New 7-Substituted Quinolone Antibacterial Agents. The Synthesis of 1-Ethyl-1,4-dihydro-4-oxo-7-(2-thiazolyl and 4-thiazolyl)-3-quinolinecarboxylic Acids

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A series of 1-ethyl-1,4-dihydro-4-oxo-7-(4-thiazolyl)-3-quinolinecarboxylic acids and 1-ethyl-1,4-dihydro-4-oxo-7-(2-thiazolyl)-3-quinolinecarboxylic acids were prepared. Also prepared was 10-[2-(aminomethyl)-4-thiazolyl]-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid. Analogs with basic amine substituents on the thiazole moiety were found to have antibacterial activity.

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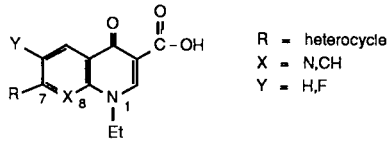
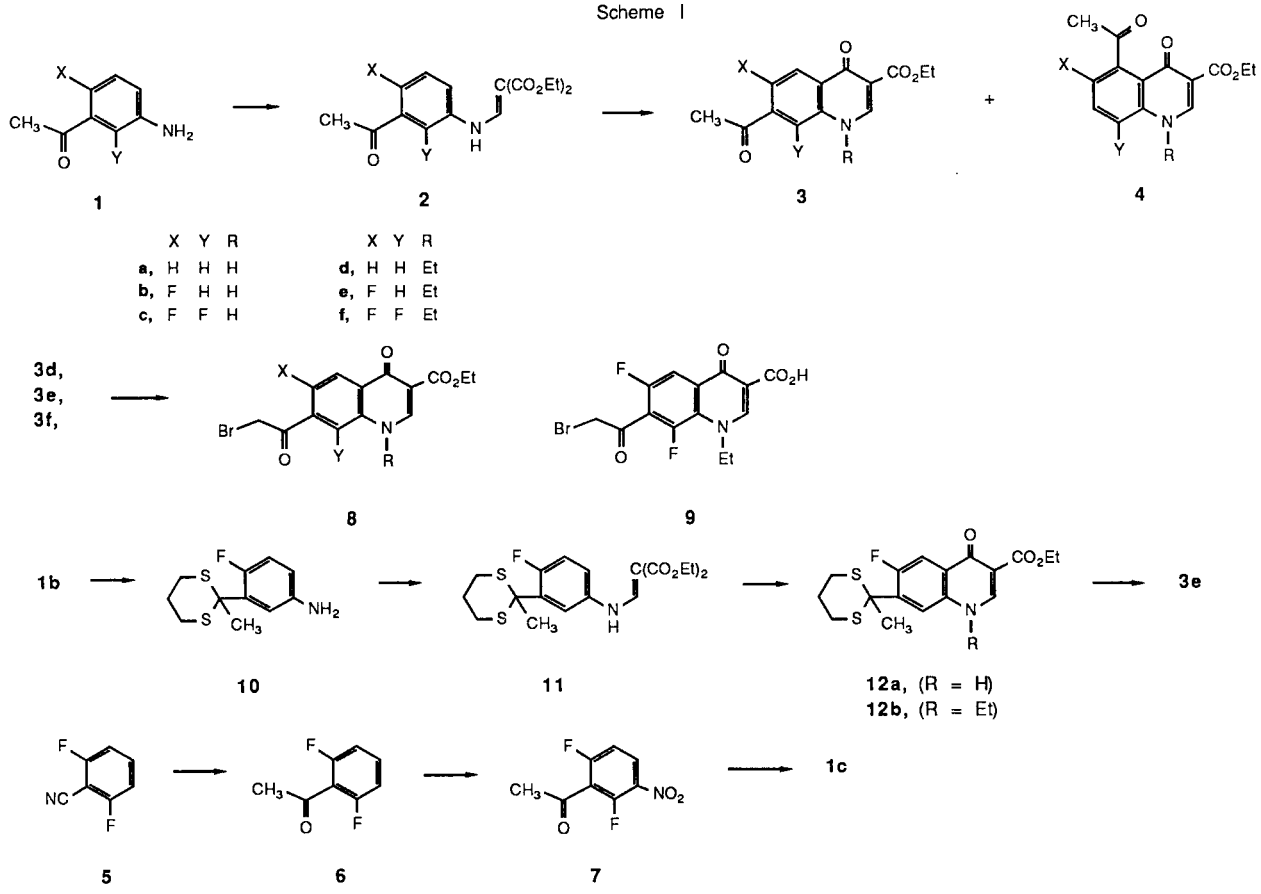
The biological spectrum and potency of 4-quinolone antibacterial agents are known to be strongly influenced by substituents at the 7-position, especially by nitrogen containing heterocycles [1]. Broad spectrum activity is known for compounds possessing either aliphatic or aromatic amine substituents, *e.g.* enoxacin (R = 1-piperazinyl, X = N, Y = F) and rosoxacin (R = 4-pyridinyl, X = CH, Y = H) [2]. Limited reports on quinolones have described various five membered heterocyclic substituents at the 7-position, *e.g.* thiophenes, isoxazoles, pyrazoles [1a], imidazoles [1b] and pyrroles [1c], but there are few examples and little significant activity. This paper describes the synthesis of 7-(4-thiazolyl) and 7-(2-thiazolyl)quinolones, some of which



Scheme I



possess potent antibacterial activity.

Since thiazoles are usually prepared by the reaction of α-bromoketones with thioamides, a 7-(bromoacetyl)quinolone intermediate was envisioned as a crucial target. The enamine **2a** was prepared by the reaction of 3-aminoacetophenone, **1a**, with diethyl ethoxymethylenemalonate (EMME). Thermal cyclization in Dowtherm A afforded a 4:1 mixture of the 5-acetyl and the 7-acetylquinolones **4a** and **3a** [3] (Scheme I) as indicated by the methyl ketone pmr singlets at δ 2.95 and 2.88, respectively. Alkylation of **3a** under phase transfer conditions afforded the 7-acetyl isomer **3d** in 36% yield after crystallization from ethanol. Bromination of **3d** with potassium bromate-hydrobromic acid in acetic acid solution [4] afforded the bromoketone **8d** containing about 10% of unbrominated starting ketone. This material was used without further purification for the preparation of thiazole derivatives.

Since quinolone antibacterial agents substituted in the 6- and 6,8-positions by fluorine are more active than the corresponding unfluorinated analogs [5], it was of interest to prepare the 7-(bromoacetyl)-6-fluoroquinolone **8e** as well. The reaction of 3-acetyl-4-fluoroaniline [6] with EMME followed by thermal cyclization of the enamine **2b** produced a mixture of the quinolones **3b** and **4b**. Alkylation of the crude product afforded a mixture of the 1-substituted quinolones **3e** and **4e** in a 1:4 ratio, respectively, which were separated by column chromatography. Quinolone **3e**, mp 120-121°, obtained in 17% yield showed two doublets for one proton each at δ 8.52 (J = 9) and 8.83 (J = 5) attributable to fluorine coupling with protons on C-5 and C-8, respectively. Similarly, the isomeric quinolone **4e**, mp 200-201°, showed a doublet of doublets at δ 8.05 (J = 8, 9) and 8.38 (J = 4, 9) for hydrogens on C-7 and C-8, respectively.

Table I

Preparation of Thioamides **21a-k**

RCN [a] → $RCSNH_2$

21 **22**

Nitrile	R	bp (°C/mm Hg)	Thioamide	Procedure	% Yield	mp °C Solvent	MF	Analysis % Cacld./Found C	H	N	S
21a	CH_3NAcCH_2-	74-80/0.1	**22a**	A	99	159-160 ethanol	$C_5H_{10}N_2OS$	41.07 41.08	6.89 6.77	19.16 19.01	21.93 21.95
21b	$C_2H_5NAcCH_2$-	93-98/0.8	**22b**	A	50	112-116 ethanol	$C_6H_{12}N_2OS$	44.97 45.17	7.55 7.65	17.48 17.59	
21c	n-$C_3H_7NAcCH_2$-	105-108/1	**22c**	A	70	103-104.5 ethanol	$C_7H_{14}N_2OS$	48.25 48.20	8.10 7.94	16.07 16.22	18.40 18.57
21d [b]	$AcOCH_2CH_2NAcCH_2$-	134-136/0.1	**22d**	A	82	116-117.5 ethanol	$C_8H_{14}N_2O_3S$	44.02 44.02	6.46 6.63	12.84 12.81	14.69 14.43
21e [b]	$AcNHCH(CH_3)$-	95-102/0.1	**22e**	A	37	152-154 ethyl acetate	$C_5H_{10}N_2OS$	41.07 41.10	6.89 6.85	19.16 19.25	21.93 21.87
21f	$(CH_3)_2NCH_2$-	—	**22f** [c]	B	35	80-81 hexanes	$C_4H_{10}N_2S$	40.64 40.98	8.53 8.21	23.70 23.98	
21g [a]	4-Morpholinyl	—	**22g** [c]	B	88	176-177 [d]	$C_5H_{10}N_2OS$	41.07 40.98	6.89 6.57	19.16 19.19	21.93 22.13
21h [e]	4-(Ethoxycarbonyl)-1-piperazinyl	117-121/0.05	**22h** [c]	B	96	149-151 [h] ethanol	$C_8H_{15}N_3O_2S$	44.22 44.54	6.96 6.97	19.34 19.40	14.76 14.96
21i [f]	$C_6H_5CH_2OCONHCH_2$-		**22i**	B	84	145-146 [g] ethanol-water	$C_{10}H_{12}N_2O_2S$				
21j	$C_6H_5CH_2OCON(CH_3)CH_2$-		**22j**	B	63	94-95 ethanol-water	$C_{11}H_{14}N_2O_2S$				
21k	$C_6H_5CH_2OCON(C_2H_5)CH_2$-		**22k**	B	70	109-110 ethanol-water	$C_{12}H_{16}N_2O_2S$				

