New 7-Substituted Quinolone Antibacterial Agents. II. The Synthesis of 1-Ethyl-1,4-dihydro-4-oxo-7-(pyrazolyl, isoxazolyl, and pyrimidinyl)-1,8-naphthyridine and quinolone-3-carboxylic Acids

John M. Domagala* and Phred Peterson

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105

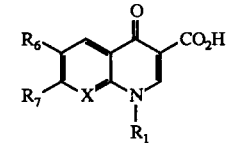
Received September 6, 1988

Synthetic methods for the construction of certain aromatic heterocyclic side chains for the quinolone antibacterials have been provided. In particular a series of 7-(pyrazol-3 or 4-yl, 4- or 5-isoxazolyl and 4- or 5-pyrimidinyl)-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine and quinoline-3-carboxylic acids have been prepared. All of the heterocycles were prepared from masked 1,3-dicarbonyl derivatives of nalidixic acid (**9**, **17**) or 7-acetyl-1-ethyl-1,4-dihydro-4-oxo-3-quinoline carboxylic acids (**8**). These masked 1,3-dicarbonyl derivatives were prepared by the use of *t*-butoxy-bis-dimethylaminomethane on the activated methyls of **9**, **19** and **8**. The pyrimidinyl analogs, substituted with a 2-amino or a 2-aminomethyl moiety, were the only derivatives with substantial antibacterial activity.

J. Heterocyclic Chem., **26**, 1147 (1989).

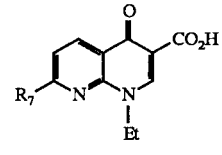
The orally active fluoroquinolone antiinfectives (Figure 1) have aroused a great deal of interest in recent years [1-3]. It has been shown that the C_7 substituent has a major influence on the antibacterial spectrum and *in vivo* efficacy of these agents [3-5]. Most of the currently significant fluoroquinolones such as enoxacin (**1**) and norfloxacin (**2**) contain the piperazinyl moiety at C_7, which has consistently demonstrated a good blend of potency and *in vivo* efficacy [2,6]. While many aliphatic heterocycles have been evaluated at C_7 [3,5], very few reports of aromatic heterocycles are available, and most of these involve aromatic heterocycles which are, like the piperazine, linked to the quinolone nucleus through a nitrogen-carbon bond [7], as in irloxacin (**3**) and S-29532 (**4**). The best known quinolone bearing an aromatic heterocycle not linked through nitrogen is rosoxacin (**5**) [8]. Many years ago, other carbon linked aromatic heterocycles, such as the 7-(pyrazol-4-yl)-and the 7-(4-pyrimidinyl)-1,8-naphthyridine derivatives of nalidixic acid (**6** and **7**), were reported by Rufer [9]. The synthesis was limited only to derivatives of nalidixic acid, and only to heterocycles with a methyl substituent α to the heterocyclenaphthyridine attachment. Such substitution, close to the quinoline or naphthyridine ring has been shown to strongly influence activity [10]. Very recently, Culbertson [11] has reported the synthesis of 7-(4-thiazolyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinoline carboxylic acids, which were all prepared from the pivotal 7-acetylquinolines **8**.

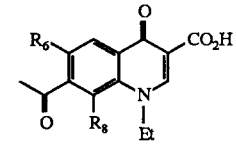
In this paper, we wish to expand upon the work of Rufer and Culbertson to provide and discuss a synthetic strategy for the preparation of the various isomeric pyrazoles, pyrimidines, and isoxazoles appended to C_7 of both the 1,8-naphthyridine and quinoline-3-carboxylic acids from readily available enamine precursors. The methods provided permit the construction of these heterocycles without the undesired alkyl substitution, and allow for the incorporation of a fluorine at C_6, which is widely recognized as a key element for overall potency [2,3].



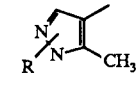
Compound	X	R_1	R_6	R_7
enoxacin **1**	N	Et	F	1-piperazine
norfloxacin **2**	CH	Et	F	1-piperazine
irloxacin **3**	CH	Et	F	1-pyrrole
S-29532 **4**	C—$CH_2CH_2CHCH_3$		F	1-imidazole
rosoxacin **5**	CH	Et	H	4-pyridine

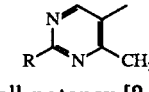
Figure 1. Clinically Singificant Quinolones





8



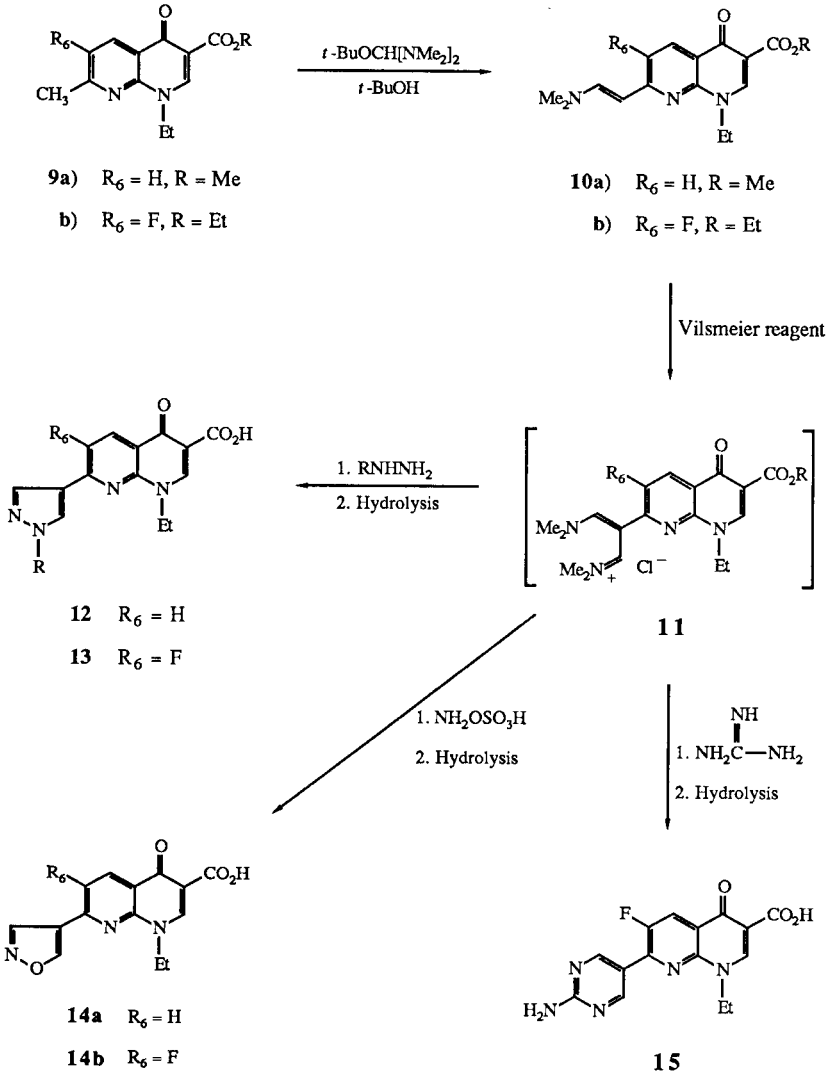


Our initial approach to the construction of C_7-heterocycles was similar to that used in the rosoxacin derivative work [8], where the heterocycle is incorporated early in the synthesis before construction of the 4-pyridone ring. Unfortunately, the thermal and acid conditions required to form the 4-pyridone ring system [5] were all too severe for

our heterocycles, and this strategy was quickly abandoned. Since Rufer had already shown that the methyl group in nalidixic acid and its esters **9a** is activated toward reaction with Bredereck's reagent (*t*-butoxy-bis-dimethylaminomethane) [12] to form the enamine **10a** (Scheme 1), we turned our attention to this pathway. In order to generate the prerequisite 2-substituted-1,3-dicarbonyl equivalents for preparing heterocycles at C_7, Rufer reacted **10a** with acetic anhydride under vigorous conditions. The acylation was successful, but all ensuing heterocycles contained the methyl substituent from the acetic anhydride. In order to avoid this methyl group, the enamine **11a** would be required. After some unsuccessful acylations with mixed formic acid anhydrides and ethyl formate, the Vilsmeier reagent [13] was chosen as a possible formic acid equivalent. At low temperatures, the Vilsmeier reagent reacted with **10a** to produce some form of the masked 1,3-dicarbonyl precursor **11a**, which was then captured by various hydrazines and hydroxylamine-*O*-sulfonic acid to give the pyrazoles **12** and isoxazole **14a** as their methyl esters (Table 1). The esters were conveniently purified from highly colored impurities by column chromatography and could be readily hydrolyzed to the acids **12** and **14a**. The pyrazole esters of **12** were amenable to hydrolysis with acid or base, but the isoxazole ester of **14a** was base labile. Isoxazole formation using hydroxylamine, as reported by Rufer, gave mixtures of products including uncyclized material. Use of the hydroxylamine-*O*-sulfonic acid improved the reaction dramatically, but the yield of the 7-(isoxazol-4-yl) ester **14a** was still only 49%. The yields of the heterocycles prepared from the enamine **11** closely parallel the results obtained by Rufer for his methylated analogs.

