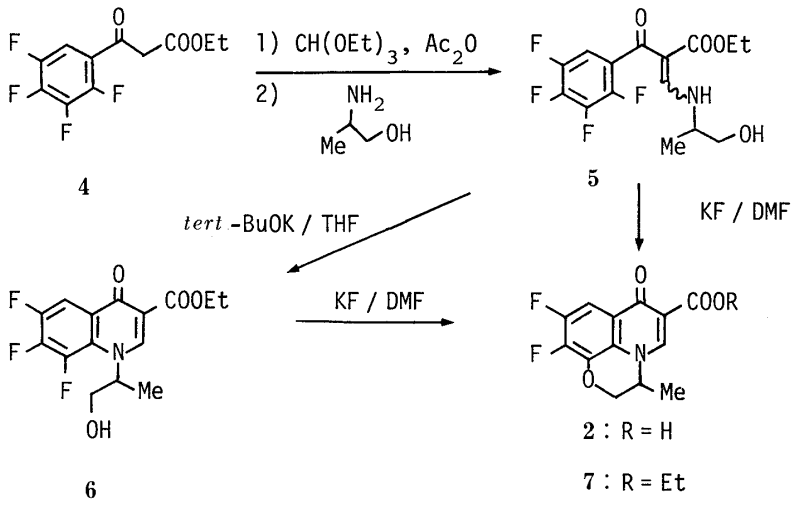

Chart 2

(*Z*)-geometrical isomers. Heating of **5** with an excess of potassium fluoride in *N*,*N*-dimethylformamide (DMF) gave exclusively the 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine derivative **7** in 76% yield. The probable intermediate **6** in this reaction was afforded along with **7** when **5** was treated with a small excess of potassium *tert*-butoxide in dry tetrahydrofuran under cooling. Cyclization of **6** to the oxazine **7** proceeded on heating with potassium fluoride in DMF or with sodium hydride in dry dioxane. The ester **7** was converted to the acid **2** by successive alkaline hydrolysis.

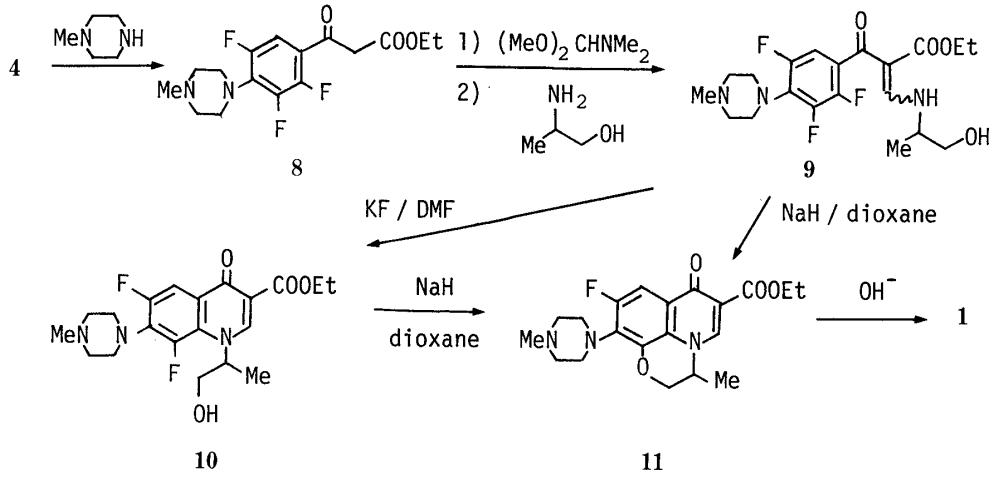

Chart 3

In order to synthesize ofloxacin (**1**) by the foregoing method, *N*-methylpiperazine was first introduced into **4**. The fluoro group at C-2 or C-4 of **4**, which is the position activated by the electron-withdrawing character of the carbonyl group, could be replaced by an appropriate amine. The displacement reaction of **4** with *N*-methylpiperazine in acetonitrile in the presence of sodium bicarbonate proceeded regioselectively to give the expected compound **8** in 88% yield. The ^{1}H-NMR spectrum of **8** shows a doublet at δ 3.91 (J=4 Hz), which is assignable to the methylene protons of the ketoester moiety, due to a long-range coupling[5] with the *ortho* fluorine atom on the benzene ring. On the basis of this observation, the site of the displacement was assigned as position 4. Compound **8** was converted to the enaminoketoester **9** on treatment with *N*,*N*-dimethylformamide dimethyl acetal in toluene followed by the reaction with 2-amino-1-propanol in ethanol. A one-step conversion of **9** into

11 would be expected, as in the reaction of **5** to **7**, if **9** were heated with potassium fluoride in DMF. However, the reaction product was not **11**, but the 4-quinolone **10** in practice. Probably, the electron-donating character of the piperazinyl group reduces the reactivity at C-8 of **10** formed as an intermediate and makes the further ring-closure of **10** difficult under the conditions used. Use of a stronger base (such as sodium hydride) than potassium fluoride permitted the conversion of **9** to **11** in a one-step process. The 4-quinolone **10** cyclized to **11** under the same conditions. Finally, alkaline hydrolysis of **11** led to ofloxacin (**1**).