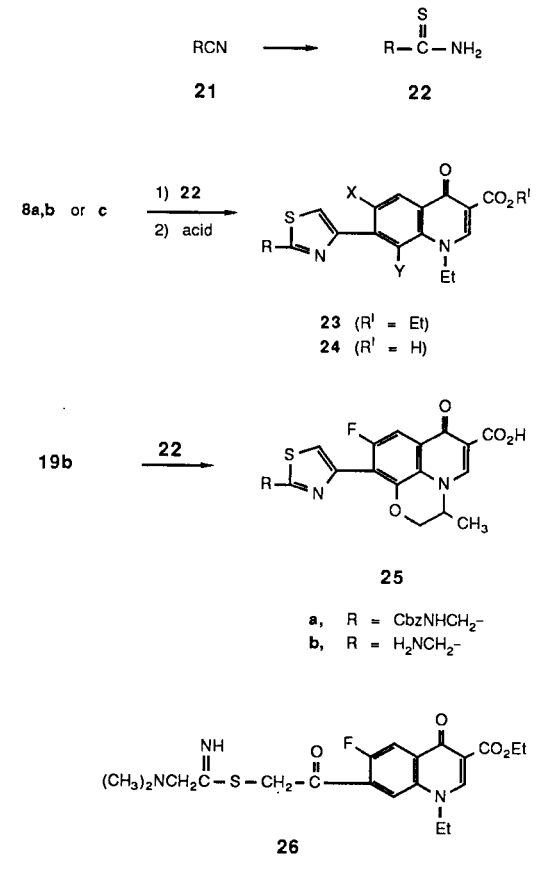
[a] Aminonitriles **21a-21e** were prepared and acetylated by standard procedures, see references [7], [8] and [12]. Nitriles **21f** and **21g** were purchased from the Aldrich Chemical Company. [b] See references [9] and [17] for the preparation of aminonitrile precursors of compounds **21d** and **21e**, respectively. [c] See referene [18] for method of preparation. [d] As precipitated from the reaction mixture of pyridine, triethylamine and hydrogen sulfide. [e] See experimental for preparation. [f] See reference [23] for preparation. [g] See reference [24] for preparation, literature mp 146-148°. [h] Literature mp 95-97°, see reference [25].

In an effort to shift the isomer ratio in the cyclization of **2b** toward the desired isomer **3e**, 3-acetyl-4-fluoroaniline, **1b**, was converted to the 1,3-dithiane derivative **10** in order to increase steric hindrance at the adjacent 2-position. Treatment of **10** with EMME gave **11**, and subsequent thermal cyclization and *N*-alkylation afforded **12b** in 66% yield which was readily deblocked with mercuric oxide-mercuric chloride-water to afford the 7-acetyl-6-fluoroquinolone **3e**. This amounted to an overall 43% yield of **3e** from **1b** versus a 17% yield when the acetyl group was left unprotected. Subsequent bromination of **3e** afforded bromoketone **8e**.

The 6,8-Difluoroquinolones were prepared by an analogous procedure by starting with 2,6-difluorobenzonitrile **5**. Treatment of **5** with methyl lithium afforded 2',6'-difluoroacetophenone, **6**, which was nitrated under carefully controlled conditions (nitric acid-sulfuric acid at -5° to +5°) to give **7**. Hydrogenation over Raney nickel catalyst gave **1c** and treatment of the reaction mixture with EMME afforded the enamine **2c** which was thermally cyclized to the quinolone **3c**. Ethylation with ethyl iodide-potassium carbonate gave **3f**, and subsequent treatment with potassium bromate-hydrogen bromide-acetic acid resulted in combined bromination and ester hydrolysis to afford **9**.

We also desired analogs having the tricyclic structure found in Ofloxacin (DL-8280) [25] and therefore required 10-(bromoacetyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]benzoxazine-6-carboxylic acid **19b** (Scheme II). Treatment of 3-acetyl-2,4-difluoronitrobenzene, **7**, with the lithium salt of ethylene ketal **13** resulted in regiospecific substitution of the fluorine adjacent to the nitro group to afford **14**. Subsequent deblocking with acetic acid-hydrochloric acid produced the diketone **15** which upon hydrogenation to **16** and immediate reaction with 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione, **17**, afforded the benzoxazine **18**. By heating in polyphosphoric ester, compound **18** cyclized to the desired tricyclic intermediate **19a** which was brominated to give bromoketone **19b**.

Scheme III



Scheme II

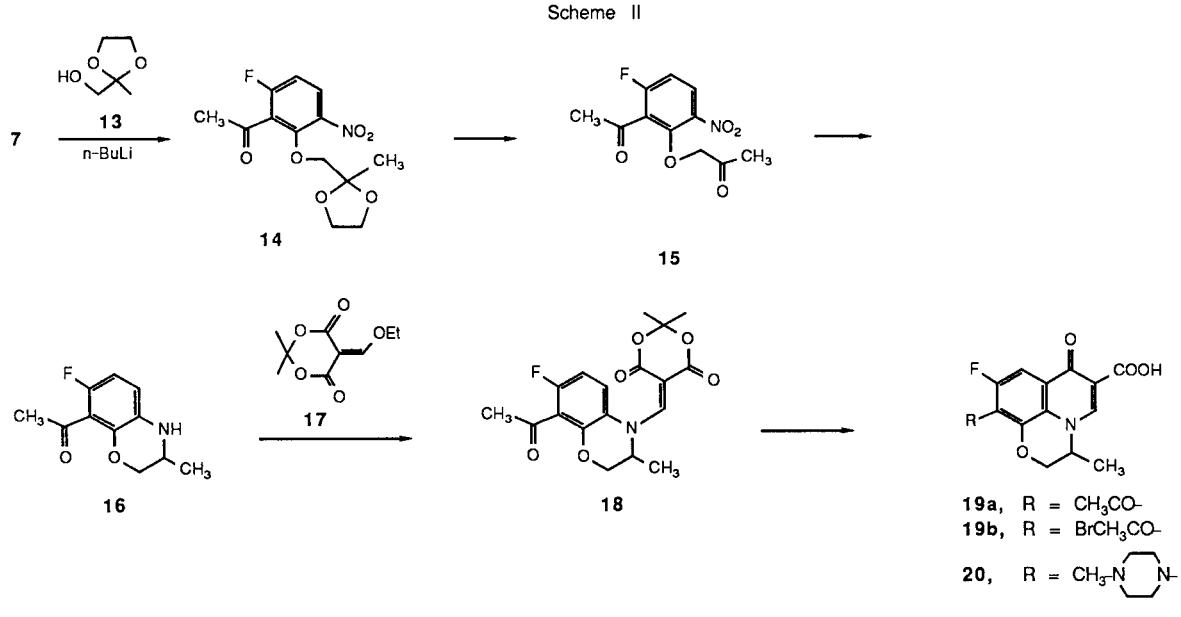
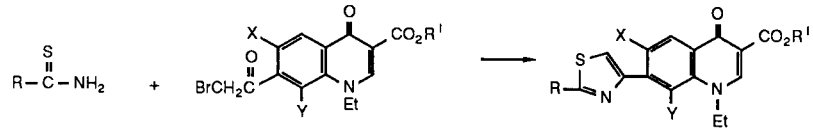


