Quinolone Antibacterials. 2. 6-Substituted-7-(2-thiazolyl and thiazolidinyl)quinolones

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A series of 6-substituted-1-ethyl-1,4-dihydro-4-oxo-7-(2-thiazolyl- and thiazolidinyl)quinoline-3-carboxylic acids were synthesized. Substitution at the 6-position was H, F or Cl. The Hantzsch method was used for the preparation of the thiazolylquinolones. The thiazolidinylquinolones were synthesized by quaternization of the corresponding thiazolyl analogues, followed by reduction of the obtained thiazolium salts with sodium borohydride in aqueous solution. Antibacterial activity was tested *in vitro*. The compounds were inactive against Gram-negative bacteria but some of them showed good activity against Gram-positive bacteria and mycobacteria. This activity pattern is rarely found among the quinolone antibacterials.

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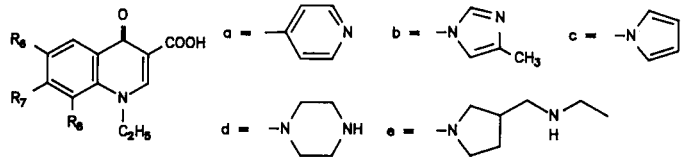
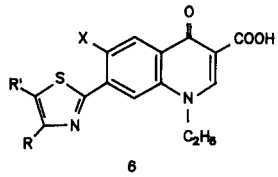
Among various structural modifications of the quinolone antibacterials, substitution with a nitrogen containing heterocyclic group of medium size (*e.g.*, five- or six-membered ring) at the C-7 position of the quinolone molecule has been the most promising one, yielding potent antibacterial analogues [1]. These C-7 substituents may be either aromatic such as pyridyl in rosoxacin (**1**) [2], imidazolyl in compound **2** [3] and pyrrolyl in irloxacin (**3**) [4] or alicyclic such as piperazinyl in norfloxacin (**4**) [5] and pyrrolidinyl in CI-934 (**5**) [6], *etc.*. Moreover, the introduction of a halogen atom (most frequently a fluorine atom) at the C-6 position is usually necessary for high antibacterial activity [1].

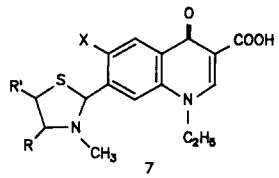


Compound No.	R_6	R_7	R_8
1	H	a	H
2	F	b	F
3	F	c	H
4	F	d	H
5	F	e	H

As we are engaged in synthesis of sulfur-containing derivatives of quinolone antibacterials and interested in C-7 structural analogues, we prepared in the first part of our work a series of 7-(2-substituted-4-thiazolyl and thiazolidinyl)quinolones [7]. In this paper, we would like to report the synthesis and antibacterial evaluation of a group of 6-substituted-1-ethyl-1,4-dihydro-4-oxo-7-(2-thiazolyl and thiazolidinyl)quinoline-3-carboxylic acids which can be represented by the general formula **6** and **7**, respectively, where R and R' is hydrogen, alkyl or aryl while X is hydrogen, fluorine or chlorine.



6



7

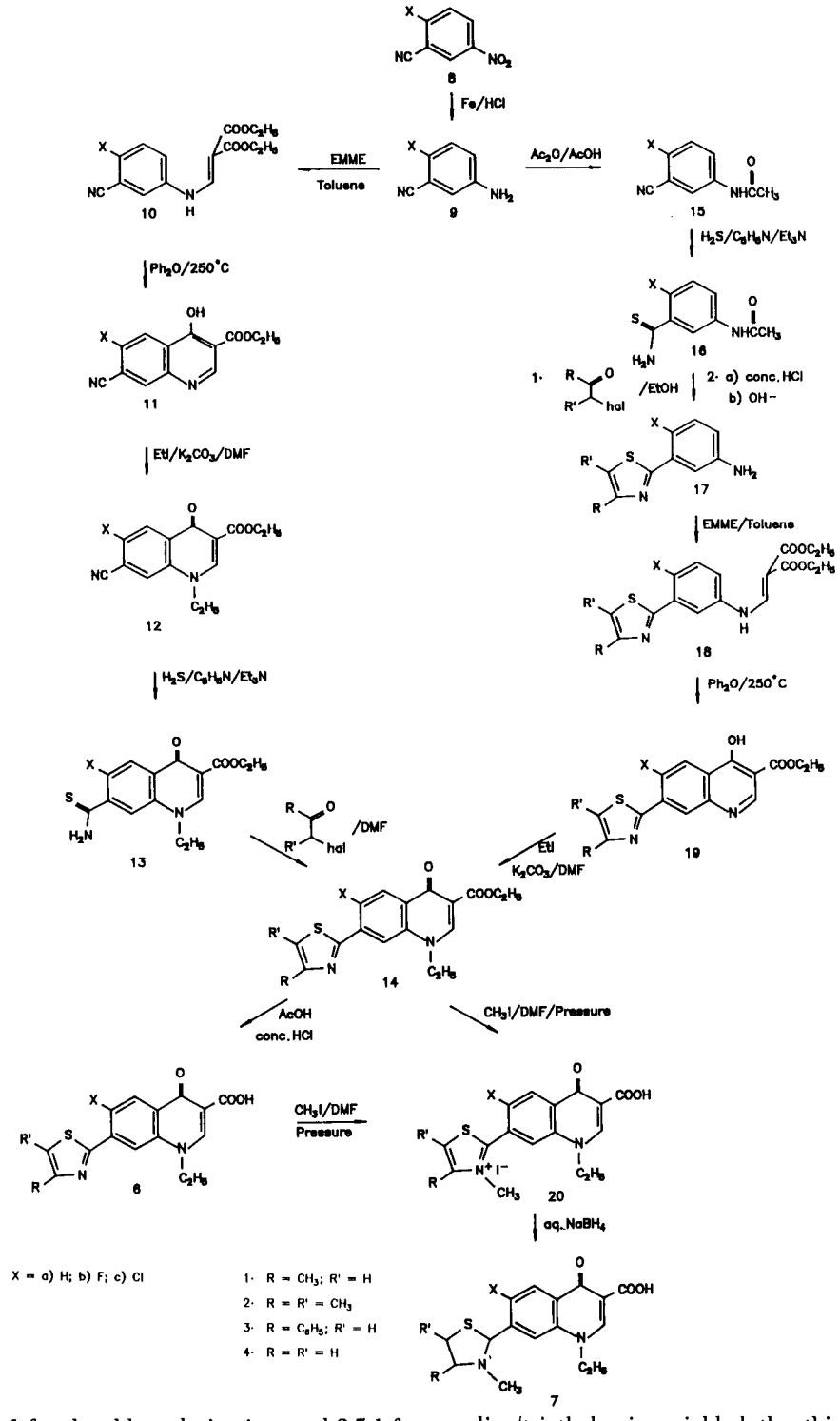
Similar but different thiazolyl derivatives of compounds **6** were reported in the literature [8]. The different synthetic strategy and the preparation of thiazolidinyl analogues **7** encourage us to report our results.

Chemistry.

Since thiazole derivatives are often prepared by the Hantzsch synthesis [9] and 4-quinolone-3-carboxylic acids are frequently obtained by the Gould-Jacobs synthesis [10], the appropriate starting materials for the target compounds **6** were 2-substituted-5-aminobenzonitriles **9** which were obtained by reduction of its nitro precursor **8** with iron powder/hydrochloric acid. The fluoro precursor **8b** was prepared by halide exchange from its chloro analogue **8c** with potassium fluoride in anhydrous acetonitrile in the presence of 18-crown-6 [11].

