Synthesis of Fluorinated Pyridines by the Balz-Schiemann Reaction. An Alternative Route to Enoxacin, A New Antibacterial Pyridonecarboxylic Acid [1]

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Fluorination of the 2,6-disubstituted 3-aminopyridines **5** and **12** by the Balz-Schiemann reaction is described. 2,6-Dichloro-3-pyridinediazonium tetrafluoroborate (**6**) and 2-substituted 6-acetylamino-3-pyridinediazonium tetrafluoroborates **13** were heated with or without a solvent to give the corresponding fluorinated pyridines **7** and **14**, respectively, in good yields. 2-Substituted 6-acetylamino-3-fluoropyridines (**14**) were converted by a known method into a series of 7-substituted 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids **21** including enoxacin [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid [(**2**)], a new potential antibacterial agent.

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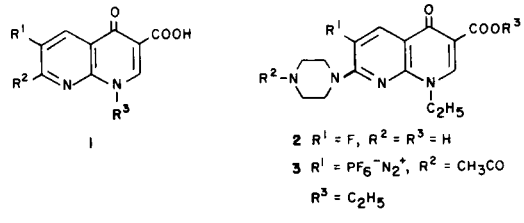
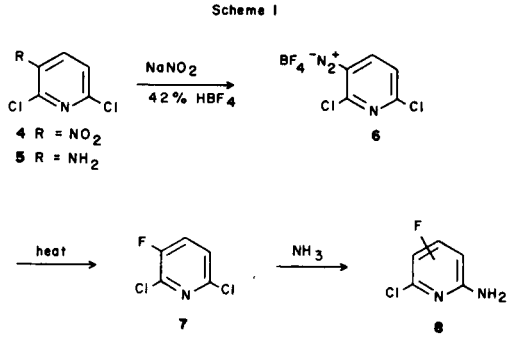
In our previous paper [2], a synthesis of 1,7-disubstituted 6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids **1** was reported. Among these compounds prepared, enoxacin (**2**) was selected as a promising candidate for a new potent antibacterial agent. The reported method for the synthesis of enoxacin involved the Balz-Schiemann reaction [3] of 7-(4-acetyl-1-piperazinyl)-3-ethoxycarbonyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-6-diazonium hexafluorophosphate (**3**). However, the yield (36%) of the fluorination process was unsatisfactory. The present study was undertaken to develop an alternative, efficient route for the synthesis of enoxacin and its analogs.

Chart I



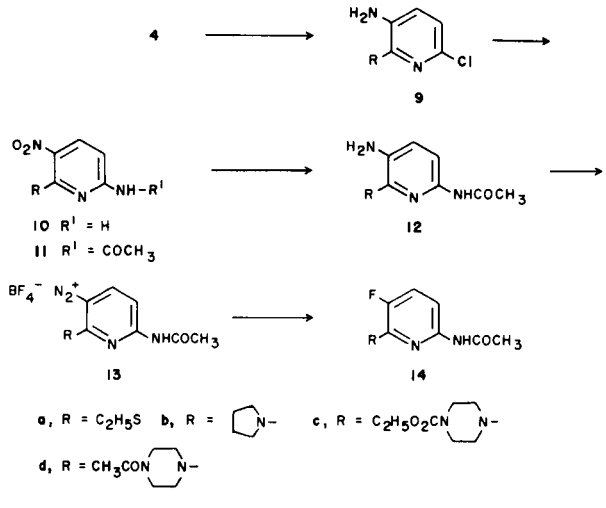
It seemed desirable to us that introduction of the fluorine atom should be carried out prior to construction of the 1,8-naphthyridine ring. We studied first the Balz-Schiemann reaction with 3-amino-2,6-dichloropyridine (**5**) leading to 2,6-dichloro-3-fluoropyridine (**7**) which would become a key intermediate in our synthesis. 2,6-Dichloro-3-nitropyridine (**4**) was converted into the 3-amino analog **5**, which was diazotized with sodium nitrite in 42% tetrafluoroboric acid to give the corresponding 3-pyridinediazonium tetrafluoroborate **6** showing ν N≡N 2260 cm^{-1} in its ir spectrum (Scheme I). Heating the salt **6** with anhydrous magnesium sulfate at about 200° under reduced pressure afforded a 67% yield of **7** which was very sublimable even at room temperature. Regioselective conversion of **7** to 6-amino-2-chloro-3-fluoropyridine caused initial difficulties since an attempted amination of **7** with ammonia in a sealed tube resulted in the formation of **5** along with the positionally unidentified 2-amino-6-chloro-3 or 5-fluoropyridine (**8**) in a 2:5 ratio as determined by gas chromatography.