Table II

Preparationof 7-(4-Thiazolyl)quinolones **23a-w**



22 **8** **23**

Compound	Thioamide, R	R′	X	Y	% Yield	mp °C Solvent	MF	Analysis % Calcd./Found C	H	N
23a	H_2N-	Et	F	H	65	274-277 DMF-MeOH	$C_{17}H_{16}FN_2O_2S$	56.50 56.52	4.46 4.67	11.63 11.45
23b	CH_3-	Et	F	H	58	200-202 EtOH-H_2O	$C_{18}H_{17}FN_2O_3S$	59.98 59.81	4.76 4.91	7.77 7.85
23c	$AcNHCH_2$- [a]	Et	F	H	58	230-233 EtOH	$C_{20}H_{20}FN_3O_4S$	57.54 57.63	4.83 5.19	10.07 9.98
23d **22a**	CH_3NAcCH_2-	Et	F	H	78	173-175 EtOH-H_2O	$C_{21}H_{22}FN_3O_4S$	58.45 58.70	5.14 5.13	9.74 9.56
23e **22b**	$C_2H_5NAcCH_2$-	Et	F	H	58	160-161 [b] EtOH-H_2O	$C_{22}H_{24}FN_3O_4S$	59.31 59.36	5.43 5.35	9.43 9.41
23f **22c**	n-$C_3H_7NAcCH_2$-	Et	F	H	55	174-175 MeOH	$C_{23}H_{26}FN_3O_4S$	60.11 59.93	5.70 5.59	9.14 9.14
23g [c] **22f**	$(CH_3)_2NCH_2$-	Et	F	H	51	>152 [d] EtOH	$C_{22}H_{22}F_4N_3O_5S$	51.16 51.38	4.29 4.57	8.14 7.94
23h **22e**	$AcNHCH(CH_3)$-	Et	F	H	58	236-238 EtOH-H_2O	$C_{21}H_{22}FN_3O_4S$	58.45 58.36	5.14 5.17	9.74 9.65
23i	$AcNHCH_2CH_2$- [e]	Et	F	H	44	233-234 [f] EtOH	$C_{21}H_{22}FN_3O_4S$	58.45 58.25	5.14 5.20	9.74 9.75
23j **22d**	$AcOCH_2CH_2NAcCH_2$-	Et	F	H	51	164-165 [g] MeOH	$C_{24}H_{26}FN_3O_6S$ ·$0.3H_2O$	56.63 56.55	5.27 5.03	8.26 8.13
23k	$(CH_3)_2$- [h]	Et	F	H	60	232-234 EtOH	$C_{19}H_{20}FN_3O_3S$	58.59 58.60	5.18 4.93	10.79 10.75
23l	3-pyridyl- [i]	Et	F	H	38	236-237 EtOH	$C_{22}H_{18}FN_3O_3S$	62.40 62.33	4.28 4.08	9.92 10.00
23m **22g**	4-morpholinyl-	Et	F	H	49	264-267 DMF-MeOH	$C_{21}H_{22}FN_3O_4S$	58.45 58.12	5.14 5.20	9.74 9.70
23n **22h**	1-(4-ethoxycarbonyl)-piperazinyl	Et	F	H	78	241-242 EtOH	$C_{24}H_{27}FN_4O_5S$	57.35 57.48	5.42 5.55	11.15 10.95
23o	H_2N-	Et	H	H	37	254-257 MeOH	$C_{17}H_{17}N_3OS$	59.45 59.07	4.99 5.12	12.24 12.33
23p	CH_3NH-	Et	H	H	48	233-235 DMF-MeOH	$C_{18}H_{18}N_3O_3S$	60.65 60.45	5.09 5.36	11.79 11.74
23q	C_6H_5NH-	Et	H	H	87	246-249 [j]	$C_{23}H_{21}N_3O_3S$	65.85 66.14	5.05 5.14	10.02 9.77
23r	$AcNHCH_2$- [a]	Et	H	H	67	204-205 EtOH	$C_{20}H_{21}N_3O_4S$	60.13 59.86	5.30 5.45	10.52 10.46
23s	HO_2CCH_2NH-	Et	H	H	75	>172 [d]	$C_{19}H_{19}N_3O_5S$ ·$0.4H_2O$	55.98 55.88	4.70 4.86	10.31 10.60
23t	3-pyridyl-	Et	H	H	45	215-217 EtOH	$C_{22}H_{19}N_3O_3S$	65.17 64.78	4.72 5.04	10.36 10.15

Table II (continued)

Compound	Thioamide, R	R'	X	Y	% Yield	mp °C Solvent	MF	Analysis % Calcd./Found C	H	N
23u	$C_6H_5OCONHCH_2$-	H	F	F	93	188-190 [k]	$C_{24}H_{18}F_2N_3O_5S$	57.83 58.14	3.61 3.60	8.43 8.33
23v	$C_6H_5CH_2OCON(CH_3)CH_2$-	H	F	F	68	167-168 [k]	$C_{25}H_{21}F_2N_3O_5S$			
23w	$C_6H_5CH_2OCON(Et)CH_2$-	H	F	F	88	150-152 [k]	$C_{26}H_{23}F_2N_3O_5S$			

[a] See reference [12]. [b] Initially melted and resolidified at 148-149°. [c] Isolated as the trifluoroacetic acid salt. [d] Decomposition. [e] mp 90-91°, literature mp 103-104.5° [13]. [f] Melted and resolidified ca 205-210°. [g] Melted and resolidified at 148-152°. [h] Obtained from Trans World Chemical Company. [i] Obtained from Aldrich Chemical Company. [j] The crude product was triturated with ethanol. [k] Precipitated from the reaction mixture by addition of water.

Table III

^{1}H-NMR Spectral Data for Quinolones **23a-u** [a]

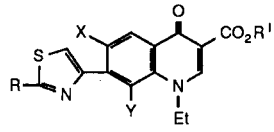
Compound	Solvent	Thiazole H	H-2	H-5	H-8	Other
23a	[b]	7.56 (S)	9.33 (S)	8.47 (d, J = 11)	8.60 (d, J = 6)	
23b	[c]	7.85 (S)	8.68 (S)	8.34 (d, J = 6)	8.00 (d, J = 3)	2.72 (S, 3H, thiazole-CH_3)
23c	[c]	8.04 (d, J = 3) [e]	8.65 (S)	7.90 (d, J = 12)	8.28 (d, J = 6)	
23d	[c]	8.10 (m)	8.62 (S)	7.88 (d, J = 12)	8.29 (d, J = 6)	
23e	[c]	8.08 (m)	8.62 (S)	7.89 (d, J = 12)	8.28 (d, J = 5)	4.76 and 4.95 (S, S, 2H, thiazole-CH_2-)
23f		Complex spectrum				
23g	[b]	8.48 (d, J = 3) [p]	9.33 (S)	8.46 (d, J = 10)	9.21 (d, J = 6)	3.30 (m, 6H, $N(CH_3)_2$)
23h	[c]	8.20 (d, J = 3) [e]	8.80 (S)	8.04 (d, J = 11)	8.48 (d, J = 6)	
23i	[c]	8.02 (d, J = 3) [e]	8.62 (S)	7.90 (d, J = 12)	8.33 (d, J = 6)	
23j	[d]	7.87 (m)	8.42 (S)	8.10 (d, J = 12)	8.33 (d, J = 6)	
23k	[b]	7.43 (S)	9.37 (S)	8.46 (d, J = 9)	8.63 (d, J = 3)	
23l	[d]	8.04 (d, J = 2)	9.29 (S)	8.25 (d, J = 12)	8.70 (d, J = 5)	
23m	[c]	7.40 (d, J = 3)	8.65 (S)	7.87 (d, J = 12)	8.26 (d, J = 7)	
23n	[d]	7.20 (d, J = 2)	8.38 (S)	8.10 (d, J = 12)	8.20 (d, J = 6)	
23o	[c]	7.30 (S)	8.56 (S)	8.12 (d, J = 9)	7.98 (S)	8.12 (d, J = 9, H-6)
23p	[c]	7.37 (S)	8.57 (S)	8.14 (d, J = 9)	8.03 (S)	7.83 (d, J = 9, H-6)
23q	[c]	Complex aromatic spectrum				
23r	[c]	8.35 (S)	8.68 (S)	8.00 (d, J = 9)	8.25 (S)	8.31 (d, J = 9, H-6)
23s	[c]	7.40 (S)	Complex			
23t	[d]	Complex aromatic				
23u	[b]	8.40 (m)	9.40 (S)	8.40 (m)		7.30 (S, phenyl)

[a] δ from internal TMS. [b] Trifluoroacetic acid solution. [c] Deuteriodimethylsulfoxide solution. [d] Deuteriochloroform solution. [e] Split by fluorine.

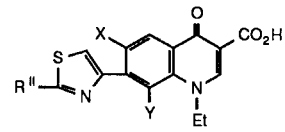
Thioamides were obtained from commercial sources or prepared by base catalyzed addition of hydrogen sulfide to nitriles, Table I. Because of the difficulty in reproducing literature procedures for the preparation of **22h** [11a,b], the cyanamide **21h** was prepared by reaction of cyanogen bromide with ethyl 1-piperazinecarboxylate in the presence of potassium carbonate [19], and subsequent treatment with hydrogen sulfide in pyridine-triethylamine then afforded **22h**. Thioamides were reacted with 7-(bromoacetyl)quinolones to afford the corresponding 7-(4-thiazolyl)quinolones **23** or **24**, Scheme III. Although thiazole formation was usually facilitated by treatment of the reaction mixture with triethylamine, an intermediate was isolated during the preparation of **23g** which had a pmr spec-