This methodology was then applied to the ethyl ester of 6-fluoronalidixic acid **9b** [14]. For each of the heterocycles

Scheme 1



9a R_6 = H, R = Me
b R_6 = F, R = Et

10a R_6 = H, R = Me
b R_6 = F, R = Et

12 R_6 = H
13 R_6 = F

11

14a R_6 = H
14b R_6 = F

15

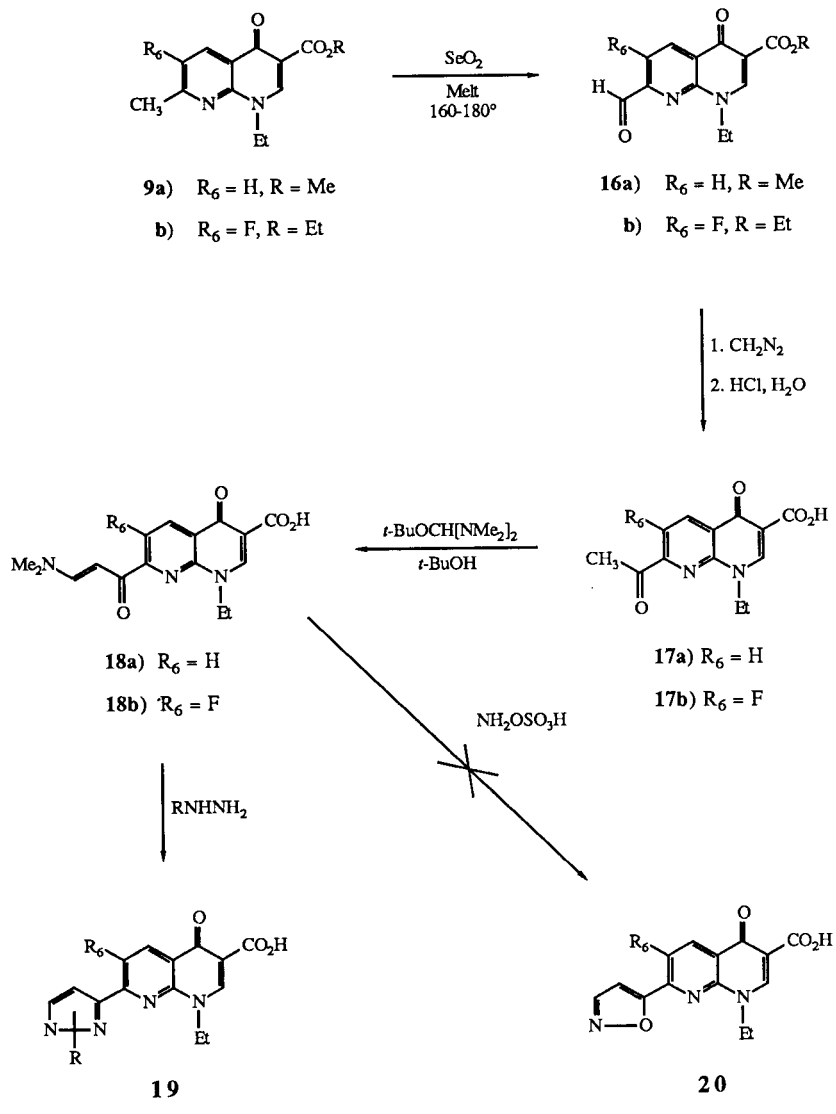
Table 1

Preparation and Physical Properties for the 7-Heterocyclic-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acids **12-14, 19**

Product Number	R in Product	R_6	Reagent	Starting Material and Method [a]		Yield % of Ester [b]	MP °C of Ester [b]	Method of Purification Ester/Acid	Yield % Product [c]	MP °C Product	Molecular Formula	Analysis % Calculated/Found C	H	N
12a	H-	H	NH_2NH_2 H_2Ox	**10a**	A	82	277-278	Si gel $CHCl_3$:EtOH 8:1/H_2O, EtOH wash	75	299-300	$C_{14}H_{12}N_4O_3$	59.15 58.93	4.22 4.50	19.72 19.88
12b	$HOCH_2CH_2$-	H	$HOCH_2CH_2NHNH_2$	**10a**	A	62	239-241	Si gel $CHCl_3$:EtOH 4:1/H_2O, EtOH wash	83	288-289	$C_{16}H_{16}N_4O_4$	58.54 58.33	4.88 4.97	17.07 16.73
12c	2-pyridyl-	H	2-pyridyl-$NHNH_2$	**10a**	A	62	228-230	Si gel $CHCl_3$: EtOH 4:1/H_2O, wash	80	324-325	$C_{19}H_{15}N_5O_3$	63.16 63.40	4.16 4.00	19.39 19.66
13a	H-	F	NH_2NH_2 H_2Ox	**10b**	A	57	244-247	Si gel $CHCl_3$:EtOH 5:1/H_2O wash	70	›290 [d]	$C_{14}H_{11}FN_4O_3$	55.57 55.77	3.64 3.91	18.52 18.71
13b	CH_3-	F	CH_3NHNH_2	**10b**	A	31	242-245	Si gel $CHCl_3$:Hex: 2-propanol 6:3:1/ H_2O, EtOH wash	55	266-269	$C_{15}H_{13}FN_4O_4$	54.22 54.61	3.92 3.68	16.87 16.80
14a	-	H	NH_2OSO_3H	**10a**	A	49	240-245 [d]	Si gel $CHCl_3$:Hex: 2-propanol 6:3:1/ H_2O wash	68	258-266 [d]	$C_{14}H_{11}N_3O_4$	58.95 58.59	3.86 4.02	14.74 14.50
14b	-	F	NH_2OSO_3H	**10b**	A	29	196-210 [d]	Si gel $CHCl_3$:Hex: 2-propanol 7:2:1/ H_2O wash	78	248-261 [d]	$C_{14}H_{10}FN_3O_4$	55.45 55.71	3.30 3.40	13.86 13.55
19a	H-	H	NH_2NH_2 H_2Ox	**18a**	B	-	-	/Ether:hexane 1:1 wash	99	315-318	$C_{14}H_{12}N_4O_3$	59.15 58.99	4.22 4.10	19.72 19.40
19b	CH_3-	H	CH_3NHNH_2 (anhydrous)	**18a**	B	-	-	/Ether:hexane 2:1 wash	91	290-295 [d]	$C_{15}H_{14}N_4O_3$	60.40 60.62	4.70 4.33	18.79 18.43
19c	$HOCH_2CH_2$-	H	$HOCH_2CH_2NHNH_2$	**18a**	B	-	-	/Ether:hexane 2/1 wash	90	215-216	$C_{16}H_{15}N_4O_4$	58.72 58.65	4.88 4.50	17.13 16.99
19d	2-pyridyl	H	2-pyridyl-$NHNH_2$	**18a**	B	-	-	/Ether:EtOH 4:1 wash	75	189-190	$C_{19}H_{15}N_5O_3$	63.16 63.20	4.16 4.33	19.39 19.50

[a] General synthetic method, see Experimental. [b] Data gathered for ester when ester intermediate was isolated and fully characterized. [c] Yield is calculated based on ester when the ester is an intermediate. [d] Slow decomposition.

Scheme 2



prepared in the 6-fluoro-1,8-naphthyridine series (**13a,b** and **14b**), the yields were always 20-30% below the corresponding 6-hydrogen examples. The reaction mixtures generally were more complex and difficult to purify when the enamine **10b** was employed, but it is not clear how the C_6-fluorine altered the course of the reaction. When guanidine was utilized as the dinucleophile, followed by hydrolysis of the isolated ester, the 6-fluoropyrimidine **15** was obtained in low yields (15-20%). The yields of the 7-(4-methyl-5-pyrimidinyl)-1,8-naphthyridines prepared by Rufer from **10a** were 40-70%. In spite of the low yields for the 6-fluoro-1,8-naphthyridines, the routes provided in Scheme 1 proved very effective for making the desired pure 7-heterocyclic derivatives **12-15** for biological testing. Of these, only the pyrimidine **15** displayed useful antibacterial potency.

We then turned our attention to obtaining the regioisomeric 7-(pyrazol-3-yl and isoxazol-5-yl)-1,8-naphthyridines **19** and **20** (Scheme 2). For these regioisomers, the masked 1-substituted-1,3-dicarbonyl intermediate **18** would be required. The synthesis of the enamine **18** once again took advantage of the activated methyl group of nalidixic acid, this time, toward oxidation with selenium dioxide [15]. The yield of the 7-formyl-1,8-naphthyridine ester **16a** was generally low (20-40%), but the major by-product was the 7-formyl-1,8-naphthyridine carboxylic acid **16a** (R = H), which was readily removable by extraction with base or could be employed in the next step. The 6-fluoronalidixic acid ethyl ester **9b** also underwent smooth oxidation to the 7-formyl-6-fluoro-1,8-naphthyridine **16b** in 57% yield. The 7-formyl group of both naphthyridines was converted to the 7-acetyl moiety (**17a,b** esters) by reaction with diazomethane in ether:dichloromethane following a procedure

outlined for pyridine aldehydes [16]. The 7-formyl-1,8-naphthyridine acid **16a** (R = H) gave the 7-acetyl methyl ester of **17a** through simultaneous ketone formation and esterification with diazomethane. Acid hydrolysis of the 7-acetyl esters produced the acids **17a** and **17b**. The unfluorinated **17a** underwent a clean reaction with Bredereck's reagent to give the enamine **18a** in 96% yield, but the fluorinated **17b** (and its ethyl ester) resisted conversion to the enamine **18b**. While the enamine **18b** appeared to be the predominate product by proton nmr analysis, several impuriteis that were present could not be removed. Attempts to carry **18b** on to the desired heterocycles only complicated the mixture further. Meanwhile, the unfluorinated enamine **18a** was reacted with various hydrazines to give the pyrazol-3-yl-1,8-naphthyridines **19** in high yields as a mixture of the 1- and 2-substituted regioisomers. The isoxazole **20** could not be obtained pure after repeated reactions with hydroxylamine or hydroxylamine-*O*-sulfonic acid. It should be noted that the methyl ester of **17a** did undergo the same reaction sequence to give the methyl esters of the 3-pyrazoles **19**, but the yields were 10-20% lower and the products required extensive chromatography. On the other hand, if the enamine acid **18a** was not reacted to completion or if impurities became numerous because of prolonged reaction times, the resultant pyrazole acids **19** tended to be very insoluble and very difficult to purify. For the examples given in Table 1, the enamine acid **18a** was the superior starting material. The ultimately poorer biological activity of the entire naphthyridine series of 7-heterocycles **12a-19** relative to the