Scheme I



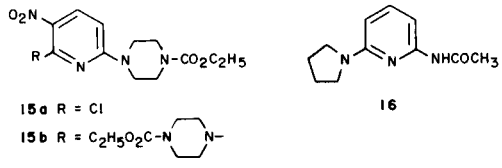
Since the foregoing process appeared to be inherently unsuited to the preparation of 6-amino-2-chloro-3-fluoropyridine, development of another route which permitted

Scheme II



the synthesis of enoxacin was required. The chloro group at position 2 in **4** could be replaced preferentially with ease by ethylthio, 1-pyrrolidinyl, 4-ethoxycarbonyl-1-piperazinyl, and 4-acetyl-1-piperazinyl groups to give the corresponding 2-substituted 6-chloro-3-nitropyridines **9a-d**

Chart II



(Scheme II). High performance liquid chromatography revealed that the products from the reaction of **4** with *N*-ethoxycarbonylpiperazine consisted of **4**, **9c**, **15a**, and **15b** in an approximately 1:100:9:3 ratio. The assigned structure **9** was supported by the ^{13}C nmr spectroscopy. The reported data for 2-chloro- and 2-dimethylaminopyridines [4] show that the replacement of the chloro group by the dimethylamino function leads to a downfield shift of 7.8 ppm for C-2 and upfield shifts of 11.0 and 2.1 ppm for C-5 and C-6, respectively. Such prominent shifts of the ring carbon signals of **9b-d** were observed similarly in their ^{13}C nmr spectra compared with that of the starting compound **4**. As shown in Table I, the spectrum of **9c**, for example, showed a downfield shift of 9.4 ppm for C-2 as well as upfield shifts of 10.3 and 1.2 ppm for C-5 and C-6 signals, respectively, being quite consistent with the reported data. In contrast, the spectrum of **15a** (the regioisomer of **9c**) revealed distinct downfield shifts of 1.3 and 4.5 ppm for C-2 and C-6, respectively, and the larger upfield shift of 20.2 ppm for C-5. These observations permit assignment of the site of the replacement as position 2 in **4**.

The chloropyridine **9** thus obtained was treated with ammonia to give the amino compound **10**. Acetylation of **10** with acetic anhydride produced the acetylaminopyridine **11**. Catalytic reduction of **11** with palladium-on-carbon followed by successive treatment of **12** with sodium nitrite in 42% tetrafluoroboric acid afforded the diazonium tetrafluoroborate **13**. 6-Acetylamino-2-(1-pyrrolidinyl)-3-pyridinediazonium tetrafluoroborate (**13b**) when heated with magnesium sulfate gave the desired 3-fluoro compound **14b** in an unsatisfactory (15%) yield, accompanied by a concomitant formation of 6-acetylamino-2-(1-pyrrolidinyl)pyridine (**16**) arising from replacement of the diazonium group by hydrogen during the thermal decomposition. The use of xylene as a reaction medium, on the other hand, effected smoothly the "fluorodediazoniation" of **13b** to give a 57% yield of **14b** without formation of the by-product **16**. Analogously, upon heating under reflux in petroleum benzine, the diazonium salts **13a,c,d** afforded the corresponding 3-fluoro compounds **14a,c,d** in good to excellent yields. In order to optimize the yield of the thermal decomposition a variety of media was examined for the diazonium salt **13d** as a representative. As summarized in Table II, the use of cyclohexane led to the best results in the highest yield at the moderate reaction time.

Table II

Thermal Decomposition of the Diazonium Salt **13d** into the Fluoropyridine **14d** Using Various Media

Medium	Reaction Temperature (°C) [a]	Reaction Time (hour)	Yield (%) [b]
Petroleum Benzine	50-90	10.5	62
Tetrachloromethane	77	18.0	67
Ethyl Acetate	77	10.5	75
Cyclohexane	81	3.5	81
Isopropyl Acetate	89	3.0	40
n-Heptane	98	0.5	64
Toluene	111	0.3	65

[a] Corresponding to the refluxing temperature. [b] Yields are of the isolated product **14d**.

With the fluoro compound **14** in hand, construction of the 1,8-naphthyridine ring followed the route described in the previous paper [5]. Thus acidic hydrolysis of **14** and the subsequent condensation of **17** with diethyl ethoxymethylenemalonate afforded diethyl *N*-(2-substituted 3-fluoro-6-pyridyl)aminomethylenemalonate (**18**) as depicted in Scheme III. The malonate **18** upon heating with Dowtherm A or tridecane gave the 1,8-naphthyridine derivative **19** in an excellent yield. Treatment of **19** with ethyl iodide gave exclusively the N^1-ethyl compound **20**. The

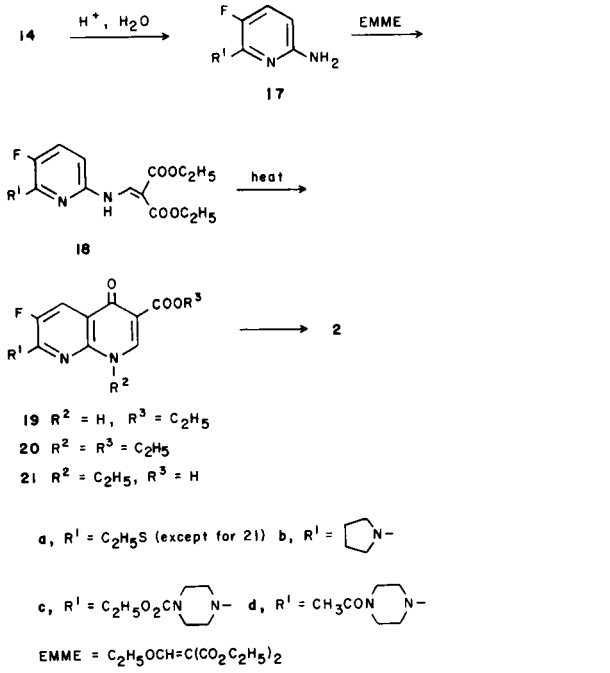
Table I

Carbon-13 NMR Chemical Shifts (in ppm) for Some Nitropyridines

Compound	C-2	C-3	C-4	C-5	C-6	ΔC-2 [a]	ΔC-5	ΔC-6
4	143.4	— [b]	136.7	124.0	153.5	0	0	0
9b	152.4	130.3	137.4	110.8	149.9	+9.0	−13.2	−3.6
9c	152.8	131.3	138.3	113.7	152.3	+9.4	−10.3	−1.2
9d	152.9	131.4	138.4	114.0	152.1	+9.5	−10.0	−1.4
15a	144.7	133.4	137.1	103.8	158.0	+1.3	−20.2	+4.5

