Pyridonecarboxylic Acids as Antibacterial Agents. VIII.1) An Alternative Synthesis of Enoxacin via Fluoronicotinic Acid Derivatives

TERUYUKI MIYAMOTO, HIROSHI EGAWA* and JUN-ICHI MATSUMOTO*

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan

(Received October 29, 1986)

An alternative synthesis of enoxacin, a 1,8-naphthyridine antibacterial agent, was developed. The present method involves 1,8-naphthyridine ring construction by the Dieckmann type cyclization of ethyl 5-fluoronicotinate having a 2-ethoxycarbonylethylamino moiety at C-2. This nicotinate was prepared in 7 steps from ethyl fluoroacetate via ethyl 2,6-dichloro-5-fluoronicotinate.

Keywords—ethyl fluoroacetate; ethyl 5-fluoronicotinate; 1,8-naphthyridine; Dieckmann cyclization; antibacterial agent; enoxacin

Enoxacin (1),2a) a pyridonecarboxylic acid antibacterial agent, has recently been introduced as a chemotherapeutic agent. Our previous methods2) for the synthesis of enoxacin have involved the introduction of a fluorine atom into a pyridine or 1,8-naphthyridine ring by means of the Balz—Schiemann reaction, which is a key step in the sequence of reactions.

Santilli et al.3) have reported a construction of the 1,8-naphthyridine skeleton of nalidixic acid by the Dieckmann-type cyclization of a nicotinate derivative. Efforts were first focussed on the preparation of ethyl 2,6-dichloro-5-fluoronicotinate (10) which would be an intermediate for enoxacin in the route involving the Dieckmann-type cyclization.

Hirota et al.4) have reported the ring transformation of 5-fluoro-1,3-dimethyluracil to 5-fluoro-2,6-dihydroxynicotinamide (5), which could be converted to the requisite compound 10. Their method, however, has the disadvantages that the yield is unsatisfactory (38%) and 5-fluourouracil is very expensive. Therefore, commercially available ethyl fluoroacetate (2) was used as a starting material in the present study.

Reaction of 2 with ethyl formate in the presence of sodium hydride in ether, followed by treatment with trimethylsilyl chloride, afforded ethyl 2-fluoro-3-(trimethylsiloxy)acrylate (3). When 3 was allowed to react with malonamide in the presence of sodium ethoxide in boiling ethanol, 5 was obtained in 65% yield. Compound 5 was identical with an authentic specimen prepared by the reported method.4a) One-pot preparation of 5 from 2 was accomplished in the following manner; 2 was treated with ethyl formate and sodium ethoxide to give the sodium salt of ethyl formylfluoroacetate (4), which, without isolation, was allowed to react with malonamide in boiling ethanol to yield 5 in 63% yield. According to the same procedure, 5-
fluoro-2,6-dihydroxynicotinonitrile (6) and the corresponding nicotinate analogue 7 were prepared from cyanoacetamide and ethoxycarbonylacetamide in 57% and 75% yields, respectively. Treatment of 5 with phosphorus pentachloride resulted in chlorination with concomitant dehydration to give 2,6-dichloro-5-fluoronicotinonitrile (8). However, attempted conversions of 6 to 8 and of 7 to 10 both failed under the same conditions. Hence, the nitrile 8 was hydrolyzed to the amide 9, which was then converted to the intermediate 10 by treatment with boron trifluoride-etherate in ethanol.

The chloro group at C-2 in 8 and 10 was replaced by an appropriate amine. The displacement reaction of 10 with N-acetylpiperazine proceeded regioselectively in a solvent such as acetonitrile, ethanol or toluene to give the corresponding 6-substituted compound 11a in good yield. In order to confirm the structure of 11a, dehalogenation of 11a to 12a was carried out by catalytic hydrogenolysis. The proton nuclear magnetic resonance (1H-NMR) spectrum of 12a shows a double doublet at δ 7.77 (J_{F,H} = 7 Hz, J_{H,H} = 2 Hz) and a triplet at δ 8.66 (J_{F,H} and J_{H,H} = 2 Hz) which are assignable to the C-4 proton and the C-2 proton, respectively. This observation permits assignment of the site of the displacement with N-acetylpiperazine as position 6 in 10. Similarly, the reaction of 8 with N-acetylpiperazine afforded preferentially the 6-substituted compound 11b, as expected. The structure of 11b was confirmed by the 1H-NMR spectrum of 12b, which was prepared from 11b by hydrogenolysis.