The structures of **1**, **2** and **7** were confirmed by direct comparison with authentic samples prepared by the reported method[3]; the structures of the other products were consistent with the spectral data and elemental analysis results.

In conclusion, the new synthetic method[6] for 7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine derivatives described in the present paper is characterized by the following features: 1) the easily accessible ketoesters **4** and **8** are used as starting materials, 2) the key reaction involves the intramolecular cyclization of the 8-fluoro-4-quinolone derivative having a hydroxyisopropyl appendage at N-1 (**6** and **10**), and 3) the present method would be applicable to the synthesis of the optically active ofloxacin (by using (*R*)- or (*S*)-2-amino-1-propanol) as well as otehr variously substituted oxazine derivatives.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 spectrometer. ^{1}H-NMR spectra were recorded at 80 MHz with a Varian FT-80A or at 300 MHz with a Varian XL 300 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard.

Ethyl 2-(2,3,4,5-Tetrafluorobenzoyl)-3-(1-hydroxyprop-2-ylamino)acrylate (5)——A mixture containing ethyl 2,3,4,5-tetrafluorobenzoylacetate (5.0 g, 18.9 mmol), ethyl orthoformate (4.7 ml, 28.6 mmol) and acetic anhydride (4.5 ml, 47.6 mmol) was heated at 140—150 °C for 2 h, during which period the resulting AcOEt was removed. The solution was concentrated under reduced pressure to leave a viscous oil. A mixture of 2-amino-1-propanol (2.5 g, 33.3 mmol), EtOH (4 ml) and iso-Pr_2O (4 ml) was added to a stirred solution of the above oil in iso-Pr_2O (10 ml) under ice-cooling. The mixture was stirred for 3 h at room temperature and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using $CHCl_3$ as an eluent, and recrystallized from a mixture of Et_2O and hexane to give **5** (4.9 g, 74%), mp 77—78 °C. *Anal.* Calcd for $C_{15}H_{15}F_4NO_4$: C, 51.58; H, 4.33; F, 21.76; N, 4.01. Found: C, 51.18; H, 4.34; F, 21.57; N, 3.99. IR ν_{max}^{KBr} cm^{-1}: 3500, 1680, 1630. NMR (300 MHz, $CDCl_3$): 0.97 and 1.10 (3H, each t, J=6.5 Hz, $-OCH_2CH_3$), 1.36 and 1.38 (3H, each d, J=6.5 Hz, $-NCHCH_3$), 1.89 and 1.91 (1H, each t, J=5 Hz, –OH), 3.58—3.71 (2H, m, $-NCHCH_2O-$), 3.73—3.84 (1H, m, $-NCHCH_2O-$), 4.02 and 4.07 (2H, each q, J=6.5 Hz, $-OCH_2CH_3$), 6.93—7.02 and 7.05—7.15 (1H, each m, aromatic H), 8.20 (1H × 1/5, dd, J=14, 0.5 Hz, $=CHN-$), 8.21 (1H × 4/5, dd, J=15, 0.5 Hz, $-CHN-$), 9.46—9.70 and 10.74—11.04 (1H, each br, $-NH$).

Ethyl 6,7,8-Trifluoro-1,4-dihydro-1-(1-hydroxyprop-2-yl)-4-oxoquinoline-3-carboxylate (6)——Potassium *tert*-butoxide (430 mg, 3.72 mmol) was added to a solution of **5** (1.0 g, 2.87 mmol) in dry tetrahydrofuran (5 ml) under ice-cooling. The mixture was stirred for 3 h at room temperature and concentrated under reduced pressure. After addition of dilute HCl, the resulting mixture was extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel using AcOEt as an eluent to give **6** (300 mg, 32%) and a small amount of **7**. **6**: mp 170—171 °C ($EtOH-H_2O$). *Anal.* Calcd for $C_{15}H_{14}F_3NO_4$: C, 54.72; H, 4.29; F, 17.31; N, 4.25. Found: C, 54.51; H, 4.36; F, 17.35; N, 4.24. IR ν_{max}^{KBr} cm^{-1}: 3470, 1720. NMR (80 MHz, $CDCl_3$): 1.35 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.65 (3H, d, J=7.5 Hz, $-NCHCH_3$), 3.7—4.5 (2H, m, $-NCHCH_2O-$), 4.25 (2H, q, J=7 Hz, $-OCH_2CH_3$), 4.60 (1H, t, J=6.5 Hz, –OH), 5.0—5.5 (1H, m, $-NCHCH_2O-$), 7.3—7.7 (1H, m, C_5-H), 8.13 (1H, s, C_2-H).