Table IV

Preparation of 3-Quinolonecarboxylic Acids **24a-w**



23



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Starting Material	Product	Method	R″	X	Y	% Yield	mp °C	Molecular Formula	Analysis %, Calcd./Found C	H	N	Cl
23a	**24a**	B	H_2N-	F	H	100	>300 [a]	$C_{15}H_{12}N_3O_3S$	54.04 54.06	3.63 3.71	12.61 12.55	
23b	**24b**	B	CH_3-	F	H	89	270-274	$C_{16}H_{13}FN_2O_3S$ ·0.4 H_2O	56.59 56.63	3.85 3.92	8.25 8.17	
23c	**24c**	A	H_2NCH_2-	F	H	83	249-254	$C_{16}H_{14}FN_3O_3S$ ·0.3H_2O	54.47 54.41	4.17 4.08	11.91 11.92	
23d	**24d**	A	CH_3NHCH_2-	F	H	61	230-234	$C_{17}H_{16}FN_3O_3S$	56.50 56.26	4.46 4.56	11.63 11.40	
23e	**24e**	A	$C_2H_5NHCH_2$- ·HCl	F	H	69	298-300	$C_{18}H_{19}ClFN_3O_3S$ ·0.3 H_2O	51.81 51.81	4.73 4.79	10.07 10.09	8.50 8.49
23f	**24f**	A	*n*-$C_3H_7NHCH_2$- ·HCl	F	H	62	265-272	$C_{19}H_{21}ClFN_3O_3S$	53.58 53.28	4.97 4.98	9.87 9.84	8.33 8.18
23g	**24g**	A	$(CH_3)_2NCH_2$- ·HCl	F	H	53	>300	$C_{18}H_{19}ClFN_3O_3S$	52.49 52.18	4.65 4.65	10.20 10.04	8.61 8.86
23h	**24h**	A	$H_2NCH(CH_3)$-	F	H	77	246-250	$C_{17}H_{16}FN_3O_3S$ ·0.2H_2O	55.94 55.92	4.53 4.51	11.51 11.68	
23i	**24i**	A	$H_2NCH_2CH_2$-	F	H	79	>240	$C_{17}H_{16}FN_3O_3S$ ·0.7 H_2O	54.59 54.40	4.69 4.57	11.23 11.23	
23j	**24j**	A	$HOCH_2CH_2NHCH_2$-	F	H	63	290	$C_{18}H_{17}ClFN_3O_4S$ ·0.4 H_2O	49.92 50.36	4.14 4.50	9.70 9.66	
23k	**24k**	B	$(CH_3)_2N$-	F	H	98	>300	$C_{17}H_{16}FN_3O_3S$	56.50 56.48	4.46 4.23	11.63 11.61	
23ℓ	**24ℓ**	B	3-pyridyl	F	H	100	>300	$C_{20}H_{14}FN_3O_3S$	60.75 60.46	3.57 3.80	10.63 10.61	
23m	**24m**	B	4-morpholinyl-	F	H	94	291-296	$C_{19}H_{18}FN_3O_4S$	56.56 56.41	4.50 4.48	10.42 10.38	
23n	**24n**	B	1-piperazinyl-	F	H	100	274	$C_{19}H_{19}FN_4O_3S$ ·1.6H_2O	52.91 52.97	5.19 5.32	12.99 12.91	
23o	**24o**	B	H_2N-	H	H	91	312-313	$C_{15}H_{13}N_3O_3S$ ·0.2H_2O	56.48 56.65	4.23 4.25	13.17 13.46	
23p	**24p**	B	CH_3NH-	H	H	49	280-281	$C_{16}H_{15}N_3O_3S$	58.34 58.29	4.59 4.54	12.76 12.76	
23q	**24q**	B	C_6H_5NH-	H	H	100	>300	$C_{21}H_{17}N_3O_3S$ ·0.25H_2O	63.70 63.71	4.46 4.51	10.61 10.53	
23r	**24r**	A	H_2NCH_2-	H	H	32	279-283	$C_{16}H_{15}N_3O_3S$ ·H_2O	55.31 55.20	4.93 4.69	12.10 11.97	
23s	**24s**	B	HO_2CCH_2NH-	H	H	95	265	$C_{17}H_{15}N_3O_5S$	54.68 54.36	4.05 3.95	11.25 11.31	
23t	**24t**	B	3-pyridyl-	H	H	100	309-311	$C_{20}H_{15}N_3O_3S$ ·0.7H_2O	61.59 61.59	4.24 4.14	10.77 10.71	
23u	**24u**	C	H_2NCH_2-	F	F	73	205-208	$C_{16}H_{13}F_2N_3O_3S$	52.60 52.34	3.56 3.59	11.51 11.40	
23v	**24v**	C	CH_3NHCH_2-	F	F	64	172-174	$C_{17}H_{15}F_2N_3O_3S$	53.83 53.64	3.96 3.86	11.08 11.20	
23w	**24w**	C	$EtNHCH_2$-	F	F	86	175-177	$C_{18}H_{17}F_2N_3O_3S$	54.96 54.72	4.33 4.46	10.69 10.53	

[a] Melting points were accompanied by decomposition.

trum consistent with the uncyclized adduct **26** and it was converted to **23g** by treatment with trifluoroacetic acid (Table II). The esters were hydrolyzed to the desired 3-quinolonecarboxylic acids, **24a-w** (Table IV).

The preparation of isomeric analogs having a 2-thiazolyl moiety at the quinolone 7-position required a reversal of substrate functionalities, *i.e.*, thioamide and bromoketone; therefore, a 7-(thiocarbamoyl)quinolone was necessary (Scheme IV). The 7-cyanoquinolone **27b** was prepared by diazotization of 7-amino-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid ethyl ester, **27a** [21], in the presence of cuprous cyanide, and treatment of **27b** with hydrogen sulfide in pyridine-triethylamine afforded 7-(thiocarbamoyl)quinolone ester **28**. Reaction of **28** with 2-(bromoacetyl)pyridine, **29e**, gave the 7-(2-thiazolyl)quinolone ester **30e** which was hydrolyzed by acid to give **31e**. Reaction of **28** with 1,3-dichloroacetone afforded **30a** which was reacted with sodium azide in dimethylformamide to form azido compound **30b**. The azide was hydrogenated to the amino compound **30c** and finally hydrolyzed to the 3-quinolonecarboxylic acid **31c**. Compound **30a** was also hydrolyzed with hydrochloric acid to afford **31a** which gave **31d** after reaction with aqueous methylamine.

All 7-thiazolyl-4-quinolones were assayed against gram positive and gram negative bacteria by standard serial dilution methods. Although all compounds were active to some extent, the most potent were those having aminomethyl substituents on the thiazole moiety, *e.g.* **24e** which showed mic < 1 μg/ml against a broad spectrum of bacteria. A more detailed analysis of the biological data as well as structure-activity relationships will be discussed in a future publication.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The infrared spectra were recorded on a nicolet MX-1 FT ir spectrometer. The ^{1}H nmr spectra were recorded on a Varian XL-200 spectrometer with shifts given in ppm downfield from tetramethylsilane and coupling constants are in Hz. Mass spectra were recorded on a Finnigan 4500 mass spectrometer. Thin layer chromatography was carried out with E. Merck Kieselgel-60 glass plates and column chromatography with Kieselgel-60, 70-230 mesh. Solutions were dried with magnesium sulfate.

1-(5-Amino-2-fluorophenyl)ethanone (**1b**).

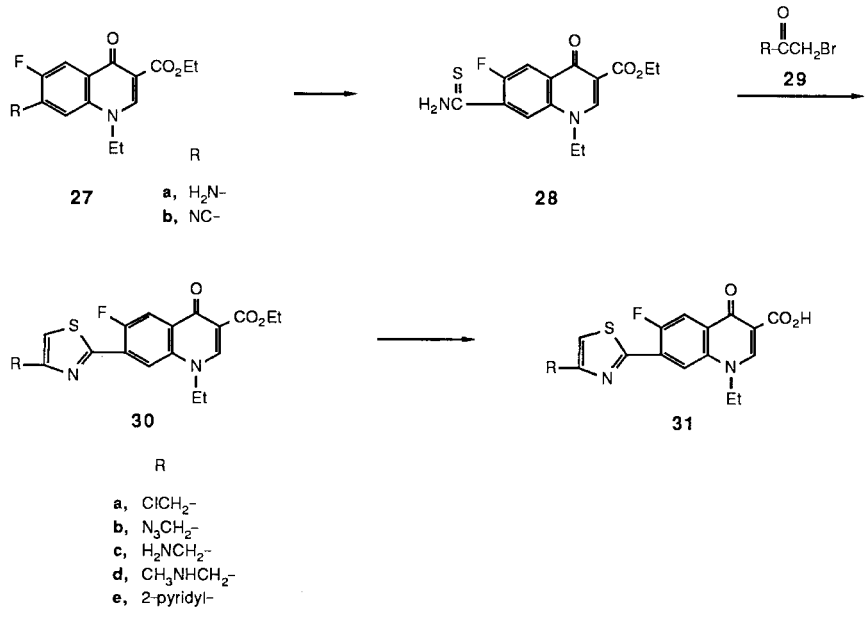
A solution of 10.8 g (80 mmoles) of 1-(3-aminophenyl)ethanone in 50 ml of water and 20 ml of concentrated hydrochloric acid was stirred at $-5°$ to 0° and treated with 6.07 g (88 mmoles) of sodium nitrite in 20 ml water. After one hour, the mixture was diluted with 50 ml of hexanes and 50 ml of ether and treated dropwise with a solution of 5.72 g (85 mmoles) of sodium azide in 20 ml of water. After stirring an additional hour at 0°, the organic layer was separated, dried, the solvent removed under vacuum (25° bath) and the residue redissolved in 50 ml of hexanes and 10 ml of dichloromethane. This solution was added dropwise over 30 minutes to 30 ml of hydrogen fluoride condensed in a polyethylene bottle and stirred in an ice bath. The dark mixture was stirred overnight at room temperature allowing the hydrogen fluoride to vent, and the evaporation was then completed under an air stream. The residue was diluted with ice water, stirred in an ice bath and made basic by the cautious addition of 50% sodium hydroxide. The product was extracted into dichloromethane, dried, evaporated and twice crystallized from cyclohexane to afford 6.15 g of **1b** (50%), mp 76-77° (lit [6], mp 68-70°); pmr (deuteriochloroform): δ 2.56 (d, 3H, J = 5, CH_3CO split by fluorine), 3.52 (br s, 2H, NH_2), 6.6-7.2 (m, 3H, aromatic H).

Anal. Calcd. for C_8H_8FNO: C, 62.74; H, 5.62; N, 9.15; F, 12.41. Found: C, 62.62; H, 5.31; N, 9.14; F, 12.42.

4-Fluoro-3-(2-methyl-1,3-dithian-2-yl)benzeneamine (**10**).