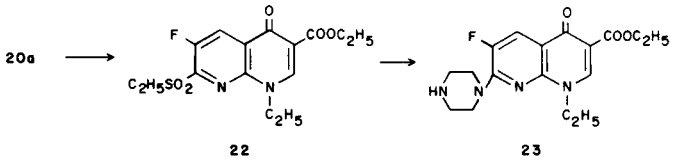
[a] Differences in chemical shifts; positive and negative signs represent downfield and upfield shifts, respectively. [b] Not observed.

Scheme III



site of the ethylation was proved by the ^{1}H nmr spectra of **20a-d** showing a singlet at the range of δ 8.5-8.7 characteristic of the signal of H-2 adjacent to the nitrogen atom in an *N*-alkyl-4-pyridone system [5,6]; if the *O*-ethyl counterpart due to a potentially tautomeric structure of **19** were the case, the H-2 resonance would appear at the lower field around δ 9.3. The mild hydrolysis of the resultant esters **20b-d** gave readily the corresponding carboxylic acids **21b-d**.

Scheme IV



Finally, the *N*-protective groups in **21c** and **21d** were removed by prolonged heating with 10% sodium hydroxide and 10% hydrochloric acid, respectively, to give enoxacin in good yields. Direct hydrolysis of either *N*-protected ester **20c** or **20d** also afforded enoxacin. A new synthetic route permitting the large-scale preparation of enoxacin has now been accomplished in ten reaction steps starting from **4** *via* the fluoropyridine **14**; the yields in most of the steps have not been optimized. Furthermore, the 7-ethylthio analog **20a** was oxidized with *m*-chloroperbenzoic acid to afford the ethanesulfonyl analog **22**. Compound **22** is a versatile intermediate for the preparation of analogs with the alicyclic amino group at position 7; for example, **22** was allowed to react with piperazine in acetonitrile, giving the enoxacin ethyl ester **23** which was hydrolyzed to enoxacin.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi model 215 spectrophotometer. The ^{1}H nmr spectra were taken at 60 or 100 MHz on either a Varian EM-360A or HA-100D spectrometer with tetramethylsilane as an internal standard. The ^{13}C nmr spectra were taken on a Varian FT-80A spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6L single focusing mass spectrometer using the direct inlet system at 70 eV ionization potential. High performance liquid chromatography was performed with a Waters Associates model 204 and model 440 absorbance detector (column, Develosil ODS-10, 0.3 × 4 mm i.d., Nomura Chemical Co.; mobil phase, a 1:1 mixture of 20% acetic acid and ethanol; flow rate, 1.2 ml/minute; monitored at 254 nm). Gas chromatography was carried out with a Yanaco G-180 apparatus (column, 10% SP-1000 on chromosorb-W AW, Gasukuro Kogyo Co., Japan, 0.75 × 3 mm i.d.; column temperature, 140-240°, 5°/minute; injection and detection temperature, 230°; carrier gas, He 0.7 kg/cm^2).

Organic solutions were dried over anhydrous sodium sulfate or magnesium sulfate. The ir, ^{1}H nmr and/or ms spectra were obtained on all compounds were consistent with assigned structures.

3-Amino-2,6-dichloropyridine (**5**).

2,6-Dichloro-3-nitropyridine (**4**) [7] (38.6 g, 0.2 mole) was hydrogenated in 400 ml of methanol with *ca.* 40 ml of Raney nickel at room temperature until the required volume of hydrogen had been taken up. The mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness *in vacuo*. The residue was taken up in water and extracted with chloroform. The extract was dried and concentrated to dryness. The residue was crystallized from *n*-hexane-diethyl ether (*ca.* 1:1 v/v), giving 28.4 g (87%) of **5**, mp 119-121° (lit [8], mp 119°).

Anal. Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; Cl, 43.50; N, 17.19. Found: C, 36.88; H, 2.68; Cl, 43.51; N, 17.26.

2,6-Dichloro-3-pyridinediazonium Tetrafluoroborate (**6**).

To a stirred solution of **5** (16.3 g, 0.1 mole) in 300 ml of 42% tetrafluoroboric acid was added dropwise an aqueous saturated solution of sodium nitrite (6.9 g, 0.1 mole) while the reaction temperature was kept at 5°. The resulting precipitate was filtered off, washed successively with cold water and diethyl ether, and dried under reduced pressure (3 torr) below 80°, giving 14.8 g (57%) of **6**, mp 167-169° dec; ir (potassium bromide): 2260 cm^{-1}.

Anal. Calcd. for $C_5H_2BCl_2F_4N_3$: C, 22.94; H, 0.76; Cl, 27.09; F, 29.03; N, 16.05. Found: C, 22.91; H, 0.77; Cl, 27.13; F, 29.24; N, 16.14.

