New Route to *N*-Aryl and *N*-Heteroaryl Derivatives of 4-Hydroxy-3-quinolinecarboxamides

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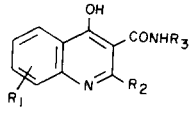
Received April 6, 1984

The synthesis of *N*-aryl and *N*-heteroaryl substituted 4-hydroxy-3-quinolinecarboxamides **1** is described. The attack of dianions **12** of *N*-aryl substituted acetamides on the C-4 carbonyl of 4*H*-3,1-benzoxazin-4-ones **11** gave rise to ketoamides **13**, which smoothly cyclised in the presence of bases to afford quinolinecarboxamides **1**. By this method, a large number of 2-substituted 4-hydroxyquinolinecarboxamides can be prepared.

J. Heterocyclic Chem., **21**, 1345 (1984).

As a part of a program aimed at discovering new peripherally acting analgesics, we studied a series of *N*-substituted 4-hydroxy-3-quinolinecarboxamides **1**.



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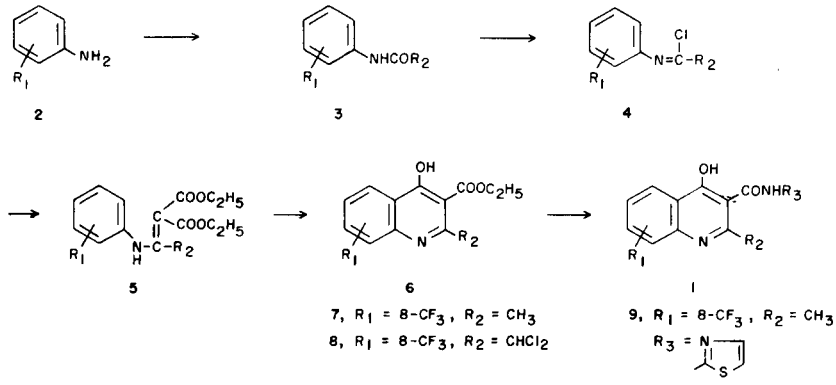
Amongst these, the compound **79** (RU 29693 - Table 3) exhibits extremely interesting analgesic activity and is very well tolerated at the gastro-intestinal level. These results will be published elsewhere. In this report, we describe a three-step synthesis of **1** from anthranilic acids **10** (Scheme 2, Method B).

In an earlier attempt to synthesize **1**, esters **6**, obtained by Just's synthesis [1], were reacted with amines (Scheme 1, Method A). Depending on the type of amine, the results of this reaction may be good, but are more often unsatisfactory as, for example, with some aromatic or heterocyclic amines [2]. Sometimes the aminolysis of the esters requires high temperature and/or a long reaction time [3], or the use of alkali metal catalysts [4]. Trialkylaluminiums can often give better results [5].

These methods enabled us to obtain certain compounds of which two examples are given in the experimental section (see access to **9** and **79**). Nevertheless, the conditions of these reactions (temperature and basicity) are often incompatible with a sensitive functionality. Thus, in the case of halogenated derivatives **77-87**, yields were unsatisfactory and we were ofen unable to obtain the desired pro-

SCHEME 1, METHOD A



SCHEME 2, METHOD B

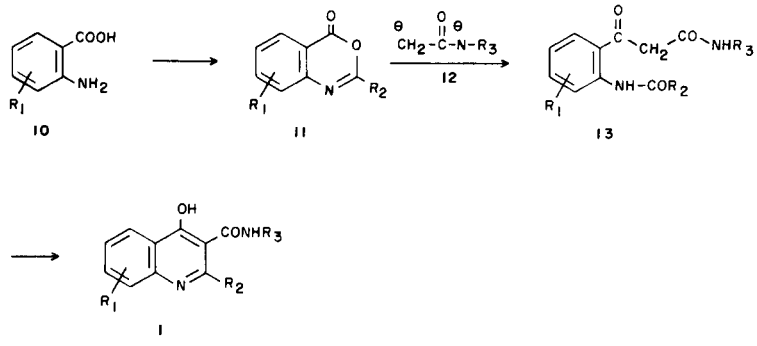
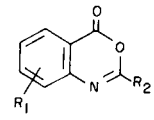