A solution of 26.4 g (0.17 mole) of **1b** and 34.6 ml (0.35 mole) of 1,3-propanedithiol in 2.5 ℓ of chloroform was cooled to 5° and saturated with gaseous hydrogen chloride. The mixture was brought to 25° and stirred for 18 hours. The mixture was concentrated, the residue dissolved in chloroform and extracted twice with dilute sodium bicarbonate. The

Scheme IV



chloroform solution was dried and concentrated to give 41.3 g (100%) of **10** as a brown oil; pmr (deuteriochloroform): δ 1.90 (m, 2H, $CH_2CH_2CH_2$), 2.80 (m, 4H, SCH_2), 3.55 (br s, 2H), 6.60 (m, 2H), 7.15 (m, 1H).

1-(2,6-Difluorophenyl)ethanone (**6**).

To a solution 73.24 g (0.52 mole) of 2,6-difluorobenzonitrile (Fairfield Chemical Co.) in 300 ml of ether at −78° was added 650 ml of 1.6 *N* methyl lithium (2 equivalents) over one hour. The reaction was continued for 2.5 hours and was quenched by the addition of 6 *N* hydrochloric acid. The mixture was brought to 5°, the layers separated, and the water layer extracted with dichloromethane. The organic layers were combined, dried, and concentrated to give an oil that was purified by flash chromatography, ether-hexane (1:1), to give 63.2 g (78%) of **1c**; pmr (deuteriochloroform): δ 2.60 (d, J = 2, 3H, $COCH_3$), 7.00 (m, 2H), 7.30 (m, 1H).

1-(2,6-Difluoro-3-nitrophenyl)ethanone (**7**).

To a solution of 16.6 g (106 mmoles) of **6** in 100 ml of concentrated sulfuric aicd at −5° was added a cold mixture of 20 ml of concentrated sulfuric acid and 10 ml of 70% nitric acid. The addition took place at a rate that kept the temperature at −5° to 5°. The reaction continued an additional 15 minutes and was poured over ice. The mixture was extracted with dichloromethane, dried and concentrated to give 14.0 g (66%) of **7** as an oil; pmr (deuteriochloroform): δ 2.60 (d, J = 1, 3H, $COCH_3$), 7.40 (dd, J = 8, J = 3 Hz, 1H), 8.25 (m, 1H).

1-[6-Fluoro-2-[(2-methyl-1,3-dioxolan-2-yl)methoxy]-3-nitrophenyl]ethanone (**14**).

To a solution of 35.45 g (0.23 mole) of the hydroxyacetone ketal·0.78 H_2O [26], **13**, in 200 ml of tetrahydrofuran was added 100 ml of 2.3 *M* *n*-butyl lithium at −78°. The mixture was warmed to −40° and was added to 46.35 g (0.23 mole) of 1-(2,6-difluoro-3-nitrophenyl)ethanone, **7**, in 200 ml of tetrahydrofuran at 0°. After stirring for 30 minutes, this mixture was poured into 1 ℓ of ethyl acetate-aqueous ammonium chloride (1:1) and the light suspension filtered through celite. The organic layer was washed with water, dried, and concentrated. The resulting oil was purified by flash chromatography (ether-hexane, 1:4) giving 41.2 g (60%) of **14** as a thick oil; pmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 2.55 (s, 3H, $COCH_3$), 3.90 (m, 4H, OCH_2), 6.90 (dd, J = 10, 9, 1H), 7.85 (dd, J = 10, 5, 1H).

Anal. Calcd. for $C_{13}H_{14}FNO_6$: C, 52.12; H, 4.68; N, 4.68. Found: C, 51.90; H, 4.88; N, 4.71.

1-(2-Acetyl-3-fluoro-6-nitrophenoxy)-2-propanone (**15**).

To 39.4 g (0.132 mole) of **14** was added 360 ml of water-hydrochloric acid-acetic acid (10:1:25). The mixture was stirred at 40-50° for 48 hours and was concentrated. The residue was diluted with chloroform, extracted twice with water and was dried and concentrated to an oil. Trituration with ether-penate (1:1) gave 26.2 g (53%) of **15**, mp 60-62°; pmr (deuteriochloroform): δ 2.10 (s, 3H, $COCH_3$), 2.50 (s, 3H, $COCH_3$), 4.60 (s, 2H, OCH_2), 7.00 (dd, J = 13, 9, 1H), 7.90 (dd, J = 9, 6, 1H).

Anal. Calcd. for $C_{11}H_{10}FNO_5$: C, 51.72; H, 3.92; N, 5.48. Found: C, 51.40; H, 3.88; N, 5.40.

1-(7-Fluoro-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine-8-yl)ethanone (**16**).

To 49.8 g (0.195 mole) of **15** was added 1 ℓ of 95% ethanol, 1.0 g of Raney Nickel and an atmosphere of hydrogen gas at 50 psi. After shaking for 19 hours the mixture was filtered, concentrated and flash chromatographed (ether-hexane, 1:1) to give 27.6 g (68%) of **16** as an oil; pmr (deuteriochloroform): δ 1.20 (d, J = 7, 3H, CH_3), 2.50 (d, J = 2, 3H, $COCH_3$), 3.30 (m, 1H, $CHCH_3$), 3.60 (dd, J = 9, 9, 1H, OCH*H*), 4.10 (dd, J = 3, 9, 1H, OC*H*H), 6.50 (m, 2H).

Anal. Calcd. for $C_{11}H_{12}FNO_2$: C, 63.10; H, 5.74; N, 6.69. Found: C, 63.38; H, 5.61; N, 7.00.

5-[(8-Acetyl-7-fluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazin-4-yl)methylene]-2,2-dimethyl-1,3-dioxan-4,6-dione (**18**).

To 25.6 g (122 mmoles) of **16** was added 27.4 g (147 mmoles) of 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxan-4,6-dione, **17**, [14] in 750 ml of methanol. The mixture was stirred at 30° for 18 hours, filtered, and the solids washed with pentane to give 36.4 g (82%) of **18**, mp 184-185°; pmr (deuteriochloroform): δ 1.30 (d, J = 6, 3H, $CHCH_3$), 1.80 (s, 6H, $2CH_3$), 2.50 (s, 3H, $COCH_3$), 4.20 (m, 2H, OCH_2), 4.90 (m, 1H, $CHCH_3$), 6.80 (dd, J = 9, 7, 1H), 7.10 (dd, J = 9, 5, 1H), 8.30 (s, 1H, vinyl *H*).

Anal. Calcd. for $C_{18}H_{18}FNO_6$: C, 59.44; H, 4.95; N, 3.85. Found: C, 59.42; H, 4.88; N, 3.87.

[(3-Acetyl-4-fluorophenyl)amino]methylenepropandioic Acid Diethyl Ester (**2b**).

A solution of 3.90 g (25.5 mmoles) of 5'-amino-2'-fluoroacetophenone and 5.62 g of (26 mmoles) diethyl ethoxymethylenemalonate in 50 ml of toluene was slowly distilled over 1.25 hours collecting 30 ml of distillate. The distillation residue crystallized after dilution with 100 ml of hexanes to afford 7.65 g (93%) of **2b**, mp 70-72°; pmr (deuteriochloroform): δ 1.32 and 1.37 (t, t, overlapping, 6H, OCH_2CH_3), 2.65 (d, 3H, J = 5, CH_3CO), 4.18 and 4.27 (q, q, overlapping 4H, OCH_2CH_3), 7.18 (m, 2H, phenyl), 8.36 (d, 1H, J = 14, NH-C*H*=C), 10.93 (br d, 1H, J = 14, NH).

Anal. Calcd. for $C_{16}H_{18}FNO_5$: C, 59.44; H, 5.61; N, 4.33. Found: C, 59.37; H, 5.76; N, 4.36.

[[[4-Fluoro-3-(2-methyl-1,3-dithian-2-yl)phenyl]amino]methylene]propanedioic Acid, Diethyl Ester (**11**).

To a solution of 41.0 g (0.169 mole) of **10** in 1.2 ℓ of toluene was added 34.4 ml (0.17 mole) of diethyl ethoxymethylenemalonate. The toluene was slowly distilled over two hours to one-fifth volume. Concentration gave an oil which was purified by column chromatography (ethyl acetate-hexane, 3:7) to give 67.0 g (96%) of **11**; pmr (deuteriochloroform): δ 1.30 (m, 6H, CH_2CH_3), 1.90 (m, 5H, $CH_2CH_2CH_2$, CH_3), 2.80 (m, 4H, SCH_2), 4.20 (m, 4H, OCH_2), 7.00 (m, 2H), 7.60 (m, 1H), 8.35 (d, J = 12, 1H, C*H*), 10.90 (d, J = 12, 1H, N*H*).

Anal. Calcd. for $C_{19}H_{24}FNO_4S_2$: C, 54.14; H, 5.51; N, 3.51; S, 16.04. Found: C, 53.97; H, 5.48; N, 3.66; S, 16.50.

[(3-Acetyl-2,4-difluorophenyl)amino]methylene]propanedioic Acid, Diethyl Ester (**2c**).

To 18.1 g (90.0 mmoles) of **7** was added 500 ml of methanol, 1.6 g of Raney Nickel and hydrogen gas at 50 psi. The mixture was shaken overnight and was filtered directly into 20 g (1.02 equivalents) of diethyl ethoxymethylenemalonate in 800 ml of toluene. The mixture was refluxed for two hours and the volume reduced by distillation to one-third. Hexane was added and the solids filtered to give 24.4 g (80%) of **2c**, mp 82-84°; pmr (deuteriochloroform): δ 1.70 (m, 6H, CH_2CH_3), 2.55 (d, J = 2, 3H, $COCH_3$), 4.20 (m, 4H, CH_2CH_3), 7.20 (m, 2H), 8.25 (d, J = 11, 1H), 10.90 (d, J = 11, 1H).