Scheme 1 shows the synthetic routes from **9** to **6** and **7**. Compound **9** was condensed with diethyl ethoxymethylenemalonate (EMME) by following the Gould-Jacobs synthesis to yield malonate **10** and was then cyclized into quinoline **11** in refluxing diphenyl ether. The pmr spectrum of the so obtained **11c** showed two doublets at δ 8.63 (J = 3 Hz) and 8.70 (J = 3 Hz) in addition to two singlets at δ 9.00 (C_5-H) and 9.10 (C_8-H). Compound **11b** obtained from thermal cyclization of **10b** showed also a spectrum with two multiplets at δ 8.15 and 8.70 in addition to two doublets at δ 8.45 (J = 9 Hz, C_5-H) and 8.90 (J = 5 Hz, C_8-H). These data suggested that the thermal cyclization of **10** in diphenyl ether gave a mixture of 7-cyano and 5-cyano isomers. The ratio of the two isomers (7-cyano and 5-cyano-

Scheme 1



quinolines) was 4:1 for the chloro derivatives and 2.5:1 for the fluoro derivatives as indicated by the integration. These isomers were separated by recrystallization of the corresponding ethylated analogues **12c** and **12b** from ethanol and acetonitrile, respectively. Treatment of the pure 7-cyano isomers **12** with hydrogen sulfide in pyridine/triethylamine yielded the thioamide **13** which was further reacted with an appropriate α-haloketone or aldehyde to give the thiazolyl quinolone **14**. Hydrolysis of **14** in acidic medium yielded the target quinolonecarboxylic acid **6**.

In order to avoid formation of isomers during the quino-

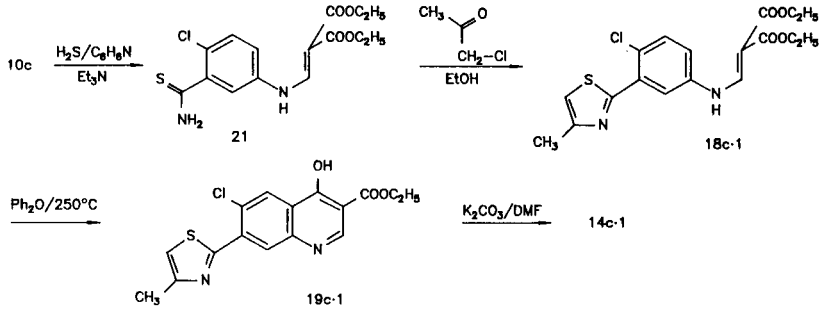
line ring closure, 3-(2-thiazolyl)aniline **17** was prepared as starting material for the Gould-Jacobs synthesis by the reaction of an appropriate α-haloketone with the thioamide **16** which was obtained by the treatment of **15** with hydrogen sulfide in pyridine/triethylamine. Thus, the malonate **18** prepared from **17** was cyclized into **19** in refluxing diphenyl ether without formation of isomers. Alkylation of **19** with ethyl iodide/potassium carbonate in *N,N*-dimethylformamide afforded **14a** in nearly quantitative yield.

During the synthetic evaluation, routes in Schemes 2 and 3 were also used for the preparation of **14c**. In Scheme 2, the compound **18c.1** was obtained from **10c** by the treatment of **10c** with hydrogen sulfide, followed by condensation with chloroacetone. The same reactions as described in Scheme 1 converted **18c.1** to quinolone **14c.1**. In Scheme 3, *N*-trifluoroacetyl analogue **23** of **16** was reacted with 3-chloro-2-butanone or 2-bromoacetophenone to afford 2-(2-chloro-5-trifluoroacetylaminophenyl)thiazoles **24** which was then ethylated and hydrolyzed to yield **25**. Compound **26** obtained from the reaction of **25** with EMME was finally cyclized into quinolone **14c.2** and **14c.3** in polyphosphoric acid (PPA) at 130°. Although these two synthetic routes (Schemes 2 and 3) proved successful for the preparation of the target quinolones, the number of reaction steps and the lower total yield (especially Scheme 3) limited the utilization of these two methods in this programme. Furthermore, quinoline ring closure in PPA often afforded products less pure than in diphenyl ether.

Thiazolidinylquinolones **7** were prepared by quaternization of the corresponding thiazolyl analogues **6** with methyl iodide in a sealed reaction tube at 130°, followed by reduction of the thiazolium salts **20** with aqueous sodium borohydride [7] (Scheme 1). It was observed that the quaternization of thiazolylquinolone esters **14** with methyl iodide yielded the same thiazolium salts **20** as the quaternization of **6** instead of their ester analogues. The quaternization of phenyl substituted thiazolylquinolones failed, probably due to sterical reasons.

As expected, the observation of two sets of resonances in the pmr and cmr of **7** suggested that these compounds

Scheme 2



Scheme 3

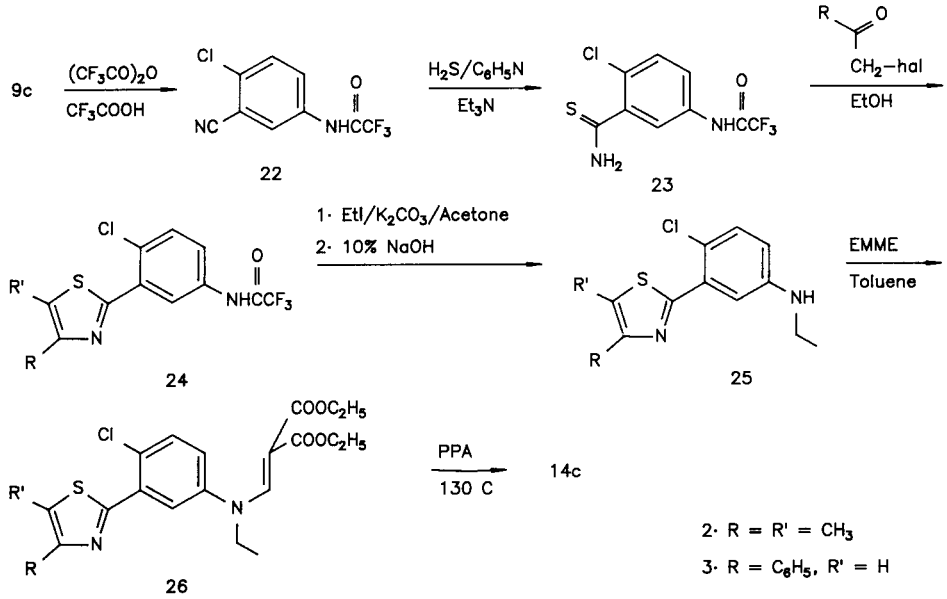
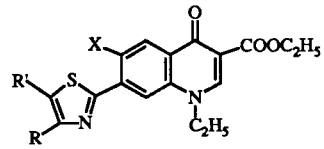


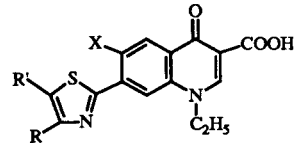
Table 1
Characteristics of Compounds **14**