Table 1

4*H*-3,1-Benzoxazin-4-ones



II

Compound No.	R_1	R_2	Mp°C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found				
25	8-CF_3	H	70	50	Crude [b]	$C_9H_4F_3NO_2$					
26	H	CH_3	81-82 [c]	85	Crude [b]	$C_9H_7NO_2$					
							C	H	N		
27	H	CH_2CH_3	86 [d]	77	Petroleum ether	$C_{10}H_9NO_2$	68.5	5.2	8.0		
							68.1	5.1	7.8		
							C	H	N	F	
28	8-CF_3	$CH=CH_2$	96	58	Petroleum ether	$C_{11}H_6F_3NO_2$	54.8	2.5	5.8	23.7	
							54.7	2.5	5.9	23.5	
							C	H	N	F	
29	8-CF_3	-$C(CH_3)_3$	46	81	Sublimated	$C_{13}H_{12}F_3NO_2$	57.6	4.5	5.2	21.0	
							57.8	4.5	5.2	21.0	
							C	H	N	F	
30	8-CF_3	*o*-trifluoro-methylphenyl	86	61	Crude [b]	$C_{16}H_7F_6NO_2$	53.8	2.0	3.4	31.7	
							53.8	2.0	3.8	30.7	
							C	H	N	Cl	F
31	8-CF_3	CH_2Cl	76-78	94	Petroleum ether	$C_{10}H_5ClF_3NO_2$	45.6	1.9	5.3	13.5	21.6
							45.6	1.9	5.3	13.7	21.8
							C	H	N	Cl	
32	H	$CHCl_2$	178 [e]	93	Methyl alcohol	$C_9H_5Cl_2NO_2$	46.9	2.2	6.1	30.8	
							46.8	2.2	6.1	30.7	
							C	H	N	Cl	F
33	8-CF_3	$CHCl_2$	179	94	Methyl alcohol	$C_{10}H_4Cl_2F_3NO_2$	40.3	1.3	4.7	23.8	19.1
							40.2	1.3	4.5	23.8	19.3
							C	H	N	Cl	
34	6-Cl	$CHCl_2$	182	96	Crude [b]	$C_9H_4Cl_3NO_2$	40.9	1.5	5.3	40.2	
							41.0	1.6	5.3	40.2	
							C	H	N	Cl	
35	8-Cl	$CHCl_2$	186	96	Crude [b]	$C_9H_4Cl_3NO_2$	40.9	1.5	5.3	40.2	
							40.8	1.4	5.4	40.4	
							C	H	N	Cl	F
36	8-F	$CHCl_2$	145	91	Crude [b]	$C_9H_4Cl_2FNO_2$	43.6	1.7	5.7	28.6	7.7
							43.5	1.5	5.7	28.8	7.5
							C	H	N	F	
37	8-CF_3	CHF_2	82	74	Petroleum ether	$C_{10}H_4F_5NO_2$	45.3	1.5	5.3	35.8	
							45.5	1.7	5.4	35.7	
							C	H	N	Cl	F
38	8-CF_3	CHCl-CH_3	96	112	Petroleum ether	$C_{11}H_7ClF_3NO_2$	47.6	2.5	5.0	12.8	20.5
							47.5	2.5	5.0	13.1	20.2
							C	H	N	Cl	F
39	8-CF_3	CCl_2-CH_3	96	120	Petroleum ether	$C_{11}H_6Cl_2F_3NO_2$	42.3	1.9	4.5	22.8	18.3
							42.2	1.9	4.6	23.0	17.9
							C	H	N	F	
40	H	CF_3	51 [f]	80	Sublimated	$C_9H_4F_3NO_2$	50.3	1.9	6.5	26.5	
							50.4	1.8	6.5	26.5	
							C	H	N	Cl	F
41	6-Cl	CF_3	106	67	Petroleum ether	$C_9H_3ClF_3NO_2$	43.3	1.2	5.6	14.2	22.8
							43.4	1.2	5.7	14.0	22.9
							C	H	N	Cl	F
42	7-Cl	CF_3	68 [g]	47	Petroleum ether	$C_9H_3ClF_3NO_2$	43.3	1.2	5.6	14.2	22.8
							43.0	1.3	5.5	14.3	22.6
							C	H	N	F	
43	8-F	CF_3	62	90	Petroleum ether	$C_9H_3F_4NO_2$	46.3	1.3	6.0	32.6	
							46.1	1.4	6.0	35.5	