Scheme 3

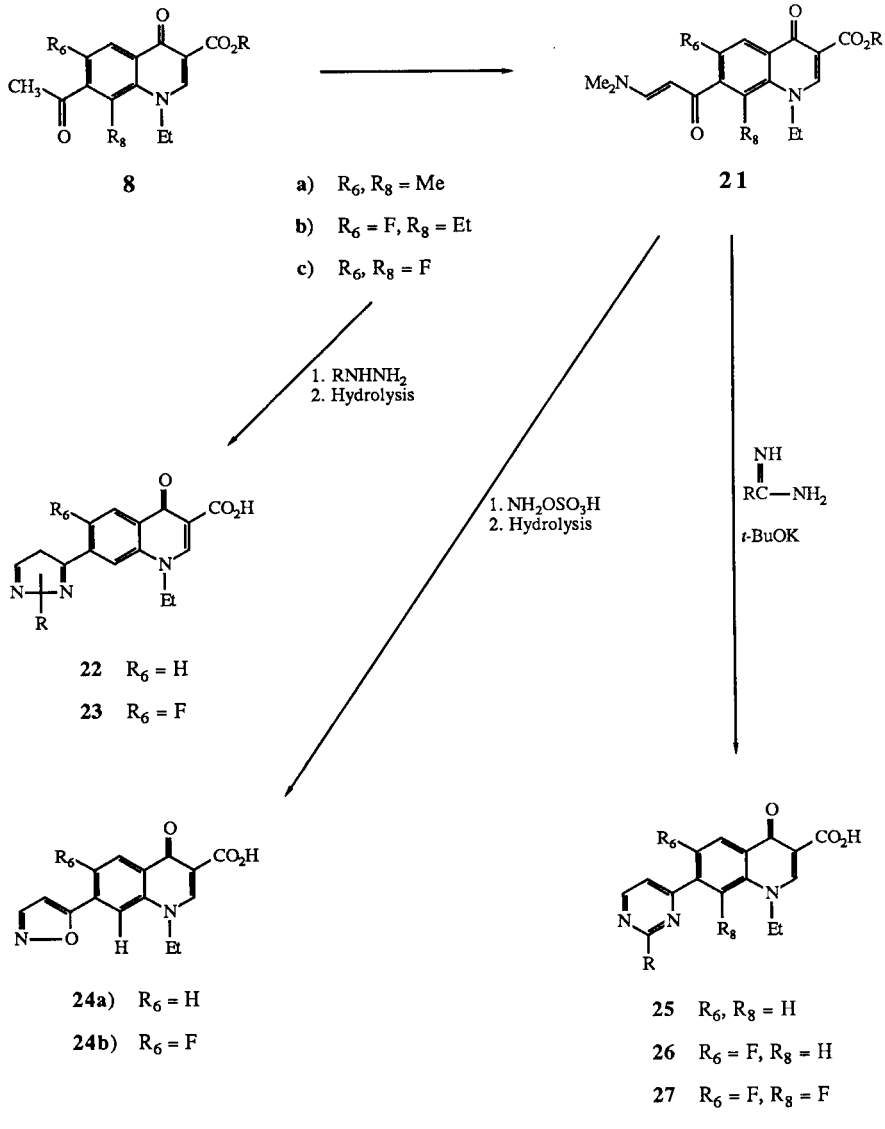


Table 2

Preparation and Physical Properties for the 7-Heterocyclic-1-ethyl-1,4-dihydro-4-oxo-3-quinoline Carboxylic Acids 22-27

Product Number	R	R_6	R_8	Reagent	Starting Material and Method [a]	Yield % of Ester [b]	MP °C of Ester [b]	Method of Purification Ester/Acid	Yield % Product [c]	MP °C Product	Molecular Formula	Analysis % Calculated/Found C	H	N
22a	H-	H	H	$NH_2NH_2\ H_2Ox$	**21a** C	80	268-271	Solids washed with ether, ether EtOH/	77	270-271	$C_{15}H_{13}N_3O_3$	63.60 63.61	4.60 4.63	14.84 15.01
22b	CH_3-	H	H	CH_3NHNH_2 (anhydrous)	**21a** C	45	247-250	Si gel $CHCl_3$:Hex: 2-propanol 6:3:1	81	255-257	$C_{16}H_{15}N_3O_3$	64.65 64.41	5.05 5.37	14.14 14.00
23a	CH_3-	F	H	CH_3NHNH_2 (anhydrous)	**21b** B	-	-	-/Ether:EtOH wash	52	292-294	$C_{16}H_{14}FN_3O_3$	60.95 61.08	4.44 4.57	13.33 13.66
23b	$HOCH_2CH_2$-	F	H	$HOCH_2CH_2NHNH_2$	**21b** C	56	235-237	Ether:EtOH wash/ H_2O wash	73	254-255	$C_{17}H_{16}FN_3O_4$	59.13 59.16	4.64 4.73	12.17 12.01
24a	-	H	H	NH_2OSO_3H	**21a** C	70	184-185	Si gel $CHCl_3$:Hex: 2-propanol 6:3:1/ H_2O wash	75 [d]	275-280 [e]	$C_{15}H_{12}N_2O_4$	63.38 63.11	4.22 4.57	9.89 10.10
24b	-	F	H	NH_2OSO_3H	**21b** B	-	-	/Si gel $CHCl_3$:AcOH: 2-propanol 9:0.5:0.5	46	266-272 [e]	$C_{15}H_{11}FN_2O_4$	59.60 59.57	3.64 3.75	9.27 9.44
25a	H	H	H	$HC(NH)NH_2$ AcOH	**21a** D	-	-	/Recrystallized DMF	38	264-266 [e]	$C_{16}H_{13}N_3O_3$	65.08 65.07	4.41 4.55	14.24 13.90
25b	CH_3-	H	H	$CH_3C(NH)NH_2 \cdot HCl$	**21a** D	-	-	/Recrystallized DMF	35	250-258 [e]	$C_{17}H_{15}N_3O_3$	66.02 66.40	4.85 4.79	13.59 13.19
25c	NH_2	H	H	$NH_2C(NH)NH_2 \cdot HCl$	**21a** D	-	-	/EtOH:H_2O, EtOH wash	65	244-251 [e]	$C_{16}H_{14}N_4O_3$	61.94 62.30	4.52 4.79	18.06 18.37 [f]
26a	H-	F	H	$HC(NH)NH_2 \cdot AcOH$	**21b** D	-	-	/H_2O:EtOH wash	71	221-222	$C_{16}H_{12}FN_3O_3$	61.34 60.99	3.83 3.76	13.42 13.40
26b	NH_2-	F	H	$NH_2C(NH)NH_2 \cdot HCl$	**21b** D	-	-	/Si gel CH_3CN:AcOH 95/5	33	245-246	$C_{16}H_{13}FN_4O_3$	58.54 58.29	3.96 3.74	17.07 17.33
26c	NH_2CH_2-	F	H	$CbzNHCH_2C(NH)$-$NH_2 \cdot HCl$	**21b** D	-	-	Si gel CH_3CN:AcOH 92:8 (on Cbz amine)/ H_2O wash	43 [g]	206-208	$C_{17}H_{15}FN_4O_3$	59.65 59.59	4.39 4.16	16.37 16.63
26d	CH_3NHCH_2-	F	H	NaH, MeI	**28**	-	-	Triturated $CHCl_3$: EtOAc (on Cbz amine)/ H_2O wash	42 [g]	238-239	$C_{18}H_{17}FN_4O_3$	60.67 60.57	4.78 4.43	15.73 15.81
27a	NH_2-	F	F	$NH_2C(NH)NH_2 \cdot HCl$	**21c** D	-	-	/Si gel $CHCl_3$:EtOH AcOH 9:0.9:0.1	35	285-286	$C_{16}H_{12}F_2N_4O_3$	55.49 55.68	3.47 3.39	16.18 16.01
27b	NH_2CH_2-	F	F	$CbzNHCH_2C(NH)$-$NH_2 \cdot HCl$	**21c** D	-	-	Si gel $CHCl_3$:EtOH: AcOH 9:0.9:0.1/ H_2O wash	57 [g]	285-289	$C_{17}H_{14}F_2N_4O_3$	56.67 56.55	3.89 3.71	15.56 15.49

[a] General synthetic method, see Experimental. [b] Data gathered for ester, when the ester intermediate was isolated and fully characterized. [c] Yield is calculated based on ester is an intermediate. [d] Only acid hydrolysis gave satisfactory results. [e] Decomposition. [f] Very hygroscopic. Results of several analyses. [g] Yield for two steps.

quinoline-3-carboxylic acids diminished our desire to overcome the problem synthesis of **18b**, and instead the synthesis of the corresponding 7-heterocyclic -3-quinolinecarboxylic acids **22-27** (Scheme 3) became high priority.