2,6-Dichloro-3-fluoropyridine (**7**).

A mixture containing 13.1 g (0.05 mole) of **6** and 13.1 g of anhydrous magnesium sulfate was heated at 170-200° under reduced pressure (4-10 torr). The product distilled and/or sublimed during the reaction course was collected under cooling with dry-ice/acetone, and taken up in chloroform. The organic solution was washed with 1*N* sodium hydroxide, dried over potassiuum carbonate, and concentrated to dryness. The residue was crystallized from *n*-hexane-diethyl ether (*ca.* 1:1 v/v) to give 5.6 g (67%) of **7** as very sublimable colorless needles, mp 44-46°; ms: 166 (M$^+$); ^{1}H nmr (deuteriochloroform): δ 7.47 (1H, d,d, $J_{H4,H5}$ = 8.5 Hz, $J_{H4,F}$ = 7.0 Hz, H-4), 7.27 (1H, d,d, $J_{H4,H5}$ = 8.5 Hz, $J_{H5,F}$ = 3.3 Hz, H-5). Elemental analysis for **7** could not be performed owing to its high sublimability.

2-Amino-6-chloro-3 or 5-fluoropyridine (**8**). Amination of **7**.

In a 100-ml sealed tube were placed 1.7 g (0.01 mole) of **7**, 20 ml of 27% aqueous ammonia, and 4 ml of ethanol. The mixture was heated at

Table III

2,3,6-Trisubstituted Pyridines

Compound	Mp (°C)	Recrystallization Solvent	Yield (%) [a]	Synthetic Method [b]	Formula	Analysis (%) Calcd. (upper), Found (lower) C	H	N	F	Cl
9b	86-87	*n*-Hexane-Ether	88.4	A	$C_9H_{10}ClN_3O_2$	47.48	4.43	18.46	—	15.58
						47.20	4.58	18.42	—	15.72
9c	80-81	Ethanol	91.3	A	$C_{12}H_{15}ClN_4O_4$	45.79	4.80	17.80	—	11.27
						45.66	4.94	17.96	—	11.57
9d	137-138	Ethyl acetate	89.0	A	$C_{11}H_{13}ClN_4O_3$	46.41	4.60	19.68	—	12.45
						46.51	4.80	19.51	—	12.28
10a	131-132	Dichloromethane	36.4	B	$C_7H_9N_3O_2S$	42.20	4.55	21.09	—	16.09 [c]
						42.00	4.47	21.41	—	16.11 [c]
10b	132-134	*n*-Hexane-Dichloromethane	88.7	B	$C_9H_{12}N_4O_2$	51.91	5.81	26.91	—	—
						51.74	5.78	26.67	—	—
10c	132-134	*n*-Hexane-Dichloromethane	54.6	B	$C_{12}H_{17}N_5O_4$	48.80	5.80	23.72	—	—
						48.68	6.02	23.52	—	—
10d	202-203	Ethanol-Chloroform	76.3	B	$C_{11}H_{15}N_5O_3$	49.80	5.70	26.40	—	—
						49.92	5.97	26.14	—	—
11a	167-168	Ethyl acetate	94.1	C	$C_9H_{11}N_3O_3S$	44.80	4.60	17.42	—	13.29 [c]
						44.93	4.67	17.65	—	13.16 [c]
11b	195-197	Acetone	97.3	C	$C_{11}H_{14}N_4O_3$	52.79	5.64	22.39	—	—
						52.80	5.61	22.23	—	—
11c	168-169	Acetone	95.0	C	$C_{14}H_{19}N_5O_5$	49.84	5.68	20.76	—	—
						49.99	5.75	20.69	—	—
11d	221-223	Acetonitrile	88.0	C	$C_{13}H_{17}N_5O_4$	50.81	5.58	22.79	—	—
						50.74	5.46	22.70	—	—
13a	132-133 dec	[d]	75.8	D	$C_9H_{11}BF_4N_4OS$	— [e]	—	—	—	—
13b	*ca.* 150 dec	[d]	84.7	D	$C_{11}H_{14}BF_4N_5O$	— [e]	—	—	—	—
13c	117-118 dec	[d]	89.3	D	$C_{14}H_{19}BF_4N_6O_3$	— [e]	—	—	—	—
13d	121-124 dec	[d]	89.5	D	$C_{13}H_{17}BF_4N_6O_2$	— [e]	—	—	—	—
14a	110-113	Ethanol-Water	40.2	E	$C_9H_{11}FN_2OS$	50.45	5.18	13.18	8.87	14.96 [c]
						50.20	5.19	13.17	9.11	15.18 [c]
14b	126-128	*n*-Hexane-Dichloromethane	56.8	E	$C_{11}H_{14}FN_3O$	59.18	6.32	18.82	8.51	—
			15.4	F		59.36	6.46	19.05	8.48	—
14c	132-133	Ethyl acetate	82.3	E	$C_{14}H_{19}FN_4O_3$	54.18	6.14	18.06	6.12	—
						54.00	6.21	18.21	6.03	—
14d	178-180	Ethyl acetate	80.5	E	$C_{13}H_{17}FN_4O_2$	55.75	6.12	20.01	6.78	—
						55.47	6.11	19.87	6.92	—
18a	78-79	*n*-Hexane	91.7	G	$C_{15}H_{19}FN_2O_4S$	52.62	5.59	8.18	9.37	5.55 [c]
						52.14	5.32	8.11	9.69	5.73 [c]
18b	109-111	*n*-Hexane-Dichloromethane	73.5	G	$C_{17}H_{22}FN_3O_4$	58.11	6.31	11.96	5.41	—
						58.32	6.36	11.94	5.12	—
18c	144-145	Methanol	92.4	G	$C_{20}H_{27}FN_4O_6$	54.78	6.21	12.78	4.33	—
						54.65	6.61	12.69	4.56	—
18d	164-165	Ethanol	80.0	G	$C_{19}H_{25}FN_4O_5$	55.87	6.17	13.72	4.65	—
						55.61	6.26	13.48	4.46	—