Table 1 continued

Compound No.	R_1	R_2	Mp°C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found				
							C	H	N	Cl	F
44	8-Cl	CF_3	98	85	Petroleum ether	$C_9H_3ClF_3NO_2$	43.3	1.2	5.6	14.2	22.8
							43.6	1.2	5.7	14.3	22.4
							C	H	N	F	
45	8-CF_3	CH_2OCH_3	106	60	Petroleum ether	$C_{11}H_8F_3NO_3$	51.0	3.1	5.4	22.0	
							51.2	3.1	5.3	22.3	
							C	H	N	F	S
46	8-CF_3	CH_2-S-CH_3	54	62	Petroleum ether	$C_{11}H_8F_3NO_2S$	48.0	2.8	5.1	20.7	11.6
							48.0	2.9	5.2	21.0	11.5

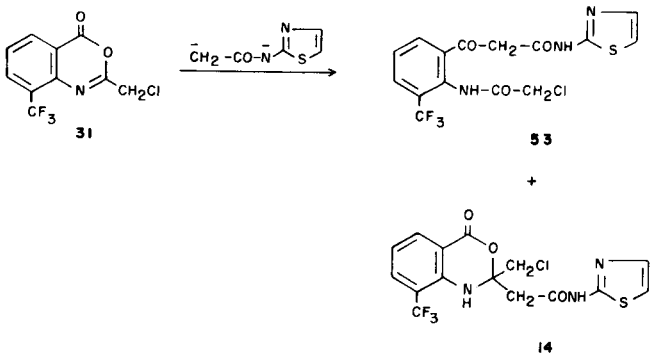
[a] Isolated yields, no efforts were made to optimise these yields. [b] Material used in next step without further purification. [c] Lit [12] mp 86. [d] Lit [13] mp 87. [e] Lit [14] mp 176. [f] Lit [15] mp 52. [g] Lit [16] mp 51-52.

ducts in this way. Moreover, we failed to prepare the corresponding halogenated esters using Just's process as for example **8**. We looked for and found a shorter synthesis of 4-hydroxy-3-quinolinecarboxamides **1**, which is shown in Scheme 2.

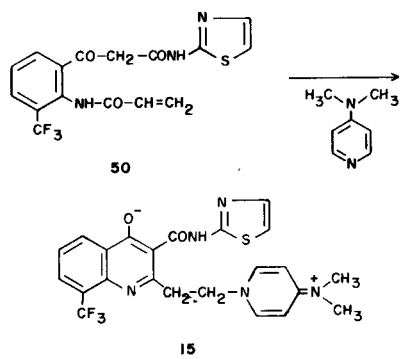
Condensation of anthranilic acids **10** with an acid anhydride or chloride in the classical way [6] gave 4*H*-3,1-benzoxazin-4-ones **25-46** in good yields (Table 1). Conversion of these compounds to 2-acylamino-β-oxopropanamides **47-70** (Table 2) was best carried out at -70°, with an excess of dianion **12** prepared from the *N*-substituted acetamide and butyllithium in tetrahydrofuran. Ring closure of **47-70** with suitable bases in a solvent readily afforded 4-hydroxy 3-quinolinecarboxamides **71-94** (Table 3). It is worth noting that this cyclisation is a special example of Camps' modification of Friedländer's synthesis [7]. The reaction was usually carried out in tetrahydrofuran or dimethylformamide. The bases used were often the amines, for instance, 4-dimethylaminopyridine, but the reaction sometimes required the presence of stronger bases such as sodium hydride or potassium *t*-butoxide. In many cases cyclisation occurred at room temperature, but heating is necessary in some cases (see Table 3). On the other hand, condensation of 4*H*-3,1-benzoxazine-4-ones **11** with dianions **12** sometimes gave rise to significant quantities of quinolinecarboxamides **1** and thus the cyclisation was performed using crude mixtures (Table 2 **47**, **57**, **60** and **68**). Furthermore, in some cases we were unable to isolate the propanamide **13**, and the quinolines **1** were obtained directly (see access to **80**, Tables 2 and 3).

Some unexpected results are worthy of note. For example, the reaction of some 4*H*-3,1-benzoxazin-4-ones **11** with dianions **12** gave unsatisfactory yields. Thus, compound **53** was only obtained in 16% yield, together with compound **14**, which was isolated in 25% yield (Scheme 3).