Since the 7-methyl group of the quinoline-3-carboxylic acid was not activated toward enamine formation, as in the naphthyridine series, the 7-(pyrazol-4-yl, isoxazol-4-yl and 5-pyrimidinyl)-3-quinolinecarboxylic acids were not available. However, the 7-acetyl-3-quinolinecarboxylic acid ethyl esters **8a-c** [11] were available for 7-heterocycle formation. The reaction of 7-acetylquinoline-3-carboxylic acid esters **8a-c** with Bredereck's reagent was uneventful giving the enamines **21a-c** (R = Et) in 83-95% yields. The presence of one or two fluorines had no effect on the conversion. Alternatively the 7-acetylcarboxylic acids **8a-c** (R = H) could be converted to the enamine acids **21a-c** (R = H) in lesser but satisfactory yields of 70-82%. For the synthesis of the pyrazoles **22** and **23** and the isoxazoles **24a,b**, either the enamine acids or esters could be employed. Table 2 lists the method that gave the best results. The 7-(pyrazol-3-yl)-3-quinolinecarboxylic acids **22** and **23** were obtained as mixtures of the 1- and 2-regioisomers, but with one isomer usually predominating (by nmr analysis) by up to 15:1. The enamines **21a-c** were attacked apparently at the *N*-terminus by the more nucleophilic Michael donor with good selectivity.

All of the pyrimidines **25-27** were prepared from the enamine esters **21a-c**. After much experimentation the optimum conditions found employed an excess of amidine and potassium *t*-butoxide in *t*-butyl alcohol, and utilized the water released in the pyrimidine formation to hydrolyze the ester *in situ*. These conditions gave reproducible yields in the 35-70% range. The 2-aminoacetamidine used in the preparation of **26c** and **27b** could be protected by any of the common nitrogen protecting groups. We chose to prepare the benzyloxycarbonyl protected 2-aminoacetamidine [17] because of the facile removal of the protecting group with hydrobromic acid and acetic acid as shown in Scheme 4. A method to alkylate the primary amino group of **26c** to produce **26d** was developed using two equivalents of sodium hydride and an excess of methyl iodide on the *N*-benzyloxycarbonyl protected **28**. A detailed discussion of the biological activity and the structure-activity relationships will be reported elsewhere, but in general, the 7-pyrimidinyl analogs displayed the best broad spectrum antibacterial activity.

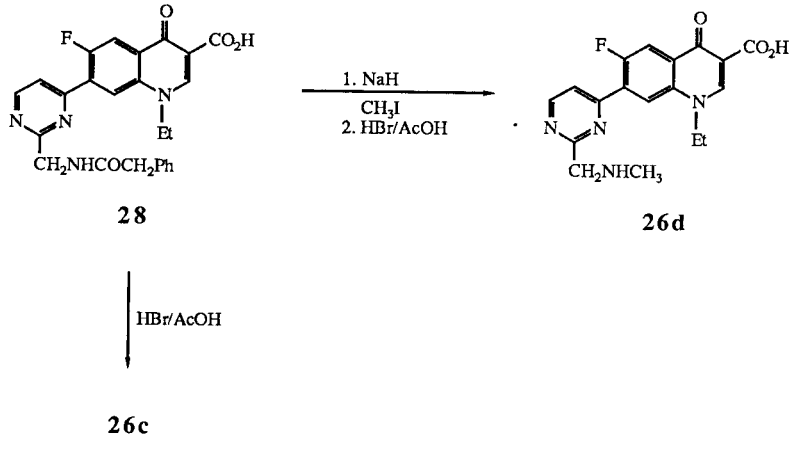
EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir), spectra were determined on a Nicolet FT IR SX-20 with 2-cm^{-1} resolution. Proton magnetic resonance (nmr) spectra were recorded on either a Varian XL 200 or IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Column chromatography was performed with E. Merck silica gel 60, 70-230-mesh ASTM. All the hydrazines and amidines used were commercially available except where indicated. Solutions were dried over magnesium sulfate. The *t*-butyl alcohol was dried over calcium hydride. The *t*-butoxy-bis-dimethylaminomethane was obtained from Fluka. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. All new products and intermediates had analytical results within ±0.4% of theoretical values. Spectral data has been provided for the selected examples, but all compounds in Tables 1 and 2 were consistent with their spectral properties.

7-[2-(Dimethylamino)ethenyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid, Ethyl Ester (**10b**).

Using the method of Rufer [9] 2.0 g (7.2 mmoles) of 6-fluoronalidixic acid, ethyl ester, (**9b**) [14] was converted to 1.88 g (72%) of the enamine **10b**, mp 175-176°; ir: 1720, 1677, 1637, 1610 cm^{-1}; pmr (deuteriochloroform); δ 8.55 (s, 1H, C_2H), 8.15 (d, J = 11 Hz, 1H, C_5H), 7.85 (d, J = 12 Hz, 1H, $Me_2NCH{=}CH$), 5.4 (dd, J = 12 , 2 Hz, 1H, $Me_2NCH{=}CH$), 4.45 (q, J = 7 Hz, 4H, $2CH_2$), 3.1 (s, 6H, Me_2N), 1.5 (m, 6H, $2CH_3$).

Scheme 4



1-Ethyl-1,4-dihydro-4-oxo-7-(1*H*-pyrazol-4-yl)-1,8-naphthyridine-3-carboxylic Acid (**12a**).

General Procedure A. For Compounds **12-14**.

To 0.88 g (2.9 mmoles) of the enamine **10a** [9] in 25 ml of dichloromethane at 10° was added 0.38 g (2.9 mmoles) of *N,N*-dimethylchloroformiminium chloride, Vilsmeier reagent [13], suspended in 5 ml of dichloromethane. (The Vilsmeier reagent was prepared at 50° from *N,N*-dimethylformamide and thionyl chloride mixed in 1:1 stoichiometry, and concentrated overnight at 0.1 mm Hg). The reaction mixture was gradually brought to room temperature for 4 hours and was then concentrated to dryness. The residue was dissolved in 10 ml of anhydrous ethanol and 0.22 g (5.8 mmoles) of hydrazine hydrate was added. After 16 hours of refluxing, the mixture was concentrated to one-half volume and the solids collected by filtration. The crude solid was purified by column chromatography using chloroform:ethanol (8:1), to yield 0.71 g (82%) of the methyl ester of **12a**; ir: 1725, 1615 cm^{-1}; pmr (trifluoroacetic acid): δ 9.55 (s, 1H, C_2H), 9.05 (m, 3H, C_6H and pyrazole *H*), 8.4 (d, J = 9 Hz, 1H, C_5H), 5.2 (q, J = 7 Hz, 2H, CH_2CH_3), 4.3 (s, 3H, OCH_3), 1.85 (t, J = 7 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.70; N, 18.79. Found: C, 60.30 H, 4.70; N, 19.02.

Alternatively to using two equivalents of hydrazine, one equivalent of triethylamine could be employed. The use of triethylamine improved the ease of purification.

General Hydrolysis to **12a**.

To 0.6 g (2.0 mmoles) of the methyl ester of **12a** was added 5 ml of 2*N* sodium hydroxide (or alternatively 2*N* hydrochloric acid) and the mixture refluxed for 2 hours. The mixture was cooled and neutralized with 6*N* hydrochloric acid. The waxy precipitate was collected by filtration to give 430 mg (75%) of the pyrazole **12a**; ir: 3400-2600, 1710, 1615 cm^{-1}; pmr (trifluoroacetic acid): 9.7 (s, 1H, C_2H), 9.15 (m, 3H, C_6H and pyrazole *H*), 8.45 (d, J = 9 Hz, 1H, C_5H), 5.2 (q, J = 7 Hz, 2H, 2H, CH_2CH_3), 1.8 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-7-[1-(2-hydroxyethyl)-1*H*-pyrazol-4-yl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**12b**) and its Methyl Ester.

Using the general procedure and one equivalent of the hydrazine the methyl ester of **12b** was obtained as a light yellow powder; ir: 1695, 1630, 1610 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): 9.6 (s, 1H, C_2H), 8.35 (m, 2H, pyrazole *H* and C_6H), 8.1 (s, 1H, pyrazole *H*), 7.65 (d, J = 9 Hz, 1H, C_5H), 4.9 (t, J = 5 Hz, 1H, $CHHCH_2OH$), 4.5 (q, J = 7 Hz, 2H, CH_2CH_3), 4.2 (t, J = 5 Hz, 2H, CH_2OH), 3.7 (m, 4H, $CHHCH_2OH$ and OCH_3), 1.4 (t, J = 7 Hz, 3H, CH_2CH_3). Base hydrolysis produced the desired acid **12b**; ir: 3320, 1720 cm^{-1}; pmr (trifluoroacetic acid): 9.55 (s, 1H, C_2H), 9.1 (m, 3H, C_6H, *pryrazole H*), 8.3 (d, J = 8 Hz, C_5H), 5.15 (q, J = 7 Hz, 2H, CH_2CH_3), 4.9 (m, 2H), 4.4 (m, 2H), 1.8 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-4-oxo-7-[1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-1,8-naphthyridine-3-carboxylic Acid (**12c**) and its Methyl Ester.