14

Compound No.	Mp °C	Yield %	Method	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max
14a.1	219 dec	95	B	$C_{18}H_{18}N_2O_3S$	63.14 63.22	5.29 5.28	8.18 8.20	9.36 9.34	1720 (C=O) 1600 (C=C)
14a.2	215 dec	96	B	$C_{19}H_{20}N_2O_3S$	64.02 64.11	5.65 5.76	7.86 7.83	9.00 9.01	1715 (C=O) 1600 (C=C)
14a.3	223 dec	97	B	$C_{23}H_{20}N_2O_3S$	68.30 68.23	4.98 4.99	6.93 6.95	7.93 7.93	1710 (C=O) 1615 (C=C)
14b.1	252 dec	84	A	$C_{18}H_{17}FN_2O_3S$	59.99 60.04	4.75 4.77	7.77 7.80	8.90 8.89	1710 (C=O) 1605 (C=C)
14b.2	255 dec	81	A	$C_{19}H_{19}FN_2O_3S$	60.95 61.10	5.11 5.10	7.48 7.48	8.56 8.58	1720 (C=O) 1605 (C=C)
14b.3	261 dec	90	A	$C_{23}H_{19}FN_2O_3S$	65.39 65.31	4.53 4.52	6.63 6.61	7.59 7.60	1705 (C=O) 1620 (C=C)
14c.1	223 dec	89 92	A B	$C_{18}H_{17}ClN_2O_3S$	57.37 57.40	4.54 4.55	7.43 7.41	8.51 8.52	1710 (C=O) 1620 (C=C)
14c.2	221 dec	93 81	A C	$C_{19}H_{19}ClN_2O_3S$	58.38 58.41	4.89 4.88	7.17 7.15	8.20 8.21	1720 (C=O) 1610 (C=C)
14c.3	232 dec	91 85	A C	$C_{23}H_{19}ClN_2O_3S$	62.94 62.89	4.36 4.37	6.38 6.37	7.30 7.31	1710 (C=O) 1615 (C=C)
14c.4	219 dec	78	A	$C_{17}H_{15}ClN_2O_3S$	56.28 56.16	4.16 4.17	7.72 7.74	8.84 8.83	1715 (C=O) 1610 (C=C)

Table 2
Characteristics of Compounds **6**



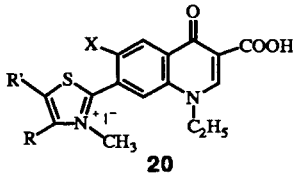
6

Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max	PMR (deuteriotrifluoroacetic acid) δ ppm
6a.1	277 dec (DMF)	88	$C_{16}H_{14}N_2O_3S$	61.13 61.21	4.48 4.49	8.91 8.90	10.20 10.19	1720 (C=O)	1.87 [a], 2.83 (s, 3H, CH_3), 5.10 [b], 7.90 (s, 1H, thiazole H), 8.47 (dd, 1H, J = 7, C_6-H), 8.97 (m, 2H, C_5- and C_8-H), 9.60 (s, 1H, C_2-H)
6a.2	>300 (EtOH)	83	$C_{17}H_{16}N_2O_3S$	62.18 62.16	4.91 4.90	8.53 8.51	9.76 9.74	1710 (C=O)	1.87 [a], 2.80 (s, 6H, CH_3), 5.10 [b], 8.50 (d, 1H, J = 8, C_6-H), 8.95 (m, 2H, C_5- and C_8-H), 9.60 (s, 1H, C_2-H)
6a.3	>300 (DMF)	85	$C_{21}H_{16}N_2O_3S$	67.01 66.95	4.28 4.27	7.44 7.45	8.52 8.50	1720 (C=O)	1.87 [a], 5.10 [b], 7.70 (s, 5H, phenyl H), 8.25 (s, 1H, thiazole H), 8.53 (d, 1H, J = 8, C_6-H), 9.07 (m, 2H, C_5- and C_8-H), 9.60 (s, 1H, C_2-H)
6b.1	279 dec (*i*-PrOH)	86	$C_{16}H_{13}FN_2O_3S$	57.82 57.88	3.94 3.93	8.43 8.45	9.65 9.66	1700 (C=O)	1.85 [a], 2.80 (s, 3H, CH_3), 5.02 [b], 7.97 (s, 1H, thiazole H), 8.65 (d, 1H, J = 9, C_5-H), 9.03 (d, 1H, J = 5, C_8-H), 9.62 (s, 1H, C_2-H)

6b.2	>300 (DMF)	82	$C_{17}H_{15}FN_2O_3S$	58.95 58.89	4.36 4.37	8.09 8.07	9.26 9.24	1720 (C=O)	1.85 [a], 2.85 (s, 6H, CH_3), 5.03 [b], 8.63 (d, 1H, J = 9, C_5-H), 9.10 (d, 1H, J = 5, C_8-H), 9.63 (s, 1H, C_2-H)
6b.3	>300 (DMF)	89	$C_{21}H_{15}FN_2O_3S$	63.95 63.88	3.83 3.84	7.10 7.12	8.13 8.11	1725 (C=O)	1.85 [a], 5.03 [b], 7.70 (s, 5H, phenyl H), 8.33 (s, 1H, thiazole H), 8.70 (d, 1H, J = 9, C_5-H), 9.22 (d, 1H, J = 5, C_8-H), 9.65 (s, 1H, C_2-H)
6c.1	275 dec (DMF)	91	$C_{16}H_{13}ClN_2O_3S$	55.10 55.02	3.75 3.77	8.03 8.01	9.19 9.18	1710 (C=O)	1.87 [a], 2.83 (s, 3H, CH_3), 5.05 [b], 7.95 (s, 1H, thiazole H), 8.97 (s, 1H, C_5-H), 9.22 (s, 1H, C_8-H), 9.75 (s, 1H, C_2-H)
6c.2	>300 (DMF)	89	$C_{17}H_{15}ClN_2O_3S$	56.28 56.21	4.16 4.16	7.72 7.74	8.84 8.81	1725 (C=O)	1.87 [a], 2.80 (s, 6H, CH_3), 5.07 [b], 8.98 (s, 1H, C_5-H), 9.22 (s, 1H, C_8-H), 9.70 (s, 1H, C_2-H)
6c.3	>300 (DMF)	88	$C_{21}H_{15}ClN_2O_3S$	61.39 61.44	3.68 3.69	6.82 6.84	7.80 7.81	1720 (C=O)	1.87 [a], 5.10 [b], 7.70 (s, 5H, phenyl H), 8.30 1H, thiazole H), 9.00 (s, 1H, C_5-H), 9.22 (s, 1H, C_8-H), 9.75 (s, 1H, C_2-H)
6c.4	>300 (DMF)	78	$C_{15}H_{11}ClN_2O_3S$	53.82 53.78	3.31 3.32	8.37 8.38	9.58 9.60	1720 (C=O)	1.87 [a], 5.17 [b], 8.64 (d, 1H, J = 4, C_5'-H), 8.76 (d, 1H, J = 4, C_4'-H), 9.10 (s, 1H, C_5-H), 9.22 (s, 1H, C_8-H), 9.80 (s, 1H, C_2-H)

[a] t, 3H, J = 7, CH_2CH_3 [b] q, 2H, J = 7, CH_2CH_3.

Table 3
Characteristics of Compounds **20**



20

Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max	MS (FAB) e/m	MW
20a.1	>290	86	$C_{17}H_{17}IN_2O_3S$	44.75	3.75	6.14	7.03	1720	329 (M^++1)	455
		75 [a]		44.69	3.76	6.16	7.00	(C=O)		
20b.1	>290	83	$C_{17}H_{16}FIN_2O_3S$	43.05	3.40	5.91	6.76	1715	347 (M^++1)	473
		80 [a]		43.12	3.41	5.89	6.73	(C=O)		
20b.2	>290	87	$C_{18}H_{18}FIN_2O_3S$	44.27	3.71	5.74	6.57	1725	361 (M^++1)	487
		82 [a]		44.30	3.70	5.76	6.55	(C=O)		
20c.1	>290	84	$C_{17}H_{16}ClIN_2O_3S$	41.61	3.28	5.71	6.53	1720	363 (M^++1)	490
		76 [a]		41.56	3.26	5.73	6.54	(C=O)		

[a] Yield obtained by the quaternization of the corresponding quinoline esters **14**.