Scheme 3



Scheme 4



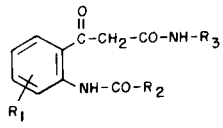
Concerning the last step of our synthesis, the choice of reagents may depend on special structural features. For instance, in the case of propanamide **50** bearing a vinyl group the use of dimethylaminopyridine as a base is impossible, since this amine added to the double bond giving compound **15** (Scheme 4).

On the other hand, when an analogous reaction was performed with hindered propanamides **16**, quinolinecarboxamides **17** were obtained in poor yield together with significant quantities of **18** arising from loss of the amide group (Scheme 5).

Although 2-chloroalkyl substituted quinolinecarboxamides **22** were obtained in good yields from propanamides **21** by the method shown in Scheme 6, using dimethylam-

Table 2

2-Acylamino-β-oxopropanamides



13

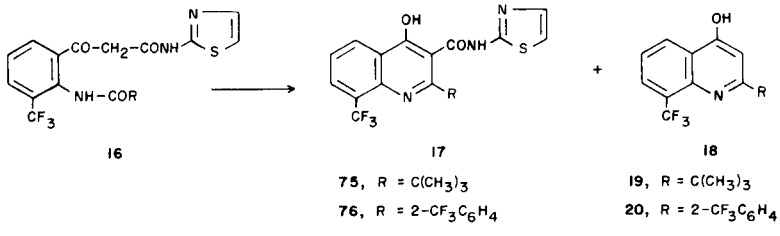
Compound No.	R_1	R_2	R_3	Mp °C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found					
47	3-CF_3	H	2-thiazolyl-	235	51 [b]	Crude [c]	$C_{14}H_{10}F_3N_3O_3S$						
48	H	CH_3	3,4-dihydro-2-thiazolyl-	184	59	Acetonitrile	$C_{14}H_{15}N_3O_3S$	C 55.1 55.4	H 4.9 4.9	N 13.8 13.5	S 10.5 10.3		
49	H	CH_2CH_3	*p*-methoxyphenyl	166	75	Acetonitrile	$C_{19}H_{20}N_2O_4$	C 67.0 66.7	H 5.9 5.9	N 8.2 8.2			
50	3-CF_3	$CH=CH_2$	2-thiazolyl-	196	43	Ethyl acetate	$C_{16}H_{12}F_3N_2O_3S$	C 50.1 49.9	H 3.1 3.1	N 10.9 10.8	Cl 8.4 8.7	F 14.9 15.2	
51	3-CF_3	$C(CH_3)_3$	2-thiazolyl-	162	70	Ether	$C_{18}H_{18}F_3N_3O_3S$	C 52.2 52.4	H 4.4 4.4	N 10.2 10.0	F 13.8 13.7	S 7.8 7.6	
52	3-CF_3	o-trifluoromethylphenyl	2-thiazolyl-	252	73	Acetonitrile	$C_{21}H_{13}F_6N_3O_3S$	C 50.3 50.1	H 2.6 2.6	N 8.4 8.2	F 22.7 22.7	S 6.4 6.6	
53	3-CF_3	CH_2Cl	2-thiazolyl-	192-194	16	Chromatography Ethyl acetate Cyclohexane	$C_{15}H_{11}ClF_3N_3O_3S$	C 44.4 44.8	H 2.7 2.7	Cl 10.4 10.2	N 8.7 8.9	S 7.9 8.2	
54	H	$CHCl_2$	2-thiazolyl-	200	55	Ethyl alcohol	$C_{14}H_{11}Cl_2N_3O_3S$	C 45.2 45.3	H 3.0 3.0	Cl 19.0 18.7	N 11.3 11.0	S 8.6 8.7	
55	3-CF_3	$CHCl_2$	2-thiazolyl-	224	64	Ethyl alcohol	$C_{15}H_{10}Cl_2F_3N_3O_3S$	C 40.8 41.1	H 2.3 2.4	N 9.5 9.4	Cl 16.1 16.0	S 7.3 7.4	
56	3-CF_3	$CHCl_2$	2-oxazolyl-	non isolated									
57	5-Cl	$CHCl_2$	2-thiazolyl-	260 dec	35 [b]	Crude [c]	$C_{14}H_{10}Cl_3N_3O_3S$						
58	3-Cl	$CHCl_2$	2-thiazolyl-	240 dec	53	Crude [c]	$C_{14}H_{10}Cl_3N_3O_3S$	C 41.3 41.3	H 2.5 2.6	N 10.3 10.3	Cl 26.1 25.3	S 7.9 7.8	
59	3-F	$CHCl_2$	2-thiazolyl-	256 dec	59	Ethyl alcohol	$C_{14}H_{10}Cl_2FN_3O_3S$	C 43.1 43.1	H 2.6 2.6	N 10.8 10.7	Cl 18.2 17.9	F 4.9 4.8	S 8.2 8.1
60	3-CF_3	$CHCl_2$	2-pyridyl-		100 [b]	Crude [c]	$C_{17}H_{12}Cl_2F_3N_3O_3$						
61	3-CF_3	CHF_2	2-thiazolyl-	206 then 226	57	Acetonitrile	$C_{13}H_{10}F_3N_3O_3S$	C 44.2 44.4	H 2.5 2.5	N 10.3 10.4	F 23.3 23.5	S 7.0 8.2	
62	3-CF_3	$CHCl-CH_3$	2-thiazolyl-	216	69	Acetonitrile	$C_{16}H_{13}ClF_3N_3O_3S$	C 45.8 46.0	H 3.1 3.3	N 10.0 10.1	Cl 8.5 8.5	S 7.6 7.6	
63	3-CF_3	CCl_2-CH_3	2-thiazolyl-	136-138	54	ether	$C_{16}H_{12}Cl_2F_3N_3O_3S$	C 42.3 42.7	H 2.7 2.9	N 8.8 9.0			
64	H	CF_3	2-thiazolyl-	230 then 280	73	Acetonitrile	$C_{14}H_{10}F_3N_3O_3S$	C 47.1 47.1	H 2.8 2.8	N 11.8 11.7	F 16.0 16.2	S 9.0 9.1	
65	5-Cl	CF_3	2-thiazolyl-	235 dec	64	Ethyl alcohol	$C_{14}H_9ClF_3N_3O_3S$	C 42.9 42.9	H 2.3 2.3	N 10.7 10.7	Cl 9.1 9.2	F 14.5 14.5	S 8.2 8.5