Using the general procedure with 1.2 equivalents of hydrazine, the methyl ester of **12c** was obtained as a yellow powder; pmr (trifluoroacetic acid): 9.6 (s, 1H), 9.4 (s, 1H), 9.1 (d, J = 9 Hz, 1H), 8.75 (m, 3H), 8.25 (m, 2H), 8.1 (m, 1H), 5.2 (q, J = 6 Hz, 2H, NCH_2CH_3), 4.2 (s, 3H, OCH_3), 1.8 (q, J = 6 Hz, 3H, NCH_2CH_3). Base hydrolysis produced **12c** as a tan powder; ir: 1725, 1620 cm^{-1}; pmr (trifluoroacetic acid): 9.6 (s, 1H), 9.4 (s, 1H), 9.1 (d, J = 9 Hz, 1H), 8.8 (m, 3H), 8.4 (m, 2H), 8.0 (m, 1H), 5.2 (q, J = 7 Hz, 2H, CH_2CH_3), 1.85 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1*H*-pyrazole-4-yl)-1,8-naphthyridine-3-carboxylic Acid (**13a**) and its Ethyl Ester.

Using the generl procedure with one equivalent of hydrazine, the ethyl ester of **13a** was obtained as yellow solid; pmr (hexadeuteriodimethyl sulfoxide): 8.7 (s, 1H, C_2H), 8.2 (m, 3H), 4.5 (q, J = 6 Hz, 2H, NCH_2CH_3), 4.2 (q, J = 7 Hz, 2H, OCH_2CH_3), 1.35 (m, 6H). Base hydrolysis produced **13a** as a white powder; ir: 1720, 1620 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): 9.1 (s, 1H, C_2H), 8.35 (m, 3H), 4.6 (q, J = 6 Hz, 2H), 1.45 (t, J = 6 Hz, 3H).

1-Ethyl-6-fluoro-1,4-dihydro-7-[1-methyl-1*H*-pyrazol-4-yl]-4-oxo-1,8-naphthyridine-3-carboxyl Acid (**13b**), and its Ethyl Ester.

Using the general procedure with 2 equivalents of the hydrazine the ethyl ester of **13b** was obtained; pmr (deuteriochloroform): 8.5 (s, 1H, C_2H), 8.3 (d, J = 10 Hz, 1H, C_6H), 8.1 (m, 2H), 4.4 (m, 4H), 3.95 (s, 3H, NCH_3), 1.4 (m, 6H). Base hydrolysis produced **13b** as a white powder; pmr (trifluoroacetic acid): 9.5 (s, 1H, C_2H), 8.9 (m, 3H), 5.15 (q, J = 6 Hz, 2H), 2H), 4.4 (s, 3H, NCH_3), 1.8 (t, J = 6 Hz, 3H).

1-Ethyl-1,4-dihydro-7-(4-oxazolyl)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**14a**) and its Methyl Ester.

Using the general procedure and 2 equivalents of the hydroxylamine, the methyl ester of **14a** was obtained as a white powder; pmr (trifluoroacetic acid): 9.4 (m, 2H), 9.2 (s, 1H), 9.0 (d, J = 8 Hz, 1H, C_6H), 8.2 (d, J = 8 Hz, 1H, C_5H), 5.15 (q, J = 7 Hz, 2H), 4.2 (s, 3H, OCH_3), 1.8 (t, J = 7 Hz, 3H). Acid hydrolysis produced **14a** as a white powder; ir: 1722, 1620 cm^{-1}; pmr (trifluoroacetic acid): 9.55 (s, 1H), 9.4 (s, 1H), 9.3 (s, 1H), 9.05 (d, J = 7 Hz, 1H, C_6H), 8.3 (d, J = 7 Hz, 1H, C_5H), 5.2 (q, J = 7 Hz, 2H), 1.85 (t, J = 7 Hz, 3H).

1-Ethyl-6-fluoro-1,4-dihydro-7-(4-isoxazolyl)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**14b**) and its Ether Ester.

Using the general procedure with 2 equivalents of hydroxylamine, the ethyl ester of **14b** was produced as a white powder; pmr (deuteriochloroform): 9.1 (d, J = 2 Hz, 1H, isoaxzole *H*), 8.8 (s, 1H), 8.5 (s, 1H), 8.45 (d, J = 9 Hz, 1H, C_5H), 4.4 (m, 4H), 1.5 (m, 6H). Acid hydrolysis gave **14b** as a white powder; ir: 1720 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): 9.7 (d, J = 2 Hz, 1H, isoxazole *H*), 9.3 (s, 1H), 9.05 (s, 1H), 8.4 (d, J = 8 Hz, 1H, C_5H), 4.6 (q, J = 6 Hz, 2H), 1.4 (t, J = 6 Hz, 3H).

7-(2-Amino-5-pyrimidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**15**).

To 1.0 g (3.0 mmoles) of **10b** in 40 ml of dichloromethane at −35° was added 423 mg (3.3 mmoles) of the Vilsmeier reagent as described above for **12a**. In another vessel, 860 mg (9.0 mmole) of guanidine in *t*-butyl alcohol was partially neutralized with 1 equivalent of potassium *t*-butoxide. To this slurry was added **11b** suspended in 25 ml of *t*-butyl alcohol. After 18 hours at 65°, another equivalent of potassium *t*-butoxide was added. The reaction mixture was taken up in chloroform:water and the *p*H adjusted to 2.5. The chloroform was dried and concentrated. The residue was purified by column chromatography to give 180 mg (17%) of the ethyl ester of **15**, mp 290-292°; ir: 3380, 3320, 1725, 1690 cm^{-1}; pmr (trifluoroacetic acid): δ 9.7 (s, 2H, pyrim *H*), 9.6 (s, 1H, C_2H), 9.65 (s, br, 1H, N*H*), 8.85 (d, J = 10 Hz, 1H, C_5H), 8.7

(s, br, 1H, N*H*), 5.2 (q, J = 7 Hz, 2H, CH_2CH$_3$), 4.7 (d, J = 7 Hz, 2H, CH_2CH$_3$), 1.8 and 1.6 (t, J = 7 Hz, 2 CH$_2$CH_3).

The ester of **15** was treated with 1 equivalent of 1*N* sodium hydroxide in 3 ml of ethanol at 70° for 16 hours. The clear solution was added to water and the *p*H adjusted to 6.0. The yellow solid was collected by filtration to give 120 mg (73%) of **15**, mp 329-330°; ir: 3400-2600, 1720, 1610 cm^{-1}; pmr (trifluoroacetic acid): δ 9.7 (m, 3H, pyrim *H*, C$_2$*H*), 8.7 (m, 3H, C$_5$*H*, NH_2), 5.15 (q, J = 7 Hz, 2H, CH_2CH$_3$), 1.8 (t, J = 7 Hz, 3H, CH$_2$CH_3).

Anal. Calcd. for $C_{15}H_{12}FN_5O_3$: C, 54.71; H, 3.65; N, 21.28. Found: C, 54.71; H, 4.02; N, 21.46.

1-Ethyl-6-fluoro-7-formyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, Ethyl ester (**16b**).

6-Fluoronalidixic acid (**9b**, 5.56 g, 20 mmoles) was heated at 170-180°. To the melt was added 3.4 g (30.6 mmoles) of selenium dioxide using the method of Nishigaki [15]. The mixture was cooled, diluted with 400 ml of chloroform and refluxed for 4 hours. The hot chloroform was filtered, cooled, and extracted with 0.1 *N* sodium hydroxide. The chloroform was dried and concentrated to give a yellow powder. Chromatography using chloroform:hexane:isopropanol, 6:3:1, gave 3.3 g (57%) of **16b** as a white solid, mp 170-175°: pmr (hexadeuteriodimethyl sulfoxide): δ 10.0 (s, 1H, C*H*O), 9.2 (s, 1H, C$_2$*H*), 8.6 (d, J = 9 Hz, C$_5$*H*), 4.7 (q, J = 7 Hz, 2H, CH_2CH$_3$), 1.5 (t, J = 7 Hz, 3H, CH$_2$CH_3). This material was not analytical and was characterized by conversion to **17b** and its subsequent derivative.

7-Acetyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**17a**).

To 1.38 g (5.2 mmoles) of 7-formyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methyl ester [15] (**16a**) in 15 ml of ether and 15 ml of dichloromethane, was added, over 15 minutes, 26 ml of 0.2 *M* diazomethane solution in ether. The mixture was stirred for 16 hours, concentrated to dryness, and the solids were suspended in 1 *N* hydrochloric acid and refluxed for 16 hours. The solids were collected by filtration. Column chromatography (chloroform:ethanol:acetic acid, 9:0.9:0.1) gave 1.0 g (74%) of **17a** as a white solid, mp 283-285°; ir: 1727, 1703 cm^{-1}; pmr (trifluoroacetic acid): δ 9.7 (s, 1H, C$_2$*H*), 9.2 (d, J = 8 Hz, 1H, C$_6$*H*), 8.6 (d, J = 8 Hz, 1H, C$_5$*H*), 5.2 (q, J = 7 Hz, 2H, CH_2CH$_3$), 3.0 (s, 3H, COCH_3), 1.8 (t, J = 7 Hz, 3H, CH$_2$CH_3).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 60.00; H, 4.61; N, 10.77. Found: C, 60.22; H, 4.70; N, 10.63.