Anal. Calcd. for $C_{16}H_{17}F_2NO_5$: C, 56.30; H, 4.98; N, 4.11. Found: C, 56.00; H, 4.99; N, 4.37.

7-Acetyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**3e**).

Method A.

To 75 ml Dowtherm A heated to 250° was added 7.42 g (23 mmoles) of **2b**. The mixture was heated at 250-254° for one-half hour, cooled to room temperature, and the precipitate (4.65 g) of ethyl 5-(and 7)-acetyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylates **4b** and **3b** was filtered and washed with hexanes.

The above crude product of **3b** and **4b** (4.00 g, 14 mmoles) was mixed with 2.20 g (16 mmoles) of potassium carbonate, 2.2 ml (16 mmoles) of diethyl sulfate and 0.90 g of tetra-*n*-butylammonium bromide in 200 ml of water and 100 ml of chloroform and stirred at reflux for five hours. The organic layer was washed with water, dried and evaporated to give a crude solid which showed two major spots by thin-layer chromatography at Rf 0.30 and 0.21 (ethyl acetate-methanol, 20:1). Column chromatography (ethyl acetate-methanol, 50:1) and isolation of the Rf 0.30 spot material afforded 0.72 g (17%) of **3e** which was crystallized from methanol-

water, mp 120-121°; pmr (deuteriotrifluoroacetic acid): δ 1.58 (t, 3H, J = 7), 1.82 (t, 3H, J = 7), 3.02 (d, 3H, J = 5, CH_3CO), 4.75 (q, 2H, J = 7), 5.05 (q, 2H, J = 7), 8.53 (d, 1H, J = 9, H-5), 8.83 (d, 1H, J = 5, H-8), 9.42 (s, 1H, H-2); ms: m/e 305 (M^+).

Anal. Calcd. for $C_{16}H_{16}FNO_4$: C, 62.94; H, 5.28; N, 4.59. Found: C, 62.73; H, 5.39; N, 4.50.

5-Acetyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**4e**).

Material corresponding to the Rf 0.21 spot in the above procedure was isolated after a second chromatography and crystallization from ethanol to afford **4e**, mp 200-201°; pmr (deuteriotrifluoroacetic acid): δ 1.56 (t, 3H, J = 7), 1.80 (t, 3H, J = 7), 2.71 (s, 3H, CH_3CO), 4.71 (q, 2H, J = 7), 5.00 (q, 2H, J = 7), 8.07 and 8.18 (d, d, 1H, J = 8, 9), 8.32 and 8.45 (d, d, 1H, J = 4, 9), 9.40 (s, 1H, H-2); ms: m/e 305 (M^+).

Anal. Calcd. for $C_{16}H_{16}FNO_4 \cdot 0.3H_2O$: C, 61.94; H, 5.30; N, 4.52. Found: C, 61.94; H, 5.20; N, 4.54.

Method B.

To 50 ml of refluxing Dowtherm A was added in portions 66 g (0.16 mole) of **11**. After 15 minutes the mixture was cooled, treated with pentane and the solids collected to give 40 g (68%) of cyclized product **12a** which was used without purification. This crude product was mixed with 2.7 ℓ of *N,N*-dimethylformamide, 75 g of (0.54 mole) potassium carbonate and 43.6 ml of (0.55 mole) of ethyl iodide. The mixture was warmed to 80° for 18 hours, concentrated, and the residue was partitioned between chloroform and water. The organic layer was extracted with 0.5 *N* hydrochloric acid, dried and concentrated to give 42 g (66%) of **12b** as a viscous oil which resisted analysis; pmr (deuteriochloroform): δ 1.45 (m, 6H, CH_2CH_3), 2.00 (m, 5H, $CH_2CH_2CH_2$, CH_3), 2.90 (m, 4H, SCH_2), 4.30 (m, 4H, OCH_2, NCH_2), 8.05 (d, 1H, J = 6, H-5), 8.15 (d, 1H, J = 2, H-8), 9.50 (S, 1H, H-2).

To 42 g (0.11 mole) of **12b** was added 28.9 g (0.134 mole) of mercuric oxide, 72.9 g (0.268 mole) of mercuric chloride and 3 ℓ of 80% aqueous acetonitrile. After 72 hours at room temperature the mixture was filtered through celite and the solids washed with chloroform. The organic layer was extracted with 5*M* ammonium acetate, dried and concentrated. The residue was triturated with ether to give 23.4 g (72%) of **3e** which was identical to the material prepared by method A.

7-Acetyl-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**3d**).

By using method A, **2a** [3] was cyclized to give **3d** in 36% yield, mp 184-187°, after crystallization from ethanol; pmr (hexadeuteriodimethylsulfoxide): δ 1.25 and 1.38 (t, t, overlapping 6H, CH_2CH_3), 2.70 (s, 3H, $COCH_3$), 4.20 and 4.45 (q, q, overlapping 4H, CH_2CH_3), 7.83 (d, d, 1H, J = 9, 1.5, H-6), 8.07 (s, 1H, H-8), 8.22 (d, 1H, J = 9, H-5), 8.63 (s, 1H, H-2).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.61; H, 6.11; N, 4.85.

7-Acetyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**3c**).

By using method B, 7.85 g (63%) of **3c**, mp 267-270°, was prepared from 14.4 g (42.2 mmoles) of **2c** after addition of pentane to the reaction mixture; pmr (hexadeuteriodimethylsulfoxide): δ 1.30 (t, J = 7, 3H, CH_2CH_3), 2.60 (d, J = 2, 3H, $COCH_3$), 4.20 (q, J = 7, 2H, CH_2CH_3), 7.65 (dd, J = 9, 2, 1H, H-5), 8.40 (s, 1H, H-2), 12.70 (s, 1H, N*H*).

7-Acetyl-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**3f**).

By using method B, 22.33 g (75.7 mmoles) of **3c** was reacted with ethyl iodide to give a crude product which was purified by column chromatography (chloroform-hexane-ethanol, 6:3:1) and trituration with ether to afford 20.5 g of **3f**, mp 129-130°; pmr (deuteriochloroform): δ 1.40 (m, 6H, CH_2CH_3), 2.60 (s, 3H, $COCH_3$), 4.30 (m, 4H, CH_2), 8.00 (dd, J = 8, 1, 1H, H-5), 8.35 (s, 1H, H-2).

Anal. Calcd. for $C_{16}H_{15}F_2NO_4$: C, 59.44; H, 4.64; N, 4.33. Found: C, 59.41; H, 4.61; N, 4.18.

10-Acetyl-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido[1,2,3-*de*][1,4]-benzoxazine-6-carboxylic Acid (**19a**).

To 100 g of polyphosphoric ester [16] was added 10.0 g (31.6 mmoles) of **18** and the mixture was heated at 65° for two hours. The mixture was poured over ice and extraced with chloroform. The chloroform was concentrated to give 5.3 g (63%) of **19a** as a white powder; pmr (trifluoroacetic acid): δ 1.80 (d, J = 7 Hz, 3H, $CHCH_3$), 2.90 (s, 3H, $COCH_3$), 4.70 (m, 2H, OCH_2), 5.20 (m, 1H, $CHCH_3$), 8.00 (d, J = 9, 1H, H-8), 9.50 (s, 1H, H-5).

Anal. Calcd. for $C_{15}H_{12}FNO_5$: C, 59.02; H, 3.96; N, 4.59. Found: C, 58.70; H, 4.05; N, 4.59.

7-(Bromoacetyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**8e**).

A solution of 7.97 g (26 mmoles) of 7-acetylquinolone **3e** in 165 ml of acetic acid was treated with 1.57 g (9.4 mmoles) of potassium bromate and then 12.5 ml of 48% hydrobromic acid was added dropwise over 30 minutes [15]. After stirring 24 hours, the mixture was poured into ice water, stirred until granular, filtered and dried to give 9.23 g (92%) of the bromoacetylquinolone **8e**; pmr (hexadeuteriodimethylsulfoxide): δ 1.30 and 1.38 (t, t, overlapping 6H, J = 7, 7, CH_2CH_3), 2.68 (d, J = 5, < 10% CH_3CO), 4.22 and 4.42 (q, q, overlapping 4H, J = 7, 7, CH_2CH_3), 4.95 (d, 2H, J = 1.5, $BrCH_2CO$), 7.90 (d, 1H, J = 11, H-5), 8.15 (d, 1H, J = 6, H-8), 8.67 (s, 1H, H-2). This material was used for subsequent steps without further purification. A sample was recrystallized from ethanol for analysis, mp 162-165°.

Anal. Calcd. for $C_{15}H_{15}BrFNO_4$: C, 50.02; H, 3.94; N, 3.65; Br, 20.80. Found: C, 49.73; H, 3.99; N, 3.60; Br, 20.55.

7-(Bromoacetyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**8d**).

Bromoacetylquinolone **8d** was prepared from **3d** in 78% yield by the same procedure used to prepare **8e**. It contained 10% ketone **3d** and was used without further purification. A sample was recrystallized from chloroform-hexanes, mp 148-152°; pmr (hexadeuteriodimethylsulfoxide): δ 1.28 and 1.40 (t, t, overlapping 6H, J = 7, 7, CH_2CH_3), 2.70 (s, *ca.* 5% CH_3CO), 4.20 and 4.45 (q, q, overlapping 4H, J = 7, 7, CH_2CH_3), 5.50 (s, 2H, $BrCH_2CO$), 7.88 (d, d, 1H, J = 9, *ca.* 1, H-6), 8.18 and 8.26 (s, d, 2H, J = 9, H-8 and H-5), 8.67 (s, 1H, H-2).