Table 2 continued

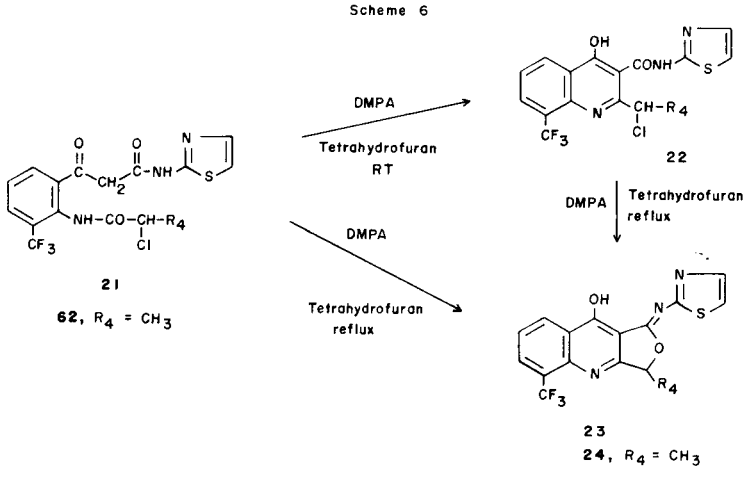
Compound No.	R_1	R_2	R_3	Mp °C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found					
								C	H	N	Cl	F	S
66	4-Cl	CF_3	2-thiazolyl-	200-210 dec	78	Ethyl alcohol	$C_{14}H_9ClF_3N_3O_3S$	42.9	2.3	10.7	9.1	14.5	8.2
								43.5	2.6	10.5	9.2	14.3	8.1
								C	H	N	F	S	
67	3-F	CF_3	2-thiazolyl-	218	83	Ethyl alcohol	$C_{14}H_9F_4N_3O_3S$	44.8	2.4	11.2	20.3	8.5	
								44.8	2.4	11.1	19.9	8.8	
68	3-Cl	CF_3	2-thiazolyl-	210 then 245	70 [b]	Crude [c]	$C_{14}H_9ClF_3N_3O_3S$						
								C	H	N	F	S	
69	3-CF_3	CH_2OCH_3	2-thiazolyl-	152	67	Diethylether	$C_{16}H_{14}F_3N_3O_4S$	47.9	3.5	10.5	14.2	8.0	
								48.1	3.6	10.2	14.6	8.2	
								C	H	N	F	S	
70	3-CF_3	CH_2SCH_3	2-thiazolyl-	190	35	Ethyl acetate	$C_{16}H_{14}F_3N_3O_3S_2$	46.0	3.4	10.1	13.7	15.4	
								45.9	3.3	9.8	13.9	15.1	