When 11a was heated at 120—130 °C with ethyl 3-(ethylamino)propionate in dimethylformamide (DMF) in the presence of sodium bicarbonate, the desired diester 13 was produced in 42% yield together with a small amount of the 2-ethylamino compound 14a. The formation of 14a was owing probably to the reaction of 11a with ethylamine which would arise from the decomposition of ethyl 3-(ethylamino)propionate during the reaction. This was supported by the fact that the formation of 14a was not observed when 13 was treated under the same conditions. On the reaction of 11b with ethyl 3-(ethylamino)propionate under the same conditions, 11b was recovered unchanged. In the reaction of 11b, the use of potassium carbonate instead of sodium bicarbonate at a temperature above 150 °C gave the undesired compound 14b as a main product. Authentic specimens of 14a and 14b were prepared by the reaction of 11a and 11b, respectively, with ethylamine in a sealed tube.

On treatment with sodium hydride or potassium tert-butoxide in toluene, the diester 13
underwent Dieckmann-type cyclization to give the tetrahydronaphthyridine derivative 15 in good yield. The $^1$H-NMR spectrum of 15 in deuteriochloroform shows that 15 exists mainly in keto form. Oxidation of 15 with an equivalent amount of chloranil and pyridine in chloroform gave the precursor 16 for enoxacin in 88% yield. Without the use of pyridine, the yield of 16 was less than 50%. Hydrolysis of 16 to enoxacin has already been described in our previous paper.2a)

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus. Boiling points and melting points are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-102 or a Hitachi 215 spectrometer. $^1$H-NMR spectra were taken at 60 MHz with a Varian EM-360A, at 80 MHz with a Varian FT-80A or at 100 MHz with a Varian HA-100D spectrometer. Chemical shifts are expressed in $\delta$ (ppm) values with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS D-300. Physical and analytical data for nicotinic acid derivatives are listed in Tables I and II, respectively.

**Ethyl 2-Fluoro-3-(trimethylsiloxy)acrylate (3)** — Ethyl fluoroacetate (2) (106 g, 1.0 mol) was added dropwise to a stirred mixture of ethyl formate (74 g, 1.0 mol), NaH (60% dispersion in mineral oil, 85 g, 2.1 mol) and dry Et$_2$O (650 ml) over a period of 2 h under ice-cooling. The mixture was vigorously stirred for 2 h at room temperature. After addition of trimethylsilyl chloride (278 ml) over a period of 1.5 h under ice-cooling, the resulting mixture was stirred for an additional 2 h at room temperature. The insoluble material was removed by filtration. The filtrate was concentrated to dryness and the resulting crude product was purified by distillation to give 3 (142 g, 69%); bp 80—86 °C (8 mmHg). Anal. Calcd for C$_8$H$_5$F$_3$Si: C, 46.58; H, 7.33; F, 9.21. Found: C, 47.00; H, 7.47; F, 9.09. IR (neat) cm$^{-1}$: 1670. NMR (60 MHz, CDCl$_3$): 1.00 (3H, t, $J$=7 Hz), 3.98 (2H, q, $J$=7 Hz), 6.76 (1H, d, $J$=19 Hz).

**5-Fluoro-2,6-dihydroxynicotinamide (5)** — Method A: A mixture of 4 (41.2 g, 0.20 mol), malonamide (41.0 g, 0.40 mol), EtONa (27.2 g, 0.40 mol) and EtOH (420 ml) was heated to reflux for 20 min with vigorous stirring. After addition of trimethylsilyl chloride (278 ml) over a period of 1.5 h under ice-cooling, the resulting mixture was stirred for an additional 2 h at room temperature. The insoluble material was removed by filtration. The filtrate was concentrated to dryness and the resulting crude product was purified by distillation to give 5 (11.2 g, 63%).

**5-Fluoro-2,6-dihydroxynicotinonitrile (6)** — According to method B for the preparation of 5, a mixture of ethyl
fluoroacetate (10.6 g), ethyl formate (9.2 ml) and EtONa (10.0 g) was treated with cyanoacetamide (9.7 g) to give 6 (9.1 g, 57%).