[a] Yields are of purified products and are not maximal. [b] Capital letters refer to the method described in the Experimental section. [c] Analysis for S. [e] Elemental analysis was not performed.

150-157° for 16 hours, cooled, and extracted with chloroform. The extracts obtained from two runs of this reaction were combined, dried, and concentrated to dryness. A small part of the residue was submitted to gas chromatography; the crude product consisted of an unknown compound A (1.55%), the unchanged compound **7** (0.52%), compound **8** (64%), an unknown compound B (5.2%), an unknown compound C (2.6%), and compound **5** (26%), which was eluted in this order. The remaining residue was crystallized from *n*-hexane-diethyl ether to give 0.60 g (18%) of **5**, mp 119-121°; this compound was identified with an authentic specimen of **5**.

From the mother-liquor of crystallization, a mixture containing **5** and **8** in an about 1:4 ratio was obtained. An attempt to isolate **8** was unsuccessful; the structure of **8** was assignable on the basis of ^{1}H nmr (deuteriochloroform): δ 7.20 (1H, d,d, J = 8, 10 Hz, H-4), 6.60 (1H, d,d, J = 3, 8 Hz, H-3 or H-5), 4.5-5.8 (2H, broad s, NH_2).

Table IV

6-Fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Derivatives

Compound	Mp (°C)	Recrystallization Solvent	Yield (%) [a]	Synthetic Method [b]	Formula	Analysis (%) Calcd. (upper), Found (lower) C	H	N	F	S
19a	280-284	DMF	75.5	H	$C_{13}H_{13}FN_2O_3S$	52.69	4.42	9.45	6.41	10.82
						52.55	4.39	9.36	6.61	11.10
19b	295-298	DMF	76.3	H	$C_{15}H_{16}FN_3O_3$	59.01	5.23	13.76	6.22	—
						59.33	5.35	13.89	6.12	—
19c	288-292	DMF	75.8	H	$C_{16}H_{21}FN_4O_5$	55.09	5.39	14.28	4.84	—
						55.09	5.65	14.27	4.85	—
19d	290-295	DMF	95.5	H	$C_{17}H_{19}FN_4O_4$	56.35	5.29	15.46	5.24	—
						56.14	5.30	15.28	5.15	—
20a	135-137	Ethyl acetate	78.4	I	$C_{15}H_{17}FN_2O_3S$	55.54	5.28	8.64	5.86	9.89
						55.26	5.26	8.36	5.90	10.16
20b	220-222	Ethanol-Chloroform	84.7	I [c]	$C_{17}H_{20}FN_3O_3$	61.25	6.05	12.61	5.70	—
						61.06	5.98	12.60	5.67	—
20c	171-173	Ethanol	87.5	I	$C_{20}H_{25}FN_4O_5$	57.13	5.99	13.33	4.52	—
						57.02	6.07	13.34	4.24	—
20d	195-197	Ethyl acetate	89.7	I [c]	$C_{19}H_{23}FN_4O_4$	58.45	5.94	14.35	4.87	—
						58.16	6.05	14.17	4.81	—
21b	229-300	Ethyl acetate	91.7	J [c]	$C_{15}H_{16}FN_3O_3$	59.01	5.28	13.76	6.22	—
						59.14	5.18	14.02	6.23	—
21c	246-247	Ethanol-Dichloromethane	72.9	J	$C_{16}H_{21}FN_4O_5$	55.10	5.39	14.28	4.84	—
						54.93	5.46	14.24	4.80	—
21d	>300	Ethanol-Dichloromethane	85.6	J	$C_{17}H_{19}FN_4O_4$	56.35	5.29	15.46	5.24	—
						56.36	5.43	15.49	5.15	—

[a] and [b] See Footnotes in Table III. [c] This compound was also prepared by the alternative method reported in the previous paper [2].

6-Chloro-2-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (**9c**). Method A.

To a cold solution of **4** (57.9 g, 0.3 mole) in 300 ml of chloroform was added dropwise a solution of *N*-ethoxycarbonyl piperazine (56.3 g, 0.35 mole) and triethylamine (46 ml, 0.33 mole) in 150 ml of chloroform over a period of 2 hours with stirring, while the reaction temperature was maintained at −5° to 0°. After an additional 2-hour stirring at the same temperature, a dilute hydrochloric acid (22 ml of concentrated hydrochloric acid and 440 ml of water) was added; the chloroform layer was separated, washed with water, dried, and concentrated to give 102 g of an oily product. A part of the chloroform layer was submitted to hplc, which revealed the crude product to consist of **9c** (88%), 2-chloro-6-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (**15a**) (8.0%), 2,6-bis(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (**15b**) (3.1%), and **4** (1.0%). A small sample of the product was purified by column chromatography on silica gel using chloroform as an eluent. From the first fraction, the unchanged compound **4** was recovered. The second fraction gave **9c**, Table III; ir (potassium bromide): 1680 cm^{-1}. The third fraction afforded **15a**, mp 140-141° (recrystallized from ethanol); ir (potassium bromide): 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.21 (1H, d, J = 9 Hz, H-4), 6.52 (1H, d, J = 9 Hz, H-5), 4.19 (2H, q, J = 7 Hz, OCH_2CH_3), 3.69 (8H, m, piperazine H), 1.29 (3H, t, J = 7 Hz, OCH_2CH_3); ^{13}C nmr, See Table I.