Ethyl 9,10-Difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (7)——i) A mixture of **5** (1.0 g, 2.87 mmol) and spray-dried KF[7] (500 mg, 8.62 mmol) in DMF (8 ml) was heated at 140—150 °C for 1 h with vigorous stirring and then allowed to cool. After addition of water (16 ml), the precipitate was collected by filtration, washed successively with water and EtOH, and recrystallized from a mixture of $CHCl_3$ and EtOH to give **7** (670 mg, 76%), mp 260—261 °C (lit.[2] mp 260 °C). NMR (300 MHz, DMSO-d_6): 1.29 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.42 (3H, d, J=7 Hz, C_3-CH_3), 4.23 (2H, q, J=7 Hz, $-OCH_2CH_3$), 4.44 (1H, dd, J=11, 2.5 Hz, C_2-H), 4.61 (1H, dd, J=11, 2.5 Hz, C_2-H), 4.76—4.86 (1H, m, C_3-H), 7.63 (1H, dd, J=11, 8 Hz, C_8-H), 8.69 (1H, s, C_5-H).

ii) A mixture of **6** (100 mg, 0.3 mmol) and spray-dried KF (26 mg, 0.45 mmol) in DMF (0.8 ml) was heated at

140—155 °C for 1 h with stirring and then allowed to cool. After addition of water (1.6 ml), the precipitate was collected by filtration, washed successively with water and EtOH, and recrystallized from a mixture of $CHCl_3$ and EtOH to give **7** (55 mg, 59%).

9,10-Difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (2)——Sodium hydride–mineral oil (60% NaH, 15 mg, 0.38 mmol) was added to a solution of **6** (100 mg, 0.3 mmol) in dry dioxane under ice-cooling. The mixture was heated at 80—85 °C for 1 h with stirring and then concentrated under reduced pressure. After addition of 0.1 N NaOH (5 ml), the mixture was heated at 100 °C for 30 min with stirring and acidified with 1 N HCl. The resulting precipitate was collected by filtration, washed with water, and recrystallized from DMF to give **2** (75 mg, 88%), mp >300 °C (lit.[3] mp >300 °C).

Ethyl 2,3,5-Trifluoro-4-(4-methyl-1-piperazinyl)benzoylacetate (8)——A mixture containing **4** (5.0 g, 18.9 mmol), *N*-methylpiperazine (2.2 ml, 19.8 mmol), $NaHCO_3$ (1.6 g, 19.0 mmol) and MeCN (25 ml) was refluxed for 3 h and then concentrated under reduced pressure. After addition of water, the resulting mixture was extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel using $CHCl_3$ as an eluent to give **8** (6.0 g, 88%), mp 60—61 °C (Et_2O–hexane). *Anal.* Calcd for $C_{16}H_{19}F_3N_2O_3$: C, 55.81; H, 5.65; F, 16.55; N, 8.14. Found: C, 55.71; H, 5.58; F, 16.50; N, 8.14. IR ν_{max}^{KBr} cm^{-1}: 1740, 1670. NMR (300 MHz, $CDCl_3$): 1.27 and 1.33 (3H, each t, J=7 Hz, $-OCH_2CH_3$), 2.34 (3H, s, $-NCH_3$), 2.49—2.57 (4H, m, piperazine H), 3.32—3.44 (4H, m, piperazine H), 3.91 (2H × 17/20, d, J=4 Hz, $-COCH_2COO-$), 4.22 and 4.26 (2H, each q, J=7 Hz, $-OCH_2CH_3$), 5.78 (1H × 3/20, s, $HOC=CH-$), 7.29—7.36 (1H, m, aromatic H), 12.64 (1H × 3/20, s, $HOC=CH-$).