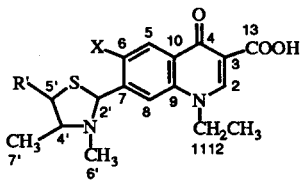
consisted of two diastereoisomers. This result is in agreement with the observations of other researchers [12,13]. No attempts were made to separate the diastereoisomers.

Microbiology.

All thiazolyl and thiazolidinyl quinolones **6** and **7** were tested *in vitro* against a series of Gram-negative and Gram-positive bacteria, as reported in the previous communication [7]. The results are summarized in Table 6. In analogy to the 4-thiazolyl derivatives no activity was found against Gram-negative bacteria. The phenyl substituted thiazolylquinolones were here again the most active against Gram-positive bacteria. The activities were comparable with the 4-thiazolyl compounds. We can emphasize again the separation between Gram-positive and Gram-negative activities.

Table 4

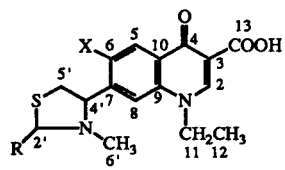
Characteristics of Compounds 7



Compound No.	Mp °C	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N	S	IR ν max	MS (FAB) e/m	MW
7a.1	146-147 dec	43	$C_{17}H_{20}N_2O_3S$	61.42 61.38	6.06 6.04	8.43 8.45	9.65 9.63	1720 (C=O)	332 (M^+), 288 (100%, M^+–COOH)	332
7b.1	181-182 dec	37	$C_{17}H_{19}FN_2O_3S$	58.27 58.31	5.46 5.45	7.99 8.01	9.15 9.14	1725 (C=O)	350 (100%, M^+)	350
7b.2	136-138 dec	34	$C_{18}H_{21}FN_2O_3S$	59.32 59.38	5.80 5.81	7.69 7.70	8.80 8.78	1720 (C=O)	364 (M^+), 304 (100%, M^+–$HSCHCH_3$)	364
7c.1	204-205 dec	46	$C_{17}H_{19}ClN_2O_3S$	55.66 55.60	5.22 5.23	7.64 7.61	8.74 8.76	1725 (C=O)	366 (M^+), 331 (100%, M^+–Cl)	366

Table 5

NMR Spectral Data of Compounds 7 [a]



4

Compound	PMR	CMR
7a.1	1.36 (d, 3H, J = 4, $CHCH_3$), 1.61 [b], 2.26 (s, 3H, NCH_3), 3.05 (m, 2H, SCH_2CH), 3.50 (m, 1H, $NCHCH_3$), 4.45 [c], 5.02 (s, 1H, $C_{2'}$-H), 7.69 (d, 1H, J = 8.3, C_6-H), 7.74 (s, 1H, C_8-H), 8.51 (d,1H, J = 8.3, C_5-H), 8.80 (s, 1H, C_2-H)	14.72 (C_{12}), 18.40 ($C_{7'}$), 37.49 ($C_{6'}$), 37.78 ($C_{5'}$), 49.81 (C_{11}), 65.06 ($C_{4'}$), 74.63 ($C_{2'}$), 109.03 (C_7), 116.25 (C_6), 126.26 (C_8), 127.72 (C_5), 139.40 (C_9), 147.92 (C_2), 156.12 (C_3), 161.20 (C_{10}), 167.08 (C_{13}), 178.17 (C_4)
7b.1	1.35 (d, 3H, J = 4.86, $CHCH_3$), 1.61 [b], 2.31 (s, 3H, NCH_3), 3.04 (m, 2H, SCH_2CH), 3.50 (m, 1H, $NCHCH_3$), 4.44 [c], 5.14 (s, 1H, $C_{2'}$-H), 7.98 (d, 1H, J = 5.86, C_8-H), 8.13 (d, 1H, J = 10.3, C_5-H), 8.78 (s, 1H, C_2-H)	14.54 (C_{12}), 18.69 ($C_{7'}$), 37.78 ($C_{5'}$), 38.08 ($C_{6'}$), 49.99 (C_{11}), 65.05 ($C_{4'}$), 66.52 ($C_{2'}$), 108.39 (C_7), 111.95 (C_8), 117.20 (C_5), 126.20 (C_6), 135.89 (C_9), 147.63 (C_2), 156.04 (C_3), 161.06 (C_{10}), 166.06 (C_{13}), 177.41 (C_4)
7b.2	1.37 (d, 3H, J = 6.35, $NCHCH_3$), 1.45 (d, 3H, J = 6.35, $SCHCH_3$), 1.61 [b], 2.28(s, 3H, NCH_3), 3.03 (m, 1H, $SCHCH_3$), 3.38 (m, 1H, $NCHCH_3$), 4.44 [c], 5.02 (s, 1H, $C_{2'}$-H), 7.98 (d, 1H, J = 5.90, C_8-H), 8.14 (d, 1H, J = 9.77, C_5-H), 8.79 (s, 1H, C_2-H)	14.66 (C_{12}), 19.86 ($C_{7'}$), 20.85 (CH_3), 37.96 ($C_{6'}$), 50.11 (C_{11}), 65.58 ($C_{4'}$), 66.87 ($C_{5'}$), 68.27 ($C_{2'}$), 108.44 (C_7), 112.07 (C_8), 117.32 (C_5), 127.18 (C_6), 136.07 (C_9), 147.69 (C_2), 156.21 (C_3), 161.05 (C_{10}), 166.84 (C_{13}), 177.53 (C_4)
7c.1	1.37 (d, 3H, J = 6.4, $CHCH_3$), 1.61 [b], 2.34 (s, 3H, NCH_3), 3.08 (m, 2H, SCH_2CH), 3.53 (m, 1H, $NCHCH_3$), 4.42 [c], 5.21 (s, 1H, $C_{2'}$-H), 8.14 (s, 1H, C_8-H), 8.51 (s, 1H, C_5-H), 8.78 (s, 1H, C_2-H)	14.48 (C_{12}), 18.86 ($C_{7'}$), 37.61 ($C_{5'}$), 38.25 ($C_{6'}$), 49.87 (C_{11}), 65.11 ($C_{4'}$), 70.43 ($C_{2'}$), 109.09 (C_7), 116.33 (C_8), 127.60 (C_5), 132.04 (C_6), 137.99 (C_9), 147.98 (C_2), 156.27 (C_3), 161.25 (C_{10}), 166.61 (C_{13}), 177.24 (C_4)

[a] δ from internal TMS in ppm in deuteriochloroform solution. Coupling constants are in Hz. [b] t, 3H, J = 7, CH_2CH_3 [c] q, 2H, J = 7, CH_2CH_3.