Anal. Calcd. for $C_{16}H_{16}BrNO_4$: C, 52.47; H, 4.40; N, 3.83. Found: C, 52.97; H, 4.57; N, 3.98.

7-(Bromoacetyl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**9**).

To 3.69 g (11.4 mmoles) of **3f** in 40 ml of acetic acid was added 0.68 g (4.0 mmoles) of potassium bromate and 5.1 ml of 48% hydrobromic acid in 10 ml of water. The reaction was heated at 60° for 72 hours. It was diluted with water and the solids collected to give 3.15 g (73%) of **9**, mp 212-213°; pmr (trifluoroacetic acid): δ 1.80 (t, J = 7, 3H, CH_2CH_3), 4.45 (s, 2H, CH_2Br), 5.00 (m, 2H, CH_2CH_3), 8.30 (dd, J = 9, 1, 1H, H-5), 9.40 (s, 1H, H-2).

Anal. Calcd. for $C_{14}H_{10}BrF_2NO_4$: C, 44.92; H, 2.67; N, 3.74; Br, 21.28. Found: C, 44.97; H, 2.79; N, 3.74; Br, 21.15.

10-(Bromoacetyl)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido-[1,2,3-*de*][1,4]-benzoxazine-6-carboxylic Acid (**19b**).

To 3.2 g (10.5 mmoles) of **19a** was added 36 ml of acetic acid, 12 ml of water, 610 mg (3.65 mmoles) of potassium bromate and 4.63 ml of 48% hydrobromic acid. The reaction was stirred at 80° for 48 hours, concentrated and the solids mixed with 2 volumes of ether and 1 volume of ethanol. The solids were removed by filtration and washed with ether to give 3.34 g (83%) of **19b**, mp 224-225°; pmr (trifluoroacetic acid): δ 1.85 (d, J = 6, 3H, $CHCH_3$), 4.50 (s, 2H, CH_2Br), 4.70 (m, 2H, OCH_2), 5.25 (m, 1H, $CHCH_3$), 8.00 (d, J = 8, 1H, H-8), 8.40 (s, 1H, H-5).

Anal. Calcd. for $C_{15}H_{11}BrFNO_5$: C, 46.88; H, 2.86; N, 3.64; Br, 20.83. Found: C, 46.48; H, 3.11; N, 3.39; Br, 20.57.

(Cyanomethyl)methylcarbamic Acid, Phenylmethyl Ester (**21j**).

A solution of 15.2 g (80 mmoles) of cyanomethylcarbamic acid, phenylmethyl ester [23] in 200 ml of dry tetrahydrofuran was added to 3.84 g (80 mmoles) of sodium hydride (50% oil suspension prewashed with pentane) in 200 ml of tetrahydrofuran at 0°. When evolution of hydrogen had ceased, 4.96 ml of methyl iodide was added. The mixture was stirred 18 hours and concentrated. The residue was dissolved in dichloromethane, washed twice with water, dried, concentrated and chromatographed by eluting with chloroform-hexanes-2-propanol (4:5.5:0.5) to give 10.5 g (64%) of **21j** as a colorless oil; pmr (deuteriochloroform): δ 3.10 (s, 3H, NCH_3), 4.30 (s, 2H, NCH_2), 5.25 (s, 2H, OCH_2), 7.40 (s, 5H, phenyl).

(Cyanomethyl)ethylcarbamic Acid, Phenylmethyl Ester (**21k**).

Using the above procedure for **21j**, 15.2 g (80 mmoles) of **21i** was reacted with ethyl iodide to give 12.5 g (72%) of **21k** as a colorless oil; pmr (deuteriochloroform): δ 1.20 (t, 3H, J = 7, CH_2CH_3), 3.40 (q, 2H, J = 7, CH_2CH_3), 4.15 (s, 2H, NCH_2), 5.10 (s, 2H, OCH_2), 7.25 (m, 5H, phenyl).

Ethyl 4-Cyano-1-piperazinecarboxylate (**21h**) [19].

A solution of 12.0 g (0.11 mole) of cyanogen bromide in 50 ml chloroform was added dropwise over one hour to a rapidly stirred mixture of 15.8 g (0.1 mole) of ethyl 1-piperazinecarboxylate in 100 ml of chloroform and 15.0 g (0.11 mole) of potassium carbonate in 100 ml of water. The reaction was maintained at room temperature by using a cold bath as needed. After stirring an additional 1.75 hours, the organic layer was washed with water, 1*N* hydrochloric acid, water, dried and concentrated. Distillation afforded 13.2 g (72%) of **21h**, bp 117-121° (0.05 mm); ir (liquid film); 2230, 1705 cm^{-1}.

Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 51.91; H, 7.15; N, 22.29.

7-Cyano-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**27b**).

To a suspension of 2.78 g (10 mmoles) of 7-amino-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid ethyl ester, **27a**, [21] in 40 ml of 1*N* hydrochloric acid stirred at 8° was added in portions a solution of 0.72 g (10.5 mmoles) of sodium nitrate in 5 ml of water. This mixture was stirred 0.5 hour at 8°, and then added dropwise over 10 minutes to a solution of 1.07 g (12 mmoles) of cuprous cyanide and 2.28 g (35 mmoles) of potassium cyanide in 25 ml of water stirred at 45-50°. The foaming mixture was heated at 50-60° for 1.25 hours, then treated with 10 ml of concentrated ammonium hydroxide and stirred at 50° for 20 minutes. The mixture was cooled with ice and the solid product collected by filtration. Recrystallization from acetonitrile afforded 0.28 g of **27**, mp 205-207°; pmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7, CH_2CH_3), 1.57 (t, 3H, J = 7, CH_2CH_3), 4.28 (q, 4H, J = 7, CH_2CH_3), 7.77 (d, 1H, J = 6, H-8), 8.22 (d, 1H, J = 9, H-5), 8.47 (s, 1H, H-2); ir (potasium bromide): 2245 cm^{-1} (CN).

Anal. Calcd. for $C_{15}H_{13}FN_2O_3$: C, 62.50; H, 4.55; N, 9.72. Found: C, 62.31; H, 4.67; N, 9.37.

General Procedure for the Preparation of Thioamides **22**.

Procedure A.

Thioamides **22a-22e** were prepared by the procedure of Johnson and Gatewood [12] by passing hydrogen sulfide gas into a mixture of the nitrile, **21**, in ethanol and concentrated ammonium hydroxide. After about two hours the flask was stoppered and let stand overnight. The solvent was evaporated and the desired product was purified by crystallization or chromatography on silica gel. For specific data see Table I.

Procedure B.

Thioamides **22f-22h** were prepared by the procedure of Fairfull, *et al.* [18]. For example, hydrogen sulfide was passed into a solution of 20 mmoles of nitrile in 20 ml of pyridine and 0.6 ml of triethylamine for three hours. After stirring overnight, the mixture was diluted with ether and the product filtered and recrystallized.

Ethyl 4-(Aminothioxomethyl)-1-piperazinecarboxylate (**22h**).

Thioamide **22h**, mp 147-149° [20], was prepared in 96% yield from **21h** according to procedure B. A sample was recrystallized from ethanol for analysis, mp 149-151°; ir (potassium bromide): 1650, 1685 cm^{-1}

Anal. Calcd. for $C_8H_{15}N_3O_2S$: C, 44.22; H, 6.96; N, 19.34; S, 14.76. Found: C, 44.54; H, 6.96; N, 19.40; S, 14.96.

7-(Aminothioxomethyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**28**).

Compound **28**, mp 198-199° dec, was prepared in 76% yield from the nitrile **27** according to procedure B; pmr (hexadeuteriodimethylsulfoxide): δ 1.38 (m, 6H, CH_2CH_3), 4.20 (m, 4H, CH_2CH_3), 7.82 (d, d, 2H, J = 6, 9, H-8 and H-5), 8.65 (s, 1H, H-2), 9.80 (br s, 1H, NH), 10.32 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}FN_2O_3S$: C, 55.88; H, 4.69; N, 8.69; S, 9.95. Found: C, 55.77; H, 4.78; N, 8.43; S, 10.15.

General Procedure for the Preparation of 7-(4-Thiazolyl)quinolone Esters **23a-23w**.

7-Bromoacetylquinolones were reacted with 1.1 equivalents of the thioamide in ethanol or dimethylformamide. After stirring overnight at room temperature, the mixture was treated with an equivalent of triethylamine and stirred an additional hour. The product was precipitated by addition of water and purified by crystallization or chromatography. See Table II for product data.

General Method for the Preparation of 7-(4-Thiazolyl)quinolone Acids **24a-24w**.

Method A.

The quinolone esters, **23**, were hydrolyzed by refluxing 1-6 hours in 6*N* hydrochloric acid. After evaporating to dryness, the crude products were dissolved in dilute sodium hydroxide (*p*H 11), filtered and back titrated to *p*H 6-7 with hydrochloric acid to afford the amino acids. Hydrochlorides were obtained by recrystallization from dilute hydrochloric acid. See Table IV for product data.

Method B.

The quinolone esters were suspended in an equal mixture of 1*N* potassium hydroxide and water, refluxed one hour on the steam batch and the resulting solutions acidified with dilute hydrochloric acid to afford the quinolone carboxylic acids.

Method C.