Ethyl 5-Fluoro-2,6-dihydroxynicotinate (7) — According to method B for the preparation of 5, a mixture of ethyl fluoroacetate (8.5 g), ethyl formate (7.4 ml) and EtONa (8.0 g) was treated with ethoxy carbonylacetamide
2,6-Dichloro-5-fluoronicotinonitrile (8) — A mixture of 5 (7.5 g, 436 mmol) and PCl₅ (30.0 g) was heated until a solution was formed at 140°C, and stirred for 2.5 h at 130°C. After removal of the resulting POCl₃ under reduced pressure, the residue was poured into ice-water while the temperature was maintained at 30–40°C. The resulting solid was collected by filtration and washed successively with water and a mixture of water and iso-PrOH (1:1) to give 8 (6.4 g, 77%).

2,6-Dichloro-5-fluoronicotinamide (9) — A stirred mixture of 8 (10.0 g, 52.4 mmol) and conc. H₂SO₄ (50 ml) was heated at 60–65°C for 1 h. The solution was poured into ice-water (200 ml) and extracted with AcOEt. The extract was dried over Na₂SO₄ and concentrated to dryness. After addition of hexane, the resulting solid was collected by filtration to give 9 (9.2 g, 84%).

Ethyl 2,6-Dichloro-5-fluoronicotinate (10) — A mixture of 9 (9.0 g, 43.1 mmol), BF₃·Et₂O (36 ml) and abs. EtOH (90 ml) was heated at 60°C for 30 min, during which period the Et₂O was removed, and then refluxed for an additional 16 h. After removal of the solvent under reduced pressure, ice-water (150 ml) was added to the residue. The mixture was extracted with toluene. The extract was dried over Na₂SO₄ and concentrated to dryness. The crude product was purified by distillation to give 10 (8.1 g, 79%).

Ethyl 4-(Acetyl-1-piperazinyl)-2-chloro-5-fluoronicotinate (11a) — A mixture of 10 (4.0 g, 16.8 mmol), N-acetylpyrrolidine (3.2 g, 25.2 mmol), triethylamine (3.5 ml) and MeCN (20 ml) was heated to reflux for 1.5 h and then concentrated to dryness under reduced pressure. After addition of dil. HCl, the mixture was extracted with toluene. The extract was dried over Na₂SO₄ and concentrated to dryness. After addition of hexane, the resulting solid was collected by filtration to give 11a (5.2 g, 94%). When EtOH or toluene was used as a solvent instead of MeCN, the yield of 11a was 87% or 84%, respectively.

6-(Acetyl-1-piperazinyl)-2-chloro-5-fluoronicotinonitrile (11b) — A mixture of 8 (1.0 g, 5.2 mmol), N-acetylpyrrolidine (0.8 g, 6.3 mmol), triethylamine (0.9 ml) and MeCN (20 ml) was stirred for 2 h at room temperature and then concentrated to dryness under reduced pressure. After addition of dil. HCl, the mixture was extracted with CHCl₃. The extract was dried over Na₂SO₄ and concentrated to dryness. After addition of AcOEt, the resulting solid was collected by filtration to give 11b (1.2 g, 81%). When EtOH or toluene was used as a solvent instead of MeCN, the yield of 11b was 95% or 74%, respectively.

Ethyl 6-(Acetyl-1-piperazinyl)-5-fluoronicotinate (12a) — In the presence of 5% palladium-on-charcoal (100 mg) and triethylamine (0.5 ml), 11a (1.0 g, 3.0 mmol) was hydrogenated in EtOH (20 ml) at room temperature until the required volume of hydrogen (ca. 70 ml) was absorbed. The catalyst was removed by filtration and then the filtrate was concentrated to dryness. After addition of hexane, the resulting solid was collected by filtration to give 12a (0.8 g, 90%)

Ethyl 6-(Acetyl-1-piperazinyl)-5-fluoronicotinonitrile (12b) — According to the method described for the preparation of 12a, 11a (0.5 g, 1.8 mmol) was worked up to give 12b (0.4 g, 91%).

Ethyl 6-(Acetyl-1-piperazinyl)-2-[N-ethyl-N-(2-ethoxy carbonylethyl)amino]-5-fluoronicotinate (13) — A mixture of 11a (2.7 g, 8.2 mmol), ethyl 3-ethyaminopropionate (2.4 g, 16.4 mmol), NaHCO₃ (1.4 g, 16.4 mmol) and DMF (54 ml) was heated at 120–130°C for 8.5 h with vigorous stirring. The insoluble material was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue was taken up in water and toluene. The toluene layer was separated and extracted with 10% HCl. The aqueous layer was made alkaline with K₂CO₃ and extracted with toluene. The extract was dried over Na₂SO₄ and concentrated to dryness. The crude product was purified by column chromatography on silica gel with CHCl₃ as an eluent to give 13 (1.5 g, 42%). MS m/z: 438 (M⁺); 423, 393, 363, 351, 337, 291.