Anal. Calcd. for $C_{12}H_{15}ClN_4O_4$: C, 45.79; H, 4.80; Cl, 11.27; N, 17.80. Found: C, 45.96; H, 4.69; Cl, 11.54; N, 17.98.

The last fraction afforded **15b**, mp 131-132° (recrystallized from ethanol); ir (potassium bromide): 1695 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.22 (1H, d, J = 9 Hz, H-4), 6.11 (1H, d, J = 9 Hz, H-5), 4.18, 4.17 (each 4H, q, J = 7 Hz, OCH_2CH_3 × 2), 1.28 (6H, t, J = 7 Hz, OCH_2CH_3 × 2).

Anal. Calcd. for $C_{19}H_{28}N_6O_6$: C, 52.28; H, 6.47; N, 19.26. Found: C, 52.10; H, 6.71; N, 19.20.

By the same procedure, compounds **9a,b,d** were prepared; see Table III. Compound **9a** was used in the next step without further purification.

2-(4-Acetyl-1-piperazinyl)-6-amino-3-nitropyridine (**10d**). Method B.

In a 1-liter autoclave equipped with a stirrer and a thermometer were placed 50 g (0.176 mole) of **9d** and 300 ml of 13% ethanolic ammonia. The mixture was heated at 70-72° for 15 hours with stirring. After cooling, the precipitate was filtered off to give 30 g of **10d**. The filtrate was concentrated to dryness *in vacuo*, and the residue was triturated with water to give an additional 5.5 g of **10d** (totally 35.5 g, 76%); see Table III.

Also prepared according to this procedure were compounds **10a-c**, Table III. The reaction temperature and time were as follows; **10a**: 80°, 16 hours; **10b**: 112-120°, 18 hours; **10c**: 100-110°, 15 hours.

6-Acetylamino-2-(4-acetyl-1-piperazinyl)-3-nitropyridine (**11d**). Method C.

A mixture containing 30.4 g (115 mmoles) of **10d**, 30 ml of acetic anhydride, and 300 ml of acetic acid was heated at 90° for 30 minutes, and concentrated to dryness *in vacuo*. The residue was triturated with acetone. The resulting solid was filtered off and washed with acetone to give 30.8 g (88%) of **11d**; see Table III.

6-Acetylamino-2-(4-acetyl-1-piperazinyl)-3-pyridinediazonium Tetrafluoroborate (**13d**). Method D.

To a stirred mixture containing 26 g (84.7 mmoles) of **11d**, 100 ml of acetic acid, and 300 ml of ethanol was added portionwise 18 g (275 mmoles) of zinc powder over a period of 10 minutes, during which time the reaction temperature rose to 80°. After reflux for an additional 10 minutes, the insoluble material was removed by filtration and the filtrate was concentrated to dryness *in vacuo* to give crude 6-acetylamino-2-(4-acetyl-1-piperazinyl)-3-aminopyridine (**12d**), which was taken up in a mixture of 42% tetrafluoroboric acid (50 ml) and ethanol (30 ml). To the reaction mixture maintained at −4° to − 7° was added a solution of sodium nitrite (6.4 g, 93.2 mmoles) in 30 ml of water over a period of 5 minutes. After an additional 10 minutes stirring, the precipitate was filtered off, and washed successively with ethanol and chloroform to give 28.5 g

(90%) of **13d**; ir (potassium bromide): 2150 cm^{-1}.

6-Acetylamino-2-(4-acetyl-1-piperazinyl)-3-fluoropyridine (**14d**). Method E.

A suspension of **13d** (7.0 g, 18.6 mmoles) in 70 ml of cyclohexane was heated to reflux for 4 hours and then allowed to cool. The resulting reddish brown solid was filtered off, and taken up in a mixture of water (20 ml) and chloroform (40 ml). The chloroform layer was washed with dilute aqueous ammonia, dried, and concentrated *in vacuo*. The residue was triturated with ether to give 4.2 g (81%) of **14d**; ir (potassium bromide): 3250, 1700, 1620 cm^{-1}; ms: 280 (M^+); ^1H nmr (deuteriochloroform): δ 7.70 (1H, d,d, $J_{H4,F}$ = 12 Hz, $J_{H4,H5}$ = 9 Hz, H-4), 7.30 (1H, d,d, $J_{H5,F}$ = 3 Hz, $J_{H5,H4}$ = 9 Hz, H-5), 3.60 (8H, m, piperazine H), 2.18, 2.13 (each 3H, s, $COCH_3$ × 2); see Table III.

Also according to this procedure, compounds **14a**, **14b**, and **14c** were prepared using petroleum benzine, xylene, and toluene, respectively, as the reaction medium (Table III).