Table 6

Antibacterial Activity of 7-(2-Thiazolyl)quinolones and 7-(2-Thiazolidinyl)quinolones

Compound	X	R'	R	MICs (μg/ml) Gram-positive				Gram-negative			
				Str. [1]	St. [2]	B. [3]	My. [4]	E. [5]	K. [6]	P. [7]	Sa. [8]	En. [9]	Ps. [10]
6a.1	H	H	CH_3	25	50	1.6	25	>100	25	>100	>100	50	>100
6a.2	H	CH_3	CH_3	25	25	1.6	12.5	>100	>100	>100	>100	>100	>100
6a.3	H	H	Ph	1.6	3.12	0.4	1.6	>100	>100	>100	>100	>100	>100
6b.1	F	H	CH_3	12.5	6.25	0.4	12.5	50	25	>100	50	50	>100
6b.2	F	CH_3	CH_3	6.25	3.12	0.4	6.25	>100	>100	>100	>100	>100	>100
6b.3	F	H	Ph	1.6	3.12	0.8	3.12	>100	>100	>100	>100	>100	>100
6c.1	Cl	H	CH_3	12.5	12.5	3.12	12.5	>100	>100	>100	>100	>100	>100
6c.2	Cl	CH_3	CH_3	6.25	6.25	3.12	6.25	>100	>100	>100	>100	>100	>100
6c.3	Cl	H	Ph	3.12	6.25	6.25	6.25	>100	>100	>100	>100	>100	>100
6c.4	Cl	H	H	12.5	25	3.12	12.5	>100	>100	>100	>100	>100	>100
7a.1	H	CH_3	H	50	50	6.25	50	>100	>100	>100	>100	>100	>100
7b.1	F	CH_3	H	50	25	0.4	50	>100	>100	>100	>100	>100	>100
7b.2	F	CH_3	CH_3	50	12.5	0.4	50	>100	>100	>100	>100	>100	>100
7c.1	Cl	CH_3	H	50	25	3.12	25	>100	>100	>100	>100	>100	>100

[1] *Streptococcus pyogenes*, [2] *Staphylococcus aureus*, [3] *Bacillus cereus*, [4] *Mycobacterium fortuitum*, [5] *Escherichia coli*, [6] *Klebsiella*, [7] *Proteus vulgaris*, [8] *Salmonella*, [9] *Enterobacter*, [10] *Pseudomonas aeruginosa*.

EXPERIMENTAL

All compounds were checked for their structures with ir spectrophotometry, pmr, mass spectrometry and elemental analysis. The thiazolidinylquinolones **7** were also checked with cmr spectrometry. The ir spectra were obtained with a Beckman Acculab-4 spectrophotometer. The ν max are given in cm^{-1}. All compounds were examined as potassium bromide pellets. The pmr of most compounds were recorded on a Varian EM 360A spectrometer, whilst the pmr and cmr spectra of the thiazolidinylquinolones **7** were recorded on a JEOL FX 200 spectrometer with Spin-Echo Fourier Transform (SEFT) technique for the cmr. Chemical shifts are given in ppm (δ) relative to tetramethylsilane and coupling constants are in Hz. Mass spectral data were registered on a VG 70 SEQ mass spectrometer with fast atom bombardment (FAB) ionization method for the thiazolium salts (20) and electron impact (EI) ionization method for the other compounds. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected.

2-Fluoro-5-nitrobenzonitrile (**8b**).

To a solution of 1.32 g (0.005 mole) of 18-crown-6 in 200 ml of dry acetonitrile was added at room temperature 8.66 g (0.15 mole) of anhydrous potassium fluoride with stirring. The stirring was continued for 30 minutes before the addition of 18.25 g (0.1 mole) of 2-chloro-5-nitrobenzonitrile (**8c**) to this heterogeneous system. The mixture was then refluxed for 6 hours. After cooling, the mixture was filtered to remove the inorganic salts and the filtrate was evaporated to dryness. The solid residue was washed well with cold water until the brown color of the solid was removed. Recrystallization from methanol gave pure white crystals, yield 86%, mp 71-73°; ir: ν max 2250 (CN), 1630 (C=C), 1270 (C-F); pmr (deuteriochloroform): δ 7.60 (dd, 1H, J = 7, C_3-H), 8.65 (m, 2H, C_4- and C_6-H); ms: m/e 166 (M^+), 120 (100%, M^+-NO_2).

5-Amino-2-fluorobenzonitrile (**9b**).

A mixture of 13.28 g (0.08 mole) of **8b** and 13.44 g (0.24 mole) of fine iron powder in 250 ml of 50% ethanol was refluxed with vigorous stirring. To this mixture was carefully added a solution of 2.4 ml of concentrated hydrochloric acid in 10 ml of 50% ethanol. After addition, the reaction was allowed to continue for 2 hours. After cooling, the reaction mixture was filtered through celite and the iron cake was washed well with acetone. The combined filtrate was then evaporated to dryness and the solid residue was washed with water. Recrystallization from chloroform gave white crystals, yield 95%, mp 89-91° (lit [14] mp 88-89°); ir: ν max 3420 (NH), 3340 (NH), 2240 (CN); pmr (deuteriochloroform): δ 3.87 (br s, 2H, NH_2), 7.00 (m, 3H, aromatic H).

5-Amino-2-chlorobenzonitrile (**9c**).

Compound **9c** was similarly prepared as **9b** by reduction of **8c**, yield 90%, mp 128-129° (ethanol); ir: ν max 3420 (NH), 3320 (NH), 2240 (CN); pmr (hexadeuteriodimethyl sulfoxide): δ 5.50 (br s, 2H, NH_2), 7.00-7.65 (m, 3H, aromatic H).

Diethyl 3-Cyano-4-fluoroanilinomethylenemalonate (**10b**).

A solution of 10.2 g (0.075 mole) of **9b** and 16.2 g (0.075 mole) of EMME in 50 ml of toluene was refluxed with stirring for 3 hours. After cooling, the white precipitate was collected by filtration. The product was used without further purification, yield 95%. A sample was recrystallized from toluene for analysis, mp 139-141°; ir: ν max 2240 (CN), 1700 (C=O), 1620 (C=C); pmr (deuteriochloroform): δ 1.33 and 1.36 (each t, 3H, J = 7, CH_2CH_3), 4.26 and 4.30 (each q, 2H, J = 7, CH_2CH_3), 7.40 (m, 3H, aromatic H), 8.40 (d, 1H, J = 13, NH-CH=C), 11.20 (br d, 1H, J = 13, NH-CH=C).

Anal. Calcd. for $C_{15}H_{15}FN_2O_4$: C, 58.82; H, 4.93. Found: C, 58.77; H, 4.89.

Diethyl 4-Chloro-3-cyanoanilinomethylenemalonate (**10c**).

Compound **10c** was similarly prepared as **10b** from **9c**, yield 91%, mp 143-145° (toluene); ir: ν max 2240 (CN), 1705 (C=O); pmr (deuteriochloroform): δ 1.33 and 1.36 (each t, 3H, J = 7, CH_2CH_3), 4.25 and 4.35 (each q, 2H, J = 7, CH_2CH_3), 7.47 (m, 3H, aromatic H), 8.42 (d, 1H, J = 13, NH-CH=C), 11.15 (br d, 1H, J = 13, NH-CH=C).

Anal. Calcd. for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68. Found: C, 55.90; H, 4.62.

Ethyl 7-Cyano-6-fluoro-4-hydroxyquinoline-3-carboxylate (**11b**).

To 500 ml of refluxing diphenyl ether was added portionwise 20 g (0.065 mole) of **10b** with stirring. After addition, the refluxing was continued for 1 hour. After cooling, the white precipitate, a mixture of the 7- and 5-isomers as indicated by pmr, was collected by filtration and washed with petroleum ether, yield 73%, mp >300°. A sample was recrystallized from *N,N*-dimethylformamide to afford the pure 7-cyano isomer for analysis; ir: ν max 2230 (CN), 1710 (C=O); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 4.80 (q, 2H, J = 7, CH_2CH_3), 8.45 (d, 1H, J = 9, C_5-H), 8.90 (d, 1H, J = 5, C_8-H), 9.60 (s, 1H, C_2-H).

Anal. Calcd. for $C_{13}H_9FN_2O_3$: C, 60.00; H, 3.48. Found: C, 60.12; H, 3.45.