The toluene layer which had been extracted with 10% HCl was washed with water and dried over Na₂SO₄. After removal of the solvent, the residue was purified by column chromatography on silica gel with CHCl₃ as an eluent to give 14a (0.1 g, 4%).

Ethyl 6-(Acetyl-1-piperazinyl)-2-ethy lamino-5-fluoronicotinate (14a) — A mixture of 11a (1.0 g, 3.0 mmol), ethylamine (70% solution in water, 5 ml) and EtOH (15 ml) was heated at 90°C for 13 h in a sealed tube. The mixture was concentrated to dryness and taken up in water and AcOEt. The organic layer was separated and dried over Na₂SO₄. After removal of the solvent, hexane was added. The resulting solid was collected by filtration and washed with iso-Pr₂O to give 14a (0.9 g, 88%).

6-(Acetyl-1-piperazinyl)-2-ethy lamino-5-fluoronicotinonitrile (14b) — i) According to the method described for the preparation of 14a, 11b (1.0 g, 3.5 mmol) was worked up to give 14b (0.8 g, 78%).

ii) A mixture of 11b (1.0 g, 3.5 mmol), ethyl 3-ethyaminopropionate (1.0 g, 6.9 mmol), K₂CO₃ (0.5 g, 3.6 mmol) and DMF (5 ml) was heated at 140–160°C for 7.5 h with vigorous stirring, and then concentrated to dryness under reduced pressure. After addition of water, the mixture was extracted with toluene. The extract was washed successively with 10% HCl and water, and dried over Na₂SO₄. After removal of the solvent, the residue was purified by column chromatography on silica gel with CHCl₃ as an eluent to give 14b (0.55 g, 53%).

Ethyl 7-(Acetyl-1-piperazinyl)-1-ethyl-6-fluoro-1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylate (15) — Potassium tert-butoxide (0.4 g, 3.5 mmol) was gradually added to a stirred solution of 13 (1.4 g, 3.2 mmol) in toluene (14 ml). The mixture was stirred for 1 h at room temperature. The resulting precipitate was collected by filtration and dissolved in 1 N AcOH (5 ml). The mixture was extracted with AcOEt, and the extract was dried over...
Na$_2$SO$_4$. After removal of the solvent, hexane was added. The resulting crystals were collected by filtration to give 15 (1.0 g, 80%), which was recrystallized from a mixture of CH$_2$Cl$_2$ and hexane, mp 141—143 °C. Anal. Calcd for C$_{19}$H$_{25}$FN$_4$O$_4$: C, 58.15; H, 6.42; F, 4.84; N, 14.28. Found: C, 57.90; H, 6.25; F, 4.59; N, 14.12. IR (KBr) cm$^{-1}$: 1725, 1635. NMR (100 MHz, CDCl$_3$): 1.17 and 1.27 (each 3H, t, J=7 Hz, CH$_2$CH$_3$), 2.13 (3H, s, COCH$_3$), 3.3—3.9 (13H, m, C-2, C-3 and piperazinyl H, NCH$_2$CH$_3$), 4.22 (2H, q, J=7 Hz, OCH$_2$CH$_3$), 7.62 (1H, d, J=13 Hz, aromatic H).

The use of NaH instead of tert-BuOK gave an 80% yield of 15.

Ethyl 7-(4-Acetyl-1-piperazinyI)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (16) —— A mixture of 15 (500 mg, 1.28 mmol), chloranil (315 mg, 1.28 mmol), pyridine (0.1 ml) and CHC$_3$ (10 ml) was heated to reflux for 30 min. The solution was washed with 1 N NaOH (5 ml) and dried over Na$_2$SO$_4$. After removal of the solvent, Et$_2$O was added. The resulting crystals were collected by filtration to give 16 (440 mg, 88%), which was recrystallized from AcOEt, mp 195—197 °C (lit. 195—197 °C).

Acknowledgements The authors wish to thank Dr. H. Nishimura, deputy director, Research and Development Headquarters, for his encouragement throughout this work. Thanks are also due to Messrs. H. Okada and K. Shibamori for their assistance in the synthetic work, and to members of the analytical section of the Laboratories for elemental analyses and spectral measurements.

References and Notes