Careful chromatography (chloroform:hexane:isopropanol, 6:3:1) of the methyl ester of **17a** gave small amounts of purified product: pmr (deuteriochloroform): δ 8.8 (d, J = 8 Hz, 1H, C$_6$*H*), 8.7 (s, 1H, C$_2$*H*), 8.0 (d, J = 8 Hz, 1H, C$_5$*H*), 4.5 (q, J = 7 Hz, 2H, CH_2CH$_3$), 3.9 (s, 3H, OCH_3), 2.7 (s, 3H, COCH_3), 1.55 (t, J = 7 Hz, 3H, CH$_2$CH_3).

7-Acetyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**17b**).

Using the procedure above for **17a**, 1.24 g (4.25 mmoles) of **16b** was converted to 1.31 g of the crude ethyl ester of **17b**. Hydrolysis and chromatography gave 0.31 g (26%) of **17b** as a white solid, mp 224-226°; ir: 1715, 1611 cm^{-1}; pmr (trifluoroacetic acid): δ 9.7 (s, 1H, C$_2$*H*), 8.9 (d, J = 8 Hz, 1H, C$_5$*H*), 5.2 (q, J = 7 Hz, 2H, CH_2CH$_3$), 3.1 (s, 3H, COCH_3), 1.85 (t, J = 7 Hz, 3H, CH$_2$CH_3).

Anal. Calcd. for $C_{13}H_{11}FN_2O_4$: C, 56.12; H, 3.96; N, 10.07. Found: C, 56.13; H, 4.03; N, 10.08.

7-[3-(Dimethylamino)-1-oxo-2-propenyl-1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**18a**).

To 1.63 g (6.26 mmoles) of **17a** in 35 ml of dry *N,N*-dimethylformamide was added 2.0 ml (9.4 mmoles) of *t*-butoxy-bis-(dimethylamino)methane. The mixture was heated to 85° for 4 hours. The solids initially dissolved, and a yellow precipitate quickly formed. The crystals were collected by filtration to give 1.90 g (96%) of **18a**, mp 177-181°; ir 2640, 1730, 1645, 1618 cm^{-1}; pmr (trifluoroacetic acid): δ 9.7 (s, 1H, C$_2$*H*), 9.3 (d, J = 8 Hz, 1H, C$_6$*H*), 9.0 (d, J = 10 Hz, 1H, CHC*H*), 8.7 (d, J = 8 Hz, 1H, C$_5$*H*), 6.95 (d, J = 10 Hz, 1H, C*H*CH), 5.2 (q, J = 7 Hz, 2H, CH_2CH$_3$), 3.9 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 1.85 (t, J = 7 Hz, 3H, CH$_2$CH_3). This material was not analytical and was fully characterized by its conversion to the pyrazoles **19**.

1-Ethyl-1,4-dihydro-4-oxo-7-(1*H*-pyrazol-3-yl)-1,8-naphthyridine-3-carboxylic Acid **19a**.

General Procedure B. For Compounds **19a-d**, **23a**, **24b**.

To 315 mg (1.00 mmole) of the enamine **18** in 15 ml of ethyl alcohol was added 0.25 ml (5.5 equivalents) of hydrazine hydrate. The mixture was refluxed overnight. The solids that formed upon cooling were collected by filtration to give 280 mg (99%) of **19a**, mp 315-318°; ir: 1700, 1630 cm^{-1}; pmr (trifluoroacetic acid): δ 9.6 (s, 1H, C$_2$*H*), 9.25 (d, J = 8 Hz, 1H, C$_6$*H*), 8.5 (d, J = 8 Hz, 1H, C$_5$*H*), 8.35 (d, J = 3 Hz, 1H, pyrazole *H*), 7.6 (d, J = 3 Hz, 1H, pyrazole *H*), 5.25 (q, J = 7 Hz, 2H, CH_2CH$_3$), 1.8 (t, J = 7 Hz, 3H, CH$_2$CH_3).

1-Ethyl-1,4-dihydro-7-(1-methyl-1*H*-pyrazole-3-yl)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**19b**).

Using the general procedure **19b** was obtained as a 2:1 mixture of positional isomers; ir: 1722, 1615, 1460 cm^{-1}; pmr (trifluoroacetic acid): 9.7 and 9.65 (s, 1H, 2:1), 9.3 and 9.25 (d, J = 8 Hz, 1H, 2:1), 8.5 (d, J = 8 Hz, 1H), 8.3 and 8.2 (d, J = 3 Hz, 1H, 2:1), 7.5 (m, 1H), 5.15 (m, 2H, CH_2CH$_3$), 4.7 and 4.35 (s, 3H, 2:1), 1.75 (m, 3H, CH$_2$CH_3).

1-Ethyl-1,4-dihydro-7-[1-(2-hydroxyethyl)-1*H*-pyrazole-3(5)-yl]-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**19c**).

Using the general procedure, **19c** was obtained as a 2:1 mixture of positional isomers; ir: 1709, 1557 cm^{-1}; pmr (trifluoroacetic acid): 9.7 and 9.65 (s, 1H, 2:1), 9.25 (m, 1H), 8.3 (m, 2H), 7.4 (m, 1H), 5.25 (m, 4H, NCH_2CH$_3$ and CH_2OH), 4.3 (m, 2H), 1.8 (t, J = 7 Hz, 3H, CH$_2$CH_3).

1-Ethyl-1,4-dihydro-4-oxo-7-[1-(2-pyridinyl)-1*H*-pyrazol-3(5)-yl]-1,8-naphthyridine-3-carboxylic Acid (**19d**).

Using the general procedure **19d** was obtained as a 4:1 mixture of positional isomers; ir: 3070, 1723, 1620, 1470, 1430 cm^{-1}; pmr (trifluoroacetic acid): 9.5-7.2 (m, 9H), 5.0 (m, 2H), 1.7 (m, 3H).

1-Ethyl-6-fluoro-1,4-dihydro-7-[1-methyl-1*H*-pyrazol-3-yl]-4-oxo-3-quinolinecarboxylic Acid (**23a**).

Using the general procedure **23a** was obtained as an 18:1 mixture of positional isomers; ir: 1730, 1620, 1520, 1470 cm^{-1}; pmr (trifluoroacetic acid): 9.7 (s, 1H), 8.95 (s, 1H), 8.5 (d, J = 9 Hz, 1H, C$_5$*H*), 8.0 (d, J = 3 Hz, 1H), 7.75 (d, J = 3 Hz, 1H), 6.6 (d, J = 3 Hz, 1H), 4.4 (q, J = 7 Hz, 2H, NCH_2CH$_3$), 3.7 (s, 3H, NCH_3), 1.25 (t, J = 7 Hz, 3H, NCH$_2$CH_3).

1-Ethyl-6-fluoro-1,4-dihydro-7-(5-isoxazolyl)-4-oxo-3-quinolinecarboxylic Acid (**24b**).

Using the general procedure **24b** was obtained as a 15:1 mixture of positional isomers; ir: 1730, 1620, 1520; pmr (trifluoroacetic acid): 9.5 (s, 1H, C_2H), 8.9 (d, J = 5 Hz, 1H isoxazole *H*), 8.75 (d, J = 3 Hz, 1H, C_8H), 8.55 (d, J = 10 Hz, 1H, C_5H), 7.4 (m, 1H), 5.1 (q, J = 7 Hz, 2H), 1.9 (t, J = 7 Hz, 3H).

7-[(2-(dimethylamino)-1-oxo-2-propenyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester **21b** (R = Et).

A General Procedure for **21a-c** (R = Et).

To 2.0 g (6.5 mmoles) of the ketone **8b** (R = Et) in 50 ml of *N,N*-dimethylformamide was added 1.71 g (1.25 equivalents) of the *t*-butoxy-bis-dimethylaminomethane. The mixture was heated at 70° for 16 hours. The mixture was concentrated *in vacuo* and the residue triturated with ether:ethanol. The solids were collected by filtration to give 1.95 g (83%) of the enamine ester **21b** (R = Et), mp 176-179°; ir: 1728, 1655 cm^{-1}, pmr (deuteriochloroform): δ 8.45 (s, 1H, C_2H), 8.1 (d, J = 11 Hz, 1H, CHC*H*), 7.85 (m, 2H, C_5H, C_8H), 5.7 (dd, J = 2 Hz, J = 11 Hz, 1H, CHC*H*), 4.25 (m, 4H, $2CH_2CH_3$), 3.1 (m, 6H, $2CH_3$), 1.45 (m, 6H, $2CH_2CH_3$).

7-[(2-(dimethylamino)ethenyl)carbonyl]-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**21a**).

Using the general procedure **21a** was obtained as a bright yellow solid, mp 189-191°; pmr (deuteriochloroform): δ 8.5 (m, 2H, C_2H, C_6H), 8.0 (s, 1H, C_8H), 7.75 (m, 2H, CHC*H*, C_5H), 5.7 (d, J = 12 Hz, 1H, CHC*H*), 4.3 (m, 4H, $2CH_2CH_3$), 3.2 and 3.0 (2s, 6H, $2CH_3$), 1.5 (m, 6H, $2CH_2CH_3$).

7-[(2-dimethylamino)ethenyl)carbonyl]-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Ethyl Ester (**21c**).