[a] Isolated yields, no efforts were made to optimise these yields. [b] Mixture of structures **13** and **1**. [c] Material used in the next step without further purification.

Scheme 5



Scheme 6



inopyridine (DMPA) in tetrahydrofuran at room temperature, it is interesting to note that refluxing this mixture gave rise to compound **23** (Scheme 6). Moreover this compound **23** was readily obtained by refluxing a solution of **22** in tetrahydrofuran in the presence of DMPA.

In conclusion, the reactions described in this paper enable a number of *N*-aryl substituted 4-hydroxy-3-quinolinecarboxamides to be easily prepared in three steps from readily available anthranilic acids.

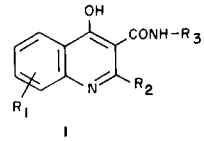
EXPERIMENTAL

Melting points were determined on a Köfler apparatus and are uncorrected. Spectral measurements were performed on the following instruments: ir on Perkin Elmer 580B, uv on Cary 14 or 15, pmr on Varian T60, Bruker WP60 or WH90, cmr on Bruker WM250, mass unless otherwise stated on MAT 311A spectrometer.

Infrared frequencies are in cm^{-1}; nmr chemical shifts δ in ppm with respect to internal tetramethylsilane and coupling constants J (first order analysis) in hertz; s, d, t, q, m, b refer to singlet, doublet, triplet, quadruplet, multiplet and broad. Ultra-violet λ nm (ϵ) refer to maxima $\sim\lambda$ nm (ϵ) to inflexions. "Ethanol" refers to 95% ethanol; "ethanol-