Ethyl 6-Chloro-7-cyano-4-hydroxyquinoline-3-carboxylate (**11c**).

Compound **11c** was similarly prepared as **11b** from **10c**, yield 70%, mp >300°; ir: ν max 2230 (CN), 1705 (C=O); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 4.88 (q, 2H, J = 7, CH_2CH_3), 9.00 (s, 1H, C_5-H), 9.10 (s, 1H, C_8-H), 9.77 (s, 1H, C_2-H).

Anal. Calcd. for $C_{13}H_9ClN_2O_3$: C, 56.43; H, 3.28. Found: C, 56.29; H, 3.23.

Ethyl 7-Cyano-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12b**).

A mixture of 9.62 g (0.037 mole) **11b**, 10.21 g (0.074 mole) potassium carbonate and 11.54 g (0.074 mole) of ethyl iodide in 100 ml of dry *N,N*-dimethylformamide was stirred at about 80° overnight. After removing the solvent, the residue was taken up by chloroform and the chloroform solution, after washed with water and dried with sodium sulfate, was evaporated to dryness. Recrystallization of the solid residue from acetonitrile afforded the pure 7-cyano compound as white crystals, yield 64%, mp 223-225° (lit [8,9] mp (205-207°); ir: ν max 2240 (CN), 1720 (C=O); pmr (deuteriotrifluoroacetic acid): δ 1.60 and 1.85 (each t, 3H, J = 7, CH_2CH_3), 4.85 and 5.13 (each q, 2H, J = 7, CH_2CH_3), 8.43 (d, 1H, J = 8, C_5-H), 8.80 (d, 1H, J = 4, C_8-H), 9.70 (s, 1H, C_2-H).

Ethyl 6-Chloro-7-cyano-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**12c**).

Compound **12c** was similarly prepared as **12b** from **11c**, yield 80%, mp 193-194° (ethanol); ir: ν max 2240 (CN), 1720 (C=O); pmr (deuteriotrifluoroacetic acid): δ 1.60 and 1.83 (each t, 3H, J = 7, CH_2CH_3), 4.85 and 5.15 (each q, 2H, J = 7, CH_2CH_3), 8.70 (s, 1H, C_5-H), 8.75 (s, 1H, C_8-H), 9.77 (s, 1H, C_2-H).

Ethyl 7-(Aminothioxomethyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (**13b**).

Hydrogen sulfide was passed through a solution of 2.88 g (0.01 mole) of **12b**, 3 g (0.03 mole) of triethylamine in 100 ml of pyridine for 3 hours. The dark green solution, containing slightly more than 3 g (0.09 mole) of hydrogen sulfide, was then transfered to a reaction tube which was sealed tightly and allowed to stand at 110° for 4 hours. After removing the solvent, the oily residue was crystallized by adding water and the solid product was collected by filtration, yield 77%, mp 193-195° dec (lit [8,9] mp 198-199° dec); ir: ν max 3360 (NH), 3200 (NH), 1715 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 1.45 and 1.60 (each t, 3H, J = 7, CH_2CH_3), 4.60 and 4.88 (each q, 2H, J = 7, CH_2CH_3), 8.37 (d, 1H, J = 8, C_5-H), 8.55 (d, 1H, J = 3, C_8-H), 9.10 (s, 1H, C_2-H), 9.55 (br s, 1H, NH), 10.25 (br s, 1H, NH).

Ethyl 7-(Aminothioxomethyl)-6-chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (**13c**).

Compound **13c** was similarly prepared as **13b** from **12c**, yield 79%, mp 210-211° dec (ethanol); ir: ν max 3310 (NH), 3150 (NH), 1715 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 1.55 and 1.60 (each t, 3H, J = 7, CH_2CH_3), 4.75 and 4.85 (each q, 2H, J = 7, CH_2CH_3), 8.55 (s, 1H, C_5-H), 8.60 (s, 1H, C_8-H), 9.10 (s, 1H, C_2-H), 9.55 (br s, 1H, NH), 10.20 (br s, 1H, NH).

General Procedure for the Preparation of 7-(2-Thiazolyl)quinolone Esters **14**.

Method A.

7-(Aminothioxomethyl)quinolones **13b** or **13c** was added to a solution of 1.2 equivalents of the α-haloketone or aldehyde in 15 ml of *N,N*-dimethylformamide. After stirring overnight at about 100°, the product was precipitated by adding water and adjusting to *p*H 7 with aqueous sodium hydrogen carbonate solution. The product was purified by recrystallization from an appropriate solvent; see Table 1 for product data.

Method B.

7-(2-Thiazolyl)quinoline **19** was added to a solution of 2 equivalents of ethyl iodide in *N,N*-dimethylformamide in the presence of 2 equivalents of potassium carbonate. The mixture was stirred at 100° overnight. The same work up procedure as described under **12b** afforded the crude product **14** which was purified by recrystallization from an appropriate solvent.

Method C.

Compound **26** was added to 15 g of polyphosphoric acid and the obtained mixture was heated at 130° for 0.5 hour. After cooling the mixture water was added and the precipitate was collected by filtration and washed with water, ethanol and diethyl ether. Recrystallization from an appropriate solvent afforded the pure product.

General Procedure for the Preparation of 7-(2-Thiazolyl)quinolone Acids **6**.

The quinolone esters **14** were hydrolyzed by refluxing 3 hours in a mixture of 2*N* hydrochloric acid/90% acetic acid. The product was precipitated by addition of ice-water and collected by filtration. Recrystallization from an appropriate solvent afforded the pure compound; see Table 2 for product data.

3-Acetylamidobenzonitrile (**15**).

To a solution of 23.6 g (0.2 mole) of 3-aminobenzonitrile in 100 ml of glacial acetic acid was added 31.5 g (0.3 mole) of acetic anhydride. After refluxing for 6 hours, the solution was poured into cracked ice and allowed to stand for 2 hours at room tempera-

ture. The white precipitate was collected by filtration and dried at 50°, yield 82%, mp 77-78°; ir: ν max 3300 (NH), 3270 (NH), 2230 (CN), 1725 (C=O); pmr (deuteriochloroform): δ 2.35 (s, 3H, $COCH_3$), 7.30-7.70 (m, 4H, aromatic H), 8.65 (br s, 1H, NH).

3-Acetylaminothiobenzamide (**16**).

A solution of 3.2 g (0.02 mole) of **15** and 3 g (0.03 mole) of triethylamine in 100 ml of dry pyridine was saturated with hydrogen sulfide for 1 hour. The solution which contained about 3 g (0.09 mole) of hydrogen sulfide was then stirred in a sealed bottle at room temperature for 6 hours. After removing the solvent, the solid residue was washed with water and collected by filtration to afford a slightly yellow crystalline product which was pure enough for analysis, yield 96%, mp 168-172°; ir: ν max 3410 (NH), 3260 (NH), 1700 (C=O); pmr (deuteriochloroform): δ 2.18 (s, 3H, $COCH_3$), 7.20-8.00 (m, 4H, aromatic H), 8.60 (br s, 1H, NHCO), 8.95 (br s, 1H, H_2NCS), 9.70 (br s, 1H, H_2NCS).

Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.65; H, 5.18. Found: C, 55.58; H, 5.14.

General Procedure for the Preparation of 2-(3-Aminophenyl)thiazoles **17.1-17.3**.

Compound **16** (0.015 mole) was reacted with 1.2 equivalents of an appropriate α-haloketone in ethanol. After refluxing overnight, the solution was evaporated to dryness. To the residue was added 25 ml of concentrated hydrochloric acid and refluxed for 2 hours. After cooling, the reaction mixture was filtered to remove insoluble material and the acid filtrate was neutralized with aqueous sodium hydrogen carbonate solution. The precipitate was collected by filtration and purified by recrystallization form toluene-petroleum ether. The products and data are described below.