Using the general procedure the ethyl ester **21c** was obtained as a bright yellow solid, mp 181-183°; pmr (deuteriochloroform): δ 8.3 (s, 1H, C_2H), 7.9 (dd, J = 2 Hz, J = 10 Hz, 1H, C_5H), 7.4 (m, 1H, C*H*CH), 5.25 (d, J = 13 Hz, 1H, CHC*H*), 4.3 (m, 4H, $2CH_2CH_3$), 3.0 and 2.8 (2s, 6H, $2CH_3$), 1.4 (m, 6H, $2CH_2CH_3$).

7-[(2-(dimethylamino)ethenyl)carbonyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxyl Acid (**21b**) (R = H).

Using the general procedure **21b** (R = H) was obtained as a bright yellow solid, mp 208-211; pmr (trifluoroacetic acid): δ 9.5 (s, 1H, C_2H), 8.9 (d, J = 12 Hz, 1H, C*H*CH), 8.7 (d, J = 5 Hz, 1H, C_8H), 8.5 (d, J = 10 Hz, 1H, C_5H), 6.3 (d, J = 12 Hz, 1H, CHC*H*), 5.0 (q, J = 7 Hz, 2H, CH_2CH_3).

1-Ethyl-6-fluoro-1,4-dihydro-7-[2-(2-hydroxyethyl)-1*H*-pyrazol-3(or 5)-yl]-4-oxo-3-quinolinecarboxylic Acid (**23b**).

General Procedure C. For Compounds **22**, **23b** and **24a**.

To 200 mg (0.55 mmole) of the enamine **21b** (R = Et) in 10 ml of absolute ethanol was added 0.037 ml (0.58 mmole) of β-hydroxyethylhydrazine. The mixture was heated at 70° for 16 hours. The solids were collected by filtration to give 145 mg (71%) of the ethyl ester of **23b**, which did not require further purification, mp 235-237°; pmr (hexadeuteriodimethyl sulfoxide): δ 8.8 (s, 1H, C_2H), 8.35 (d, J = 7 Hz, 1H, C_8H), 8.1 (d, J = 9 Hz, 1H, C_5H), 7.7 (d, J = 2 Hz, 1H, pyrazol *H*), 6.6 (m, 1H, pyrazole *H*), 5.05 (t, J = 6 Hz, 1H, O*H*), 4.3 (m, 6H, $HOCH_2CH_2$, NCH_2CH_3, OCH_2CH_3), 3.8 (m, 2H, NCH_2CH_2), 1.4 (m, 6H, $2CH_2CH_3$).

To 140 mg (0.38 mmole) of the ethyl ester of **23b** in 5 ml of absolute ethanol was added 0.5 ml of 2 *N* sodium hydroxide. The mixture was stirred at 45° for 16 hours. The solution was diluted with 10 ml of water and brought to *p*H 4.5. The solids were collected to give 90 mg (69%) of **23b** as a white solid, mp 254-255°; pmr (trifluoroacetic acid): δ 9.5 (s, 1H, C_2H), 8.75 (d, J = 6 Hz, 1H, C_8H), 8.6 (d, J = 9 Hz, 1H, C_5H), 8.4 (d, J = 3 Hz, 1H, pyrazol *H*), 7.15 (d, J = 3 Hz, 1H, pyrazol *H*), 5.05 (q, J = 7 Hz, 2H, NCH_2CH_3), 4.8 (m, 2H, CH_2CH_2OH), 4.25 (m, 2H, CH_2CH_2OH), 1.85 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-4-oxo-7-(1*H*-pyrazol-4-yl)-3-quinolinecarboxylic Acid (**22a**) and its Ethyl Ester.

Using the general procedure the ethyl ester of **22a** was obtained; ir: 3177, 1720, 1620, 1230 cm^{-1}; pmr (trifluoroacetic acid): 9.45 (s, 1H, C_2H), 8.95 (d, J = 8 Hz, 1H, C_5H), 8.7 (d, J = 2 Hz, 1H, C_8H), 8.3 (m, 2H, C_6H and pyrazole H), 7.4 (d, J = 3 Hz, 1H, pyrazole *H*), 5.1 (q, J = 7 Hz, 2H, NCH_2CH_3), 4.75 (q, J = 7 Hz, 2H, OCH_2CH_3), 1.85 (t, J = 7 Hz, 3H), 1.6 (t, J = 7 Hz, 3H). Base hydrolysis produced the acid **22a** as a white powder; ir: 1710, 1615 cm^{-1}; pmr (trifluoroacetic acid): 9.5 (s, 1H, C_2H), 8.9 (d, J = 8 Hz, 1H, C_5H), 8.7 (d, J = 2 Hz, 1H, C_8H), 8.35 (m, 2H), 7.4 (d, J = 3 Hz, 1H, pyrazole *H*), 5.1 (q, J = 7 Hz, 2H, NCH_2CH_3), 1.9 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-7-[1-methyl-1*H*-pyrazol-3-yl]-4-oxo-3-quinolinecarboxylic Acid (**22b**), and its Ethyl Ester.

Using the general procedure, the ethyl ester of **22b** was obtained as a single positional isomer; ir: 1722, 1683, 1631 cm^{-1}; pmr (deuteriochloroform): 8.45 (m, 2H), 7.35 (m, 3H), 6.3 (d, 2 Hz, 1H, pyrazole *H*), 4.25 (m, 4H), 3.8 (s, 3H, N-CH_3), 1.4 (m, 6H). Base hydrolysis produced the acid **22b** as a white powder; ir: 3430, 1729, 1615, 1563 cm^{-1}; pmr (trifluoroacetic acid): 9.55 (s, 1H, C_2H), 9.0 (d, J = 7 Hz, 1H, C_5H), 8.5 (d, J = 2 Hz, 1H, C_8H), 8.25 (d, J = 3 Hz, 1H, pyrazole *H*), 8.15 (d, J = 7 Hz, 1H, C_6H), 7.1 (d, J = 3 Hz, 1H, pyrazole H), 5.0 (q, J = 7 Hz, 2H, NCH_2CH_3), 4.3 (s, 3H, NCH_3), 1.8 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-7-(5-isoxazolyl)-4-oxo-3-quinolinecarboxylic Acid (**24a**) and its Ethyl Ester.

Using the general procedure, the ethyl ester of **24a** was obtained as a white powder; ir: 1730, 1700, 1690 cm^{-1}; pmr (deuteriochloroform): 8.5 (m, 2H, C_2H, C_5H), 8.3 (d, J = 2 Hz, 1H, isoxazole H), 7.9 (d, J = 1 Hz, 1H, C_8H), 7.6 (dd, J = 8 Hz, 1 Hz, 1H, C_6H), 6.6 (d, J = 2 Hz, 1H, isoxazole H), 4.3 (m, 4H), 1.5 (m, 6H). Acid hydrolysis produced the acid **24a** as a white powder; ir: 1724, 1613, 1465 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): 14.85 (s, 1H), 9.0 (s, 1H), 8.8 (d, J = 2 Hz, 1H, isoxazole H), 8.35 (m, 2H), 8.05 (d, J = 9 Hz, 1H, C_6H), 7.35 (d, J = 2 Hz, 1H, isoxazole H), 4.65 (q, J = 7 Hz, 2H), 1.45 (t, J = 7 Hz, 3H).

7-[2-(Aminomethyl)-4-pyrimidinyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**26c**).

General Procedure D. For Synthesis of Pyrimidinyl Analogs (**25-27**).

To 1.22 g (5.0 mmoles) of 2-[(phenylmethoxy)carbonyl]aminoacetamidine [16] suspended in 15 ml of *t*-butyl alcohol, was added 0.57 g (5.0 mmoles) of potassium *t*-butoxide in 10 ml of warm *t*-butyl alcohol. The mixture was stirred rapidly for 45 minutes. This mixture was then added rapidly to 1.0 g (2.8 mmoles) of **21b** (R = Et) in 15 ml of *t*-butyl alcohol. The reaction was stirred at 50° for 4.5 hours. Without cooling, 316 mg (2.8 mmoles) of powdered potassium *t*-butoxide was added, and the reaction stirred for 16 hours. The mixture was then cooled, poured over ice water with 2% acetic acid and the water was extracted with

dichloromethane three times. The dichloromethane was dried and concentrated. The residue was purified by column chromatography using acetonitrile:acetic acid (92:8), to give 1.1 g (46%) of the Cbz-protected pyrimidine **28**, mp 238-239; ir: 1725, 1610 cm^{-1}; pmr (trifluoroacetic acid): δ 9.5 (s, 1H, C_2H), 9.2 (m, 2H, C_5H, pyrim *H*), 8.6 (m, 2H, C_6H, pyrim *H*), 7.2 (s, br, 6H, phenyl, N*H*), 5.2 (m, 4H, CH_2Ph, CH_2NH), 4.9 (q, J = 7 Hz, 2H, CH_2CH_3), 1.8 (t, J = 7 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{25}H_{21}FN_4O_5$: C, 63.02; H, 4.41; N, 11.76. Found: C, 62.77; H, 4.24; N, 11.80.

To 200 mg (0.4 mmole) of **28** was added 5 ml of hydrobromic acid in acetic acid. The mixture was stirred for 2 hours and poured into ethyl acetate:ether (100 ml:800 ml). The solids were collected, dissolved in water, and taken to *p*H 11.0 with ammonium hydroxide. The solution was concentrated to one-third volume and the solids were collected to give 130 mg (95%) of **26c** as a white solid, mp 206-208; ir: 1725, 1640 cm^{-1}; pmr (trifluoroacetic acid): δ 9.5 (s, 1H, C_2H), 9.25 (d, J = 6 Hz, 1H, pyrim *H*), 9.1 (d, J = 6 Hz, 1H, pyrim *H*), 8.5 (m, 2H, C_6H, C_5H), 8.0 (s, br, 2H, NH_2), 5.15 (m, 4H, CH_2NH_2, CH_2CH_3), 1.8 (t, J = 7 Hz, 3H, CH_2CH_3).