Ethyl 2-[2,3,5-Trifluoro-4-(4-methyl-1-piperazinyl)]benzoyl-3-(1-hydroxyprop-2-ylamino)acrylate (9)——A mixture of **8** (2.5 g, 7.3 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.5 ml, 11.3 mmol) in toluene (10 ml) was heated at 100—120 °C for 1 h with stirring. The solution was concentrated under reduced pressure to give a viscous oil. A mixture of 2-amino-1-propanol (0.9 g, 12 mmol) and EtOH (2 ml) was added to a stirred solution of the above oil in EtOH (10 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of $CHCl_3$ and EtOH (20 : 1, v/v) as an eluent to give a viscous oil **9** (a 3 : 7 or 7 : 3 mixture of (*E*)- and (*Z*)-isomers, 3.0 g, 96%). IR ν_{max}^{neat} cm^{-1}: 1690, 1670, 1625. NMR (80 MHz, $CDCl_3$): 0.97 and 1.07 (3H, each t, J=7 Hz, $-OCH_2CH_3$), 1.33 (3H, d, J=6.5 Hz, $-NCHCH_3$), 1.8—2.2 (1H, br, –OH), 2.33 (3H, s, $-NCH_3$), 2.3—2.6 (4H, m, piperazine H), 3.1—3.4 (4H, m, piperazine H), 3.4—3.6 (3H, m, $-NCHCH_2O-$), 4.00 and 4.05 (2H, each q, J=7 Hz, $-OCH_2CH_3$), 6.6—6.7 (1H, m, aromatic H), 8.08 and 8.13 (1H, each d, J=14 Hz, $=CHN-$), 9.1—9.5 and 10.5—11.0 (1H, each br, –NH).

Ethyl 6,8-Difluoro-1,4-dihydro-1-(1-hydroxyprop-2-yl)-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylate (10)——A mixture of **9** (600 mg, 1.4 mmol) and spray-dried KF (250 mg, 4.3 mmol) in DMF (9 ml) was heated at 140—165 °C for 3 h with vigorous stirring and then concentrated under reduced pressure. After addition of saturated $NaHCO_3$, the mixture was extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The resulting solid was recrystallized from AcOEt to give **10** (290 mg, 51%), mp 195—196 °C. *Anal.* Calcd for $C_{20}H_{25}F_2N_3O_4$: C, 58.67; H, 6.15; F, 9.28; N, 10.26. Found: C, 58.56; H, 6.12; F, 9.26; N, 10.22. IR ν_{max}^{KBr} cm^{-1}: 3350, 1720, 1695. NMR (80 MHz, $CDCl_3$): 1.38 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.67 (3H, d, J=6.5 Hz, $-NCHCH_3$), 2.38 (3H, s, $-NCH_3$), 2.4—2.7 (4H, m, piperazine H), 3.2—3.5 (4H, m, piperazine H), 3.7—4.4 (2H, m, $-NCHCH_2O-$), 4.28 (2H, q, J=7 Hz, $-OCH_2CH_3$), 5.1—5.6 (2H, br, $-NCHCH_2O-$ and –OH), 7.05 (1H, dd, J=12.5, 2 Hz, C_5-H), 8.58 (1H, s, C_2-H).

Ethyl 9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (11)——i) Sodium hydride (60% NaH, 17 mg, 0.43 mmol) was added to a solution of **10** (150 mg, 0.37 mmol) in dry dioxane (3 ml). After being heated at 70—90 °C for 1 h with stirring, the mixture was cooled and poured into ice-water. The resulting mixture was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to dryness. After addition of Et_2O, the precipitate was collected by filtration and recrystallized from AcOEt to give **11** (72 mg, 50%), mp 233–235 °C. *Anal.* Calcd for $C_{20}H_{24}FN_3O_4$: C, 61.69; H, 6.21; F, 4.88; N, 10.79. Found: C, 61.81; H, 6.23; F, 5.02; N, 10.85. IR ν_{max}^{KBr} cm^{-1}: 1710, 1615. NMR (80 MHz, $CDCl_3$): 1.42 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.55 (3H, d, J=7 Hz, C_3-CH_3), 2.37 (3H, s, $-NCH_3$), 2.4—2.6 (4H, m, piperazine H), 3.2—3.4 (4H, m, piperazine H), 4.1—4.4 (2H, m, C_2- and C_3-H), 4.33 (2H, q, J=7 Hz, $-OCH_2CH_3$), 7.65 (1H, d, J=12.5 Hz, C_8-H), 8.28 (1H, s, C_5-H).

ii) Sodium hydride (60% NaH, 120 mg, 3 mmol) was added to a solution of **9** (600 mg, 1.4 mmol) in dry dioxane (15 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h and then heated at 80—90 °C for 1 h. After work-up as described above, **11** (212 mg, 39%) was obtained.

9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (1)——Sodium hydride (60% NaH, 6 mg, 0.15 mmol) was added to a solution of **10** (60 mg, 0.15 mmol) in dry dioxane (6 ml). The mixture was heated at 80—95 °C for 1 h with stirring. After addition of 0.1 N NaOH (5 ml), the reaction mixture was heated for an additional 30 min and concentrated under reduced pressure. The residue was taken up in water, neutralized with dilute AcOH, and extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The resulting solid was recrystallized from a mixture of $CHCl_3$ and EtOH to give **1** (25 mg, 47%), mp 262—264 °C (lit.[3] mp 250—257 °C).

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References and Notes

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