6-Acetylamino-3-fluoro-2-(1-pyrrolidinyl)pyridine (**14b**) and 6-Acetylamino-2-(1-pyrrolidinyl)pyridine (**16**). Method F.

A mixture containing 3.9 g (12.2 mmoles) of **13b** and 4.0 g (33.2 mmoles) of anhydrous magnesium sulfate was heated at 140-170° for 10 minutes under reduced pressure (2-3 torr). The mixture was cooled and extracted with hot chloroform. The extract was washed with saturated sodium bicarbonate, dried over potassium carbonate, and the solvent was evaporated. The residue was chromatographed on silica gel. The first fraction eluted with a 1:1 mixture of *n*-hexane and chloroform afforded 0.42 g (15%) of **14b**; ir (potassium bromide): 3200, 1660, 1610 cm^{-1}; ms: 223 (M^+); ^1H nmr (trifluoroacetic acid-d_1): δ 7.67 (1H, d,d, $J_{H4,F}$ = 12 Hz, $J_{H4,H5}$ = 8.5 Hz, H-4), 6.42 (1H, d,d, $J_{H5,F}$ = 4 Hz, $J_{H4,H5}$ = 8.5 Hz, H-5), 3.93 (4H, m, pyrrolidine H-2, H-5), 2.46 (3H, s, $COCH_3$), 2.26 (4H, m, pyrrolidine H-3, H-4); see Table III.

The crude product obtained from the second fraction was recrystallized from *n*-hexane-diethyl ether, giving 0.29 g (12%) of **16**, mp 139-140°; ^1H nmr (deuteriochloroform with $Eu(FOD)_3$): δ 7.6-8.0 (1H, broad s, NH), 7.2-7.6 (2H, m, H-3, H-4), 6.10 (1H, d,d, J = 2, 7 Hz, H-5), 3.40 (4H, pyrrolidine H-2, H-5), 2.14 (3H, s, $COCH_3$), 1.97 (4H, m, pyrrolidine H-3, H-4).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.36; H, 7.37; N, 20.47. Found: C, 64.53; H, 7.32; N, 20.33.

Diethyl *N*-[2-(4-Acetyl-1-piperazinyl)-3-fluoro-6-pyridyl]aminomethylenemalonate (**18d**). Method G.

To a hot solution of **14d** (8.9 g, 31.8 mmoles) in 90 ml of methanol was added 9 ml of 10% hydrochloric acid. The mixture was heated to reflux for 2 hours. After addition of potassium carbonate (3.3 g) and concentration to dryness, the residue was taken up in a mixture of water (50 ml) and chloroform (100 ml). The organic layer was separated, washed with water, and dried. The solvent was evaporated to give 2-(4-acetyl-1-piperazinyl)-6-amino-3-fluoropyridine (**17d**), which was then added to a solution of 6.87 g (31.8 mmoles) of diethyl ethoxymethylenemalonate in 20 ml of ethanol. The reaction mixture was heated to reflux for 2 hours with stirring. After ice-cooling, the resulting solid was filtered off, washed with cold ethanol, and recrystallized to give 10.4 g (80%) of **18d**; ir (potassium bromide): 1710, 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 11.12 (1H, d, J = 13 Hz, N*H*CH=), 9.12 (1H, d, J = 13 Hz, NHC*H*=), 6.38 (1H, d,d, $J_{H4,H5}$ = 8 Hz, $J_{H5,F}$ = 3 Hz, H-5), 7.32 (1H, d,d, $J_{H4,H5}$ = 8 Hz, $J_{H4,F}$ = 13 Hz, H-4), 4.27, 4.38 (each 2H, q, J = 7 Hz, OCH_2CH_3), 1.38, 1.42 (each, 3H, t, J = 7 Hz, OCH_2CH_3), 2.20 (3H, s, $COCH_3$), 3.65 (8H, m, piperazine H); see Table III.

Ethyl 7-(4-Acetyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**19d**). Method H.

To 46 ml of Dowtherm A maintained at 250° was added 4.6 g (11.3 mmoles) of **18d**. The mixture was heated at 248-249° for 13 minutes and allowed to cool to room temperature. After addition of diethyl ether (40 ml), the resultant solid was filtered off, washed successively with acetone and diethyl ether, and recrystallized to give 2.5 g (61%) of **19d**; ir (potassium bromide): 1690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.42 (1H, s, H-2), 8.03 (1H, d, J = 14 Hz, H-5), 4.27 (2H, q, J = 7 Hz, OCH_2CH_3), 3.72 (4H, m, $CH_2N^1CH_2$), 3.37 (4H, m, $CH_2N^4CH_2$), 2.10 (3H, s, $COCH_3$), 1.30 (3H, t, J = 7 Hz, OCH_2CH_3); see Table IV.

Alternatively, heating of **18d** with tridecane, instead of Dowtherm A, at 230-232° for 5 hours gave **19d** in 96% yield.

Ethyl 7-(4-Acetyl-1-piperazinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**20d**). Method I.