1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyrimidinyl)-3-quinolinecarboxylic Acid (**25a**).

Using the general procedure **25a** was obtained as a white powder; ir: 3050, 2660, 1726, 1613 cm^{-1}; pmr (trifluoroacetic acid): 9.75 (s, 1H), 9.6 (s, 1H), 9.3 (m, 2H), 8.85 (m, 3H), 5.1 (q, J = 7 Hz, 2H), 1.85 (t, J = 7 Hz, 3H).

1-Ethyl-1,4-dihydro-7-(2-methyl-4-pyrimidinyl)-4-oxo-3-quinolinecarboxylic Acid (**25b**).

Using the general procedure **25b** was obtained as a white powder; ir: 3040, 2620, 1723, 1610 cm^{-1}; pmr (trifluoroacetic acid): 9.55 (s, 1H), 9.0 (m, 5H), 5.25 (q, J = 8 Hz, 2H), 3.3 (s, 3H), 1.9 (t, J = 8 Hz, 3H).

7-(2-Amino-4-pyrimidinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**25c**).

Using the general procedure **25c** was obtained as a light yellow powder; ir: 3383, 1710, 1615 cm^{-1}; pmr (trifluoroacetic acid): 9.5 (s, 1H), 9.0 (m, 2H), 8.6 (m, 2H), 7.8 (d, J = 7 Hz, 1H, C_6H), 5.15 (q, J = 7 Hz, 2H), 1.85 (t, J = 7 Hz, 3H).

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-pyrimidinyl)-3-quinolinecarboxylic Acid (**26a**).

Using the general procedure **26a** was produced as a white powder; ir: 3060, 2700, 1725, 1610, 1190 cm^{-1}; pmr (trifluoroacetic acid): 9.4 (m, 2H), 9.1 (d, J = 3 Hz, 1H), 8.9 (d, J = 5 Hz, 1H), 8.45 (d, J = 9 Hz, 1H, C_5H), 6.8 (d, J = 3 Hz, 1H), 5.1 (q, J = 7 Hz, 2H), 1.85 (t, J = 7 Hz, 3H).

7-(2-Amino-4-pyrimidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**26b**).

Using the general procedure **26b** was obtained as a light brown solid; ir: 3440, 1725, 1612, 1475 cm^{-1}; pmr (trifluoroacetic acid): 9.5 (s, 1H, C_2H), 9.1 (d, J = 5 Hz, 1H), 8.5 (m, 2H), 7.7 (d, J = 8 Hz, 1H), 5.0 (q, J = 7 Hz, 2H), 1.85 (t, J = 7 Hz, 3H).

7-(2-Amino-4-pyrimidinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**27a**).

Using the general procedure **27a** was produced as a yellow powder; ir: 3400, 1720, 1615 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): 9.05 (s, 1H), 8.45 (d, J = 6 Hz, 1H), 8.1 (dd, J = 15 Hz, J = 2 Hz, 1H, C_5H), 6.95 (s, 2H), 6.85 (d, J = 7 Hz, 1H), 4.6 (m, 2H, NCH_2CH_3), 1.45 (t, J = 7 Hz, 3H).

7-(2-Aminomethyl-4-pyrimidinyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**27b**).

Using the general procedure with the deprotection step, the acid **27b** was produced as a tan solid; ir: 3420, 1720, 1620 cm^{-1}; pmr (trifluoroacetic acid): 9.45 (s, 1H), 9.3 (d, J = 6 Hz, 1H), 8.4 (d, J = 9 Hz, 1H), 8.2 (d, J = 6 Hz, 1H), 7.8 (s, 2H), 5.1 (m, 4H, NCH_2-pyrimidine and NCH_2CH_3), 1.8 (t, J = 7 Hz, 3H).

1-Ethyl-6-fluoro-1,4-dihydro-7-[(2-[methylamino)methyl]-4-pyrimidinyl]-4-oxo-3-quinolinecarboxylic Acid (**26d**).

To 560 mg (1.18 mmoles) of **28** in 35 ml of dry tetrahydrofuran, was added 262 mg of sodium hydride (50% dispersion, washed with pentane, 5.0 equivalents). The mixture was kept at 35° for 3 hours and 1.0 ml of methyl iodide (16 equivalents) was added. The temperature was maintained at 45° for 16 hours. The mixture was partitioned between chloroform:water and the *p*H adjusted to 5.5 with hydrochloric acid. The chloroform was dried and concentrated. The residue was triturated with ethyl acetate:chloroform. Filtration gave 265 mg (46%) of the Cbz protected **26d**, mp 204-205°; ir: 1725, 1700 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 9.15 (s, 1H, C_2H), 9.0 (d, J = 8 Hz, 1H, pyrim *H*), 8.5 (d, J = 7 Hz, 1H, C_6H), 8.2 (d, J = 12 Hz, 1H, C_5H), 7.95 (d, J = 8 Hz, 1H, pyrim *H*), 7.3 and 6.95 (2m, 5H, Ph*H*), 5.1 (s, 2H, OCH_2), 4.8 (s, 2H, CH_2NCH_3), 4.6 (q, J = 7 Hz, 2H, OCH_2CH_3), 3.1 (s, 3H, CH_2NCH_3), 1.4 (t, J = 7 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{26}H_{23}FN_4O_5$: C, 63.67; H, 4.69; N, 11.43. Found: C, 63.89; H, 4.70; N, 11.38.

To this material was added 4 ml of 32% hydrogen bromide in acetic acid. After 4 hours the mixture was poured into ethyl acetate:ether (1:1) and the solids collected by filtration. The solids were dissolved in ammonium hydroxide at *p*H 10.8 and the solution slowly concentrated to one-third volume. The precipitate was filtered to give 170 mg (98%) of **26d**, mp 238-239°; ir: 1715, 1640 cm^{-1}; pmr (trifluoroacetic acid): δ 9.8 (s, 1H, C_2H), 9.5 (d, J = 7 Hz, 1H, pyrim *H*), 9.3 (d, J = 7 Hz, 1H, pyrim *H*), 8.85 (d, J = 11 Hz, 1H, C_5H), 8.65 (d, J = 7 Hz, 1H, C_6H), 5.3 (m, 4H, $2NCH_2$), 3.5 (s, 3H, NCH_3), 2.1 (t, J = 7 Hz, 3H, CH_2CH_3).

Acknowledgement.

The authors wish to thank Analytical Chemistry group headed by Dr. F. A. MacKellar for all the analytical data provided, and in particular S. Uhlendorf and D. Schweiss for their helpful advice and discussions.

REFERENCES AND NOTES

[1] J. S. Wolfson and D. C. Hooper, *Antimicrob. Agents Chemother.*, **28**, 581 and 716 (1985).

[2] P. B. Fernandes and D. T. W. Chu, "Annual Reports in Medicinal Chemistry", Vol **22**, D. M. Baily, ed, Academic Press, Inc., Orlando, Fl., 1987, p 117.

[3] J. M. Domagala, L. D. Hanna, C. L. Heifetz, M. P. Hutt, T. F. Mich, J. P. Sanchez and M. Solomon, *J. Med. Chem.*, **29**, 394 (1986).

[4] J. M. Domagala, C. L. Heifetz, T. F. Mich and J. B. Nichols, *J. Med. Chem.*, **29**, 445 (1986).

[5] R. Albrecht, *Progr. Drug Res.*, **21**, 9 (1977).

[6] L. Verbist, *Pharm. Weekblad, Sci. Ed.*, **8**, 22, 1986.

[7] T. Uno, M. Takamatsu, Y. Inoue, Y. Kawahata, K. Iuchi and G. Tsukamoto, *J. Med. Chem.*, **30**, 2163 (1987).

[8] P. M. Carabateas, R. P. Brundage, K. O. Gelotte, M. D. Gruett, R. R. Lorenz, C. J. Opalka, B. Singh, W. H. Thielking, G. L. Williams and G. Y. Lesher, *J. Heterocyclic Chem.*, **21**, 1857 (1984).

[9] C. Rufer, H. J. Kessler and K. Schwarz, *Eur. J. Med. Chem.*, **12**, 27 (1977).

[10] T. P. Culbertson, J. M. Domagala, J. B. Nichols, S. Priebe and R. W. Skeean, *J. Med. Chem.*, **30**, 1711 (1987).

[11] T. Culbertson, J. M. Domagala, P. Peterson, S. Bonger and J. B. Nichols, *J. Heterocyclic Chem.*, **24**, 1509 (1987).

[12] H. Bedereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).

[13] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons Inc., New York, 1967, p 268.

[14] J. P. Sanchez and J. W. Rogowski, *J. Heterocyclic Chem.*, **24**, 215 (1987).

[15] S. Nishigaki, N. Mizushima and K. Senga, *Chem. Pharm. Bull.*, **25**, 349 (1977).

[16] G. Queguiner and P. Pastour, *Bull. Soc. Chem. France*, **11**, 4082 (1969).

[17] H. Uchida, H. Iwasawa and M. Ohta, *Bull. Soc. Chem. Japan*, **46**, 3277 (1973).