2-(3-Aminophenyl)-4-methylthiazole (**17.1**).

The α-haloketone, 2-chloroacetone gave **17.1** in a yield of 73%, mp 89-91°; ir: ν max 3440 (NH), 3320 (NH); pmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 3.75 (br s, 2H, NH_2), 6.65 (m, 1H, C_5-H), 6.80 (s, 1H, thiazole-H), 7.20 (m, 3H, other aromatic H).

Anal. Calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.29. Found: C, 62.98; H, 5.24.

2-(3-Aminophenyl)-4,5-dimethylthiazole (**17.2**).

The α-haloketone, 3-chloro-2-butanone gave **17.2** in a yield of 56%, mp 92-93°; ir: ν max 3460 (NH), 3340 (NH), 3220 (NH); pmr (deuteriochloroform): δ 2.35 (s, 6H, CH_3), 3.75 (br s, 2H, NH_2), 6.70 (m, 1H, C_5-H), 7.18 (m, 3H, other aromatic H).

Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.91. Found: C, 64.80; H, 5.88.

2-(3-Aminophenyl)-4-phenylthiazole (**17.3**).

The α-haloketone: α-bromoacetophenone gave **17.3** in a yield of 91%, mp 95-97°; ir: ν max 3420 (NH), 3320 (NH); pmr (deuteriochloroform): δ 4.03 (br s, 2H, NH_2), 7.63 (s, 1H, thiazole-H), 7.15-7.47 and 7.98 (m, m, 8H and 1H, other aromatic H).

Anal. Calcd. for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79. Found: C, 70.91; H, 4.82.

General Procedure for the Preparation of 7-(2-Thiazolyl)quinolines **19.1-19.3**.

A solution of **17** with 1 equivalent of EMME in toluene was refluxed for 4 hours. After evaporating to dryness, 50 ml of diphenyl ether was added to the oily residue and refluxed for 0.5 hour. After cooling, the diphenyl ether solution was diluted with 250 ml of petroleum ether. The precipitate was collected by filtration, washed with petroleum ether and purified by recrystallization from *N,N*-dimethylformamide. The products and data are described below.

Ethyl 4-Hydroxy-7-(4-methyl-2-thiazolyl)quinoline-3-carboxylate (**19.1**).

The yield was 98%, mp >300°; ir: ν max 1700 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.55 (t, 3H, J = 7, CH_2CH_3), 2.75 (s, 3H, CH_3), 4.67 (q, 2H, J = 7, CH_2CH_3), 7.80 (s, 1H, thiazole-H), 8.20 (m, 1H, C_6-H), 8.80 (m, 2H, C_5- and C_8-H), 9.40 (s, 1H, C_2-H).

Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.48. Found: C, 60.67; H, 4.44.

Ethyl 4-Hydroxy-7-(4,5-dimethyl-2-thiazolyl)-3-quinolinecarboxylate (**19.2**).

The yield was 91%, mp >300°; ir: ν max 1710 (C=O), 1605 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 2.70 (s, 6H, CH_3), 4.65 (q, 2H, J = 7, CH_2CH_3), 8.10 (m, 1H, C_6-H), 8.65 (d, 1H, J = 3, C_8-H), 8.90 (d, 1H, J = 8, C_5H), 9.35 (s, 1H, C_2-H).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91. Found: C, 62.04; H, 4.87.

Ethyl 4-Hydroxy-7-(4-phenyl-2-thiazolyl)quinoline-3-carboxylate (**19.3**).

The yield was 94%, mp >300°; ir: ν max 1725 (C=O), 1610 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 4.80 (q, 2H, J = 7, CH_2CH_3), 7.55 (s, 5H, phenyl H), 8.70-9.10 (m, 4H, $C_{5,6,8}$-H and thiazole-H), 9.60 (s, 1H, C_2-H).

Anal. Calcd. for $C_{21}H_{16}N_2O_3S$: C, 67.01; H, 4.28. Found: C, 67.11; H, 4.25.

Diethyl 4-Chloro-3-thiocarbamoylanilinomethylenemalonate (**21**).

Compound **10c** (3.22 g, 0.01 mole) was treated with hydrogen sulfide (3 g, 0.09 mole) in 100 ml of dry pyridine in the presence of 1 g (0.01 mole) of triethylamine in the same way as described under **13b** to afforded **21** in a yield of 60%, mp 215-216°; ir: ν max 3340 (NH), 3200 (NH), 1700 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 1.27 (m, 6H, CH_2CH_3), 4.20 and 4.30 (each q, 2H, J = 7, CH_2CH_3), 7.57 (s, 3H, aromatic H), 8.50 (d, 1H, J = 14, NH-CH=C), 9.92 (br s, 1H, H_2NCS), 10.43 (br s, 1H, H_2NCS), 10.77 (br d, 1H, J = 14, NH-CH=C).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_4S$: C, 50.49; H, 4.80. Found: C, 50.26; H, 4.76.

Diethyl 4-Chloro-3-(4-methyl-2-thiazolyl)anilinomethylenemalonate (**18c.1**).

A solution of 1 g (2.7 mmoles) of **21** and 0.25 g (2.7 mmoles) of freshly distilled chloroacetone in 20 ml of anhydrous ethanol was refluxed overnight. After removing the solvent, water was added to the residue and treated with aqueous sodium hydrogen carbonate solution. The precipitate was collected by filtration, dried at 50° and purified by recrystallization from methanol to afford white crystals, yield 51%, mp 106-107°; ir: ν max 1690 (C=O), 1600 (C=C); pmr (deuteriochloroform); δ 1.40 (t, 6H, J = 7, CH_2CH_3), 2.85 (s, 3H, CH_3), 4.40 (q, 4H, J = 7, CH_2CH_3), 7.50-7.80 (m, 3H, phenyl H), 8.87 (s, 1H, thiazole H), 9.10 (d, 1H, J = 14, NH-CH=C), 11.10 (br d, 1H, J = 14, NH-CH=C).

Anal. Calcd. for $C_{18}H_{19}ClN_2O_4S$: C, 54.75; H, 4.85. Found: C,

54.58; H, 4.87.

Ethyl 6-Chloro-4-hydroxy-7-(4-methyl-2-thiazolyl)quinoline-3-carboxylate (**19c.1**).

To 25 ml of diphenyl ether preheated to 250° was added 0.55 g (1.36 mmoles) of **18c.1**. The solution was refluxed for 0.5 hour and cooled to room temperature. The product was precipitated by addition of 150 ml petroleum ether to the mixture and collected by filtration. Recrystallization from *N,N*-dimethylformamide afforded the colorless crystalline compound, yield 65%, mp >300°; ir: ν max 1700 (C=O), 1605 (C=C); pmr (deuteriotrifluoroacetic acid): δ 1.60 (t, 3H, J = 7, CH_2CH_3), 2.90 (s, 3H, CH_3), 4.85 (q, 2H, J = 7, CH_2CH_3), 7.35 (s, 1H, thiazole H), 8.00 (s, 1H, C_5-H), 8.10 (s, 1H, C_8-H), 9.10 (s, 1H, C-H).

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3S$: C, 55.10; H, 3.75. Found: C, 54.93; H, 3.71.

Ethyl 6-Chloro-1-ethyl-1,4-dihydro-7-(4-methyl-2-thiazolyl)-4-oxoquinoline-3-carboxylate (**14c.1**).