Table 3

N-Substituted 4-Hydroxy-3-quinolinecarboxamides



I

Compound No.	R_1	R_2	R_3	Mp °C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found				
								C	H	N	F	S
71	8-CF_3	H	2-thiazolyl-	388	76	Acetic acid	$C_{14}H_8F_3N_3O_2S$	49.6	2.4	12.4	16.8	9.5
								49.7	2.4	12.3	16.9	9.7
								C	H	N	Cl	S
72	H	CH_3	3,4-dihydro-2-thiazolyl-	280	46 [b]	Water	$C_{14}H_{13}N_3O_2S$, HCl	51.9	4.4	13.0	9.9	10.9
								51.8	4.3	12.8	9.6	11.1
								C	H	N		
73	H	CH_2-CH_3	*p*-methoxy-phenyl	236	66 [b]	Acetonitrile	$C_{19}H_{18}N_2O_3$	70.8	5.6	8.7		
								70.9	5.9	8.4		
								C	H	N	F	S
74	8-CF_3	$CH=CH_2$	2-thiazolyl-	236	55 [b]	Acetonitrile	$C_{16}H_{10}F_3N_3O_2S$	52.6	2.8	11.5	15.6	8.8
								52.7	2.8	11.8	15.2	8.6
								C	H	N	F	S
75	8-CF_3	$C(CH_3)_3$	2-thiazolyl-	222	13.5 (b)	Ethyl ether	$C_{18}H_{16}F_3N_3O_2S$	54.7	4.1	10.8	14.4	8.1
								54.6	4.1	10.5	14.5	8.2
								C	H	N	F	S
76	8-CF_3	*o*-trifluoro-methylphenyl	2-thiazolyl-	275	30 [b]	Acetonitrile	$C_{21}H_{11}F_6N_3O_2S$	52.2	2.3	8.7	23.6	6.6
								51.9	2.2	8.8	23.6	6.8
								C	H	N	Cl	S
77	8-CF_3	CH_2Cl	2-thiazolyl-	218 dec	64	THF Petroleum ether	$C_{15}H_9ClF_3N_3O_2S$	46.5	2.3	10.8	9.1	8.3
								46.3	2.4	10.6	9.4	8.4
								C	H	N	Cl	S
78	H	$CHCl_2$	2-thiazolyl-	260 dec	56 [c]	Acetic acid	$C_{14}H_9Cl_2N_3O_2S$	47.5	2.6	11.9	20.0	9.1
								47.7	2.5	11.7	19.7	8.8
								C	H	N	Cl	F	S
79	8-CF_3	$CHCl_2$	2-thiazolyl-	204	86	Ethyl acetate	$C_{15}H_8Cl_2F_3N_3O_2S$	42.7	1.9	9.9	16.8	13.5	7.6
								42.4	2.0	9.8	16.9	13.8	7.5
								C	H	N	Cl	F	
80	8-CF_3	$CHCl_2$	2-oxazolyl-	220-225	42	Acetone	$C_{15}H_8Cl_2F_3N_3O_3$	44.4	2.0	10.3	17.5	14.0	
								44.6	2.0	10.3	17.2	14.0	
								C	H	N	Cl	S	
81	6-Cl	$CHCl_2$	2-thiazolyl-	184 dec	78	Ethyl alcohol	$C_{14}H_8Cl_3N_3O_2S$ ½ C_2H_5OH	43.8	2.7	10.2	25.8	7.8	
								44.0	2.7	10.2	26.2	7.7	
								C	H	N	Cl	S	
82	8-Cl	$CHCl_2$	2-thiazolyl-	232 dec	74	Ethyl alcohol	$C_{14}H_8Cl_3N_3O_2S$	43.3	2.1	10.8	27.4	8.2	
								43.5	2.0	10.9	27.3	8.0	
								C	H	N	Cl	F	S
83	8-F	$CHCl_2$	2-thiazolyl-	242	83	Ethyl alcohol	$C_{14}H_8Cl_2FN_3O_2S$	45.2	2.2	11.3	19.1	5.1	8.6
								45.5	2.1	11.4	19.1	5.1	8.6
								C	H	N	Cl	F	
84	8-CF_3	$CHCl_2$	2-pyridyl-	212 dec	40	Ethyl acetate	$C_{17}H_{10}Cl_2F_3N_3O_2$	49.1	2.4	10.1	17.1	13.7	
								49.0	2.3	10.0	17.2	13.2	
								C	H	N	F	S	
85	8-CF_2	CHF_2	2-thiazolyl-	226-228	67	Ethyl acetate	$C_{15}H_8F_5N_3O_2S$	46.3	2.1	10.8	24.4	8.2	
								46.3	2.1	10.,7	24.7	8.5	
								C	H	N	Cl	S	
86	8-CF_3	CHCl-CH_3	2-thiazolyl-	192	81	Ethyl ether	$C_{16}H_{11}ClF_3N_3O_2S$	47.8	2.8	10.5	8.8	8.0	
								47.6	2.8	10.4	8.9	8.1	
								C	H	N	Cl	S	
87	8-CF_3	CCl2-CH_3	2-thiazolyl-	220 dec	39	Ether	$C_{16}H_{10}Cl_2F_3N_3O_2S$	44.0	2.3	9.6	16.3	7.3	
								44.0	2.5	9.4	16.4	7.5	
								C	H	N	F	S	
88	H	CF_3	2-thiazolyl-	270	84	Acetic acid	$C_{14}H_8F_3N_3O_2S$	49.6	2.4	12.4	16.8	9.4	
								49.4	2.3	12.2	16.8	9.6	