Quinolone carbamates **23u-23w** dissolved in 35% hydrogen bromide in acetic acid were stirred at room temperature 18 hours, poured into ether-ethyl acetate and the solids filtered. Purification was effected by dissolving in ammonium hydroxide at *p*H 12, then concentrating to one-fifth volume. The products were filtered and washed with water, ethanol and ether. See Table II for product data.

7-[2-[(Dimethylamino)methyl]-4-thiazolyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**23g**).

The reaction of bromoketone **8e** with thioamide **22f** by the general procedure afforded the adduct **26** as a tan solid; pmr (deuteriochloroform): δ 1.40 (t, t, 6H, J = 7, 7, CH_2CH_3), 2.33 (s, 6H, NCH_3), 3.33 (s, 2H, S-CH_2-CO), 3.42 (m, 2H, $(CH_3)_2NCH_2$), 3.82 (q, 2H, J = 7, CH_2CH_3), 4.20 (q, 2H, J = 7, CH_2CH_3), 6.4 (br s, 1H, NH), 7.38 (d, 1H, J = 6, H-8), 7.95 (d, 1H, J = 10, H-5), 8.2 (s, 1H, H-2). This material in trifluoroacetic acid solution was stirred 1.5 hours, evaporated to dryness and crystallized from ethanol to afford the trifluoroacetic acid salt, **23g**. See Table II for data.

9-Fluoro-2,3-dihydro-3-methyl-7-oxo-10-[2-(aminomethyl)-4-thiazolyl-7*H*-pyrido[1,2,3-*de*][1,4]-benzoxazine-6-carboxylic Acid (**25b**).

A mixture of 1.09 g (2.84 mmoles) of bromoketone **19b** and 0.70 g (3.12 mmoles) of (2-amino-2-thioxoethyl)carbamic acid phenylmethyl ester, **22i**, in 16 ml of dimethylformamide and 8 ml of ethanol was heated 24 hours at 80° and poured over ice. The solid was filtered and washed with ether to give 1.44 g of **25a**, mp 124-125°. This material was treated with 40 ml of 32% hydrogen bromide in acetic acid at room temperature for 18 hours. The reaction mixture was poured into ethyl acetate-hexanes (1:1), stirred one hour and filtered. The solid was dissolved in dilute ammonium hydroxide at *p*H 11, concentrated to one-quarter volume and the precipitated product filtered, washed with a small amount of water and ether to afford 0.65 g (60%) of **25b** as a tan powder, mp 229-231°; pmr (trifluoroacetic acid): δ 1.90 (d, 3H, J = 7, $CHCH_3$), 4.90 (m, 2H, OCH_2), 5.35 (m, 3H, $CHCH_3$ and $NHCH_2$), 8.20 (d, 1H, J = 11, H-8), 8.60 (s, 1H, thiazole H), 9.60 (s, 1H, H-5).

Anal. Calcd. for $C_{17}H_{14}FN_3O_4S \cdot 3H_2O$: C, 53.68; H, 3.87; N, 11.05. Found: C, 53.60; H. 3.74; N, 10.75.

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-(2-pyridinyl)-2-thiazoyl]-3-quinolinecarboxylic Acid (**31e**).

A mixture of 0.64 g (2.0 mmoles) of thioamide **28** and 0.64 g (2.3 mmoles) of 2-(bromoacetyl)pyridine hydrobromide [22] in 10 ml of dimethylformamide was stirred for three hours, treated with 0.63 ml (4.5 mmoles) of triethylamine and stirred overnight. The precipitate was filtered and recrystallized from chloroform-methanol to afford 0.20 g (24%) of **30e**, mp 214-225° dec. This material was used without further purification.

A suspension of 0.19 g of **30e** is 2 ml of 1*N* methanolic potassium hydroxide and 1 ml of water was refluxed two hours, cooled, diluted with 27 ml of water, filtered and acidified with 1*N* hydrochloric acid. The precipitate was filtered, washed with water and dried to afford 0.16 g (90%) of **31e**, mp 282-284° dec; pmr (trifluoroacetic acid): δ 1.88 (t, 3H, J = 7, CH_2CH_3), 5.07 (q, 2H, J = 7, CH_2CH_3), 8.07 (m, 2H), 8.40-8.97 (complex m, 5H), 9.28 (d, 2H J = 6, H-8), 9.47 (s, 1H, H-2).

Anal. Calcd. for $C_{20}H_{14}FN_3O_3S$: C, 60.75; H, 3.57; N, 10.63. Found: C, 60.59; H, 3.72; N, 10.51.

7-[4-(Chloromethyl)-2-thiazolyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**30a**).

A solution of 0.16 g (0.5 mmole) of thioamide **28** and 0.32 g (2.5 mmoles) of 1,3-dichloroacetone was heated on a steam bath for three hours. After standing at room temperature, the crystallized product was filtered and washed with ethyl acetate to afford 0.12 g (60%) of **30a**, mp 212-214°. A sample was recrystallized for analysis from chloroform-ethyl acetate, mp 214-215°; pmr (hexadeuteriodimethylsulfoxide): δ 1.32 and 1.50 (t, t, 6H, J = 7, CH_2CH_3), 4.32 and 4.53 (q, q, 4H, J = 7, CH_2CH_3), 5.03 (s, 2H, CH_2Cl), 8.05 and 8.20 (d, s, 2H, J = 11, H-5 and thiazole H), 8.52 (d, 1H, J = 6, H-8), 8.94 (s, 1H, H-2).

Anal. Calcd. for $C_{18}H_{16}ClFN_2O_3S$: C, 54.75; H, 4.08; N, 7.10; Cl, 8.98. Found: C, 54.65; H, 3.86; N, 7.06; Cl, 8.85.

7-[4-(Azidomethyl)-2-thiazolyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**30b**).

A mixture of 1.10 g (2.78 mmoles) of compound **30a** and 0.50 g (7.6 mmoles) of sodium azide in 50 ml of dimethylformamide was stirred on a steam bath for four hours. The solvent was removed *in vacuo* and the solid residue stirred with water, filtered, dried and recrystallized from ethanol to give 0.91 g (82%) of **30b**, mp 192-194° dec; ir (potassium bromide): strong 2110 cm^{-1}. This material was used for the next step.

7-[4-(Aminomethyl)-2-thiazolyl]-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**31c**).

Hydrogen gas was bubbled into a solution of 0.87 g (2.17 mmoles) of azido-compound **30b** with 0.10 g of 10% Pd/C catalyst for 2.5 hours. Filtration, evaporation of the filtrate and trituration with ether afforded 0.77 g (95%) of **30c** as a yellow solid; ir (potassium bromide): no azide band.

A solution of 0.70 g of **30c** in 15 ml of 6*N* hydrochloric acid was heated on a steam bath for two hours. After filtering hot, the solution was diluted with 15 ml of water and allowed to crystallize at 0° to give 0.48 g of **31c** hydrochloride. The product was converted to the amino acid by dissolving in 8 ml of warm water, adjusting to *p*H 11 with 2*N* sodium hydroxide and back titrating to *p*H 6 with 2*N* hydrochloric acid. The precipitate was filtered, dried and crystallized twice from dimethylformamide to afford 0.19 g (34%) of **31c**, mp 224-226° dec; pmr (hexadeuteriodimethylsulfoxide): δ 1.50 (t, 3H, J = 7, CH_2CH_3), 4.00 (s, 2H, H_2NCH_2), 4.70 (q, 2H, J = 7, CH_2CH_3), 6.6 (br s, 2H, NH_2), 7.80 (s, 1H, thiazole-H), 8.25 (d, 1H, J = 11, H-5), 8.65 (d, 1H, J = 6, H-8), 9.10 (s, 1H, H-2).

Anal. Calcd. for $C_{16}H_{14}FN_3O_3S$: C, 55.32; H, 4.06; N, 12.10. Found: C, 55.14; H, 4.28; N, 11.79.

1-Ethyl-6-fluoro-1,4-dihydro-7-[4-[(methylamino)methyl]-2-thiazolyl]-4-oxo-3-quinolinecarboxylic Acid (**31d**).

A solution of 0.61 g (1.54 mmoles) of compound **30a** in 20 ml of 6*N* hydrochloric acid was refluxed two hours, during which time the product precipitated. The mixture was evaporated to dryness and the solid suspended in water, heated on a steam bath, cooled and filtered to afford 0.48 g of **31a**. The pmr spectrum indicated absence of the ester function and the material was used for the next step without further purification.

A solution of 0.40 g (1.09 mmoles) of **31a** in 100 ml of aqueous methylamine (40%) was stirred overnight at room temperature. After evaporating to dryness, the solid residue was dissolved in 15 ml of boiling water, filtered and crystallized at 0° to afford 0.33 g of **31d**, mp 216-218° dec; pmr (trifluoroacetic acid): δ 1.87 (t, 3H, J = 7, CH_2CH_3), 3.10 (t, 3H, J = 6, $CH_3N^+H_2$), 4.73 (t, 2H, J = 6, $CH_3N^+H_2CH_2$), 5.03 (q, 2H, J = 7, CH_2CH_3), 7.90 (br s, 2H, CH_3-N^+H_2-CH_2), 8.20 (s, 1H, thiazole H), 8.57 (d, 1H, J = 11, H-5), 9.07 (d, 1H, J = 6, H-8), 9.52 (s, 1H, H-2).

Anal. Calcd. for $C_{17}H_{16}FN_3O_3S \cdot 0.2H_2O$: C, 55.94; H, 4.53; N, 11.51. Found: C, 55.92; H, 4.41; N, 11.18.

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