A mixture containing 3.62 g (10 mmoles) of **19d**, 2.76 g (20 mmoles) of potassium carbonate, and 40 ml of DMF was heated at 100° for 30 minutes with stirring. To this mixture was added 4.68 g (30 mmoles) of ethyl iodide. The reaction mixture was allowed to stir at the same temperature for 3 hours and then filtered to remove insoluble materials. The filtrate was concentrated to dryness *in vacuo*. The residue was taken up in a mixture of water (30 ml) and chloroform (50 ml). The organic phase was separated, washed with water, dried, and chromatographed on silica gel with chloroform to give 3.5 g (90%) of **20d**; this compound was identical in all respects with an authentic specimen of **20d** prepared by the alternative method described in the previous paper [2]; ir (potassium bromide): 1720, 1680, 1620 cm^{-1}; ms: 390 (M^+), 318 ($M^+ - C_2H_4CO_2$); ^1H nmr (deuteriochloroform): δ 8.55 (1H, s, H-2), 8.23 (1H, d, J = 14 Hz, H-5), 4.45 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 4.37 (2H, q, J = 7 Hz, NCH_2CH_3), 3.80 (8H, s, piperazine H), 2.18 (3H, s, $COCH_3$), 1.50 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 1.47 (3H, t, J = 7 Hz, NCH_2CH_3).

Also prepared according to this procedure were **20a-c** from **19a-c** with ethyl iodide; see Table IV.

7-(4-Ethoxycarbonyl-1-piperazinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**21c**). Method J.

A mixture containing 1.0 g (2.4 mmoles) of **20c**, 2 ml of 15% hydrochloric acid, and 2 ml of ethanol was heated to reflux for 15 minutes, concentrated to a half volume, diluted with 10 ml of water, and allowed to cool. The precipitate was filtered off, washed with water, and recrystallized to give 0.68 g (73%) of **21c**; ir (potassium bromide): 1720, 1690, 1620 cm^{-1}; ms: 392 (M^+), 348 ($M^+ - CO_2$); see Table IV.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic Acid, Enoxacin (**2**). (a) Method K.

A mixture containing 20.1 g (47.8 mmoles) of **21c**, 180 ml (450 mmoles) of 10% sodium hydroxide, and 20 ml of ethanol was heated to reflux for 4 hours and, after cooling, adjusted to *p*H 7.0-7.5 with 30% acetic acid. The precipitate was filtered off, washed successively with water and ethanol, and recrystallized to give 13.35 g (87%) of **2**, mp 220-224°, which was identical in all respects with an authentic specimen of **2** prepared by the method reported previously [2]. Hydrolysis of **21d** into **2** was described in the previous paper [2].

(b) Method L.

A solution of **23** (1.74 g, 5 mmoles) in 15 ml of 1*N* hydrochloric acid was heated at 95° for 1 hour with stirring. The mixture was cooled to give 1.6 g (90%) of the hydrochloride salt of **2**, mp >300° [2]. The salt was suspended in a small amount of water and the suspension was neutralized with 0.5*N* sodium hydroxide giving 1.39 g (87%) of **2**.

Ethyl 1-Ethyl-7-ethylsulfonyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**22**).

To a stirred solution of **20a** (4.0 g, 12.3 mmoles) in 60 ml of chloroform was added 5.4 g (31.3 mmoles) of *m*- chloroperbenzoic acid (*m*-CPBA). The reaction mixture was allowed to stir at room temperature. After 1-hour stirring, an additional 1.0 g (5.8 mmoles) of *m*-CPBA was added and the reaction was allowed to run for 1 hour at room temperature. After addition of 2*N* potassium carbonate (25 ml), the aqueous phase was separated, and extracted with chloroform. The extract and the initial chloroform phase were combined and concentrated to dryness. The residue was crystallized from ether. Recrystallization from ethyl acetate gave 3.8 g (87%) of **22**, mp 187-189°; ir (potassium bromide): 1680, 1640 cm^{-1}; ms: 356 (M^+), 284 ($M^+ - C_2H_4CO_2$); ^1H nmr (deuteriochloroform): δ 8.69

(1H, s, H-2), 8.63 (1H, d, J = 8.5 Hz, H-5), 4.50 (2H, q, J = 7.5 Hz, NCH_2CH_3), 4.23 (2H, q, J = 7.5 Hz, $CO_2CH_2CH_3$), 3.56 (2H, q, J = 7.5 Hz, $SO_2CH_2CH_3$), 1.54 (3H, t, J = 7.5 Hz, NCH_2CH_3), 1.47 (3H, t, J = 7.5 Hz, $SO_2CH_2CH_3$), 1.41 (3H, t, J = 7.5 Hz, $CO_2WCH_2CH_3$).

Anal. Calcd. for $C_{15}H_{17}FN_2O_5S$: C, 50.55; H, 4.81; F, 5.33; N, 7.86; S, 9.00. Found: C, 50.69; H, 4.83; F, 5.47; N, 7.72; S, 9.11.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylate (**23**).

A mixture containing 1.0 g (2.8 mmoles) of **22**, 1.2 g (14 mmoles) of anhydrous piperazine, and 30 ml of acetonitrile was heated to reflux for 1 hour and concentrated to dryness *in vacuo*. The residue was taken up in a mixture of chloroform and water. The organic phase was separated, dried, and chromatographed on silica gel with a 30:1 mixture of chloroform and methanol, giving 0.65 g (56%) of **23**, mp 150-151° (recrystallized from ethyl acetate); ir (potassium bromide): 1710, 1680 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}FN_4O_3$: C, 58.61; H, 6.03; F, 5.45; N, 16.08. Found: C, 58.52; H, 6.36; F, 5.44; N, 15.94.

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