Compound **14c.1** was prepared by Method B described under **14**. The product was identical to the material prepared by Method A; see Table 1 for product data.

2-Chloro-5-trifluoroacetylaminobenzonitrile (**22**).

Compound **22** was prepared in a 96% yield by the reaction of **9c** with trifluoroacetic anhydride using the same method as described under **15**, mp 196-198°; ir: ν max 3300 (NH), 3200 (NH), 2250 (CN), 1730 (C=O); pmr (deuteriochloroform): δ 7.35-7.70 (m, 3H, aromatic H), 10.15 (br s, 1H, NH).

2-Chloro-5-trifluoroacetylaminothiobenzamide (**23**).

Compound **23** was prepared in a 94% yield by the same treatment with hydrogen sulfide as described under **16**, mp 164-166°; ir: ν max 3410 (NH), 3320 (NH), 1710 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 7.50-8.10 (m, 3H, aromatic H), 9.25 (br s, 1H, H_2NCS), 10.10 (br s, 1H, H_2NCS), 11.10 (br s, 1H, NHCO).

2-(2-Chloro-5-trifluoroacetylamino)phenyl-4,5-dimethylthiazole (**24.2**).

A solution of 2.8 g (0.01 mole) of **23** and 1.07 g (0.01 mole) of 3-chloro-2-butanone in 50 ml of ethanol was refluxed for 4 hours. After removing the solvent, water was added to the residue and aqueous sodium hydrogen carbonate solution was added to *p*H 7. The precipitate was collected by filtration and purified by recrystallization from methanol, yield 70%, mp 125-127°; ir: ν max 3320 (NH), 1705 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 2.45 (s, 6H, CH_3), 7.70 (m, 2H, C_5- and C_6-H), 8.65 (d, 1H, J = 3, C_2-H), 11.45 (br s, 1H, NH).

2-(2-Chloro-5-trifluoroacetylamino)phenyl-4-phenylthiazole (**24.3**).

Compound **24.3** was similarly prepared as **24.2** by the reaction of **23** and 1 equivalent of α-bromoacetophenone, yield 81%, mp 168-169° (ethanol); ir: ν max 3280 (NH), 1705 (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 7.65-7.80 (m, 7H, C_5-, C_6- and phenyl H), 8.00 (d, 1H, J = 3, C_2-H), 8.30 (s, 1H, thiazole H), 11.25 (br s, 1H, NH).

2-(2-Chloro-5-ethylamino)phenyl-4,5-dimethylthiazole (**25.2**).

A mixture of 1.7 g (5.1 mmoles) of **24.2**, 1.38 g (10.2 mmoles) of potassium carbonate and 1.56 g (10.2 mmoles) of ethyl iodide in 50 ml of dry acetone was refluxed with stirring for 6 hours. After removing the solvent, the residue was taken up in chloroform to remove the inorganic salts. The chloroform solution was evaporated to dryness and the residue was dissolved in a mixture of 20 ml of ethanol and 20 ml of 10% aqueous sodium hydroxide solution. The mixture was then refluxed for 2 hours. After cooling, the solution was diluted with water and extracted with chloroform. The product was obtained by removing the chloroform and purified by recrystallization from toluene-petroleum ether, yield 53%, mp 58-60°; ir: ν max 3405 (NH), 3360 (NH), 1605 (C=C); pmr (deuteriochloroform): δ 1.23 (t, 3H, J = 7, CH_2CH_3), 2.43 (s, 6H, CH_3), 3.20 (q, 2H, J = 7, CH_2CH_3), 3.70 (br s, 1H, NH), 6.65 (m, 1H, C_6-H), 7.25-7.43 (m, 2H, C_2- and C_5-H).

Anal. Calcd. for $C_{13}H_{15}ClN_2S$: C, 58.53; H, 5.66. Found: C, 58.38; H, 5.59.

2-(2-Chloro-5-ethylamino)phenyl-4-phenylthiazole (**25.3**).

Compound **25.3** was similarly prepared as **25.2**, yield 75%, mp 61-62°; ir: ν max 3460 (NH), 3400 (NH), 1600 (C=C); pmr (deuteriochloroform): δ 1.27 (t, 3H, J = 7, CH_2CH_3), 3.30 (q, 2H, J = 7, CH_2CH_3), 3.70 (br s, 1H, NH), 6.85 (m, 1H, C_6-H), 7.35-7.80 (m, 7H, C_2-, C_5- and phenyl H), 8.15 (s, 1H, thiazole H).

Anal. Calcd. for $C_{17}H_{15}ClN_2S$: C, 64.85; H, 4.80. Found: C, 64.97; H, 4.77.

Diethyl *N*-Ethyl-4-chloro-3-(4,5-dimethyl-2-thiazolyl)anilinomethylenemalonate (**26.2**).

Compound **25.2** (0.7 g, 2.6 mmoles) and EMME (0.56 g, 2.6 mmoles) were heated with stirring for 4 hours. After removing the ethanol produced during the reaction, the residue was recrystallized from methanol to afford a pure crystalline compound, yield 65%, mp 107-109°; ir: ν max 1700 (C=O), 1610 (C=C); pmr (deuteriochloroform): δ 1.40 (m, 9H, CH_2CH_3), 2.45 (s, 6H, CH_3), 4.35 (m, 6H, CH_2CH_3), 7.00-7.50 (m, 3H, aromatic H), 8.80 (d, 1H, J = 13, NH-CH=C), 11.05 (br s, 1H, J = 13, NH-CH=C).

Anal. Calcd. for $C_{21}H_{25}ClN_2O_4S$: C, 57.72; H, 5.76. Found: C, 57.59; H, 5.81.

Diethyl *N*-Ethyl-4-chloro-3-(4-phenyl-2-thiazolyl)anilinomethylenemalonate (**26.3**).

Compound **26.3** was similarly prepared as **26.2**, yield 69%, mp 133-136°; ir: ν max 1690 (C=O), 1610 (C=C); pmr (deuteriochloroform): δ 1.40 (m, 9H, CH_2CH_3), 4.37 (m, 6H, CH_2CH_3), 7.60-8.45 (m, 9H, aromatic H), 8.80 (d, 1H, J = 13, NH-CH=C), 11.10 (br d, 1H, J = 13, NH-CH=C).

Anal. Calcd. for $C_{25}H_{25}ClN_2O_4S$: C, 61.91; H, 5.19. Found: C, 61.66; H, 5.13.

General Procedure for the Preparation of 2-(4-Oxoquinolinyl)-3-methylthiazolium Iodide **20**.

A solution of 3 mmoles of thiazolylquinolone acid **6** (or ester **14**) and 15 mmoles of methyl iodide in 20 ml of dry *N,N*-dimethylformamide was added to a reaction tube. The sealed tube was heated at 130° for 5 hours. After cooling to room temperature, the precipitate was collected by filtration, washed with dry diethyl ether and dried at 50°. The products were purified by recrystallization from *N,N*-dimethylformamide; see Table 3 for product data.

General Procedure for the Preparation of 7-(3-methyl-2-thiazolidinyl)quinolone Acids **7**.

To a solution of 2 mmoles of 3-methylthiazolium iodide **20** in 50 ml of water was added portionwise 6 mmoles of sodium boro-

hydride at 5-10°. After addition, the reaction mixture was stirred at room temperature for 4 hours. The solution was then carefully adjusted to *p*H 4 with 10% hydrochloric acid and extracted with chloroform. After drying with sodium sulfate, the chloroform extracts were evaporated to dryness, compound **7** was filtered off as slightly yellow crystalline products which were further purified by recrystallization from ethanol; see Tables 4 and 5 for product data.

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