Table 3 continued

Compound No.	R_1	R_2	R_3	Mp °C	Yield % [a]	Recrystallisation solvent	Molecular formula	Analysis % Calcd/Found					
								C	H	N	Cl	F	S
89	6-Cl	CF_3	2-thiazolyl-	310	68	Ethyl alcohol	$C_{14}H_7ClF_3N_3O_2S$	45.0	1.9	11.2	9.5	15.2	8.6
								44.9	2.0	11.5	9.4	14.9	8.8
								C	H	N	Cl	F	S
90	7-Cl	CF_3	2-thiazolyl-	305	69	Ethyl alcohol	$C_{14}H_7ClF_3N_3O_2S$	45.0	1.9	11.2	9.5	15.2	8.6
								45.0	1.9	11.2	9.7	15.3	8.3
								C	H	N	F	S	
91	8-F	CF_3	2-thiazolyl-	240	70	Ethyl alcohol	$C_{14}H_7F_4N_3O_2S$	47.1	2.0	11.8	21.3	9.0	
								47.3	2.0	11.8	21.6	9.1	
								C	H	N	Cl	F	S
92	8-Cl	CF_3	2-thiazolyl-	250	88	Ethyl alcohol	$C_{14}H_7ClF_3N_3O_2S$	45.0	1.9	11.2	9.5	15.3	8.6
								45.3	1.9	11.3	9.7	14.9	8.6
								C	H	N	F	S	
93	8-CF_3	CH_2OCH_3	2-thiazolyl-	260	84	Dioxane	$C_{16}H_{12}F_3N_3O_3S$	50.1	3.1	10.9	14.9	8.6	
								50.3	3.1	10.8	14.5	8.4	
								C	H	N	S	F	
94	8-CF_3	CH_2-S-CH_3	2-thiazolyl-	250	76	Acetonitrile	$C_{16}H_{12}F_3N_3O_2S_2$	48.1	3.0	10.5	16.1	14.3	
								48.3	3.1	10.3	15.9	14.5	

[a] Isolated yields, no efforts were made to optimise these yields. [b] Used base sodium hydride (refluxing DMF). [c] Used base potassium *t*-butoxide (refluxing THF).

hydrochloric acid" and "ethanol-sodium hydroxide" refer to 1 volume of aqueous *N* hydrochloric acid or sodium hydroxide diluted to 10 volume with 95% ethanol. Mass (sample temperature) low resolution peaks m/e are given in decreasing order of intensity. Only major and most significant peaks are shown. (M) refers to the molecular peak.

Anthranilic acid was purchased from commercial sources; substituted anthranilic acids were prepared according to previously published procedures [8].

Unless otherwise stated in Table 3, the base used in the cyclisation step was dimethylaminopyridine in tetrahydrofuran at room temperature.

2-Methyl-4-hydroxy-8-(trifluoromethyl)-*N*-(2-thiazolyl)-3-quinolinecarboxamide (**9**). Method A from Scheme 1.

To a solution of 6 g (0.02 mole) of **7** [9] in 100 ml of dry xylene was added 2 g (0.02 mole) of 2-aminothiazole and the solution was stirred at reflux for 44 hours. Additional amounts of 2 g (0.02 mole) of 2-aminothiazole were added after 6, 24 and 36 hours. The resulting suspension was cooled and filtered. Recrystallization from acetic acid gave 6.4 g (93%) of **9**, mp 270°; ir (chloroform): 3444 (NH), 1669 (C=O), 1630 cm^{-1}; pmr (DMSO-d_6): 2.93 (s, CH_3, 3H), 7.26 (d, H_5 thiazole, 1H, J = 4), 7.53 (d, H_4 thiazole, 1H, J = 4), 7.63 (t, H_6 quinoline, 1H, J = 8), 8.57, 8.19 (2d, b H_5 and H_7 quinoline, 2H, J = 8).

Anal. Calcd. for $C_{15}H_{10}F_3N_3O_2S$: C, 51.0; H, 2.8; N, 11.9; F, 16.13; S, 9.07. Found: C, 50.7; H, 2.8; N, 11.6; F, 16.4; S, 9.4.

2-(Dichloromethyl)-4-hydroxy-8-(trifluoromethyl)-*N*-(2-thiazolyl)-3-quinolinecarboxamide (**79**). Method A from Scheme 1.

2-(Dichloromethyl)-4-hydroxy-8-(trifluoromethyl)-3-quinolinecarboxylic Acid Ethyl Ester (**8**).

A mixture of 47.9 g (0.16 mole) of **7**, 51.2 g (0.384 mole) of *N*-chlorosuccinimide and 2.4 g of 2,2' azabisisobutyronitrile in 1600 ml of carbon tetrachloride was refluxed for 24 hours. The precipitate was filtered and the solvent removed under reduced pressure. The crude product was dissolved in 300 ml of diethyl ether, washed with saturated sodium hydrogen carbonate solution and water. After drying over magnesium sulfate, the solution was filtered, concentrated and the residue was chromatographed on a silica gel column using 50% methylene chloride/petroleum ether as eluent, yield 42 g (71%) of **8**, mp 88°; ir (chloroform): 3402 (OH chelated, NH), 1663 cm^{-1} (C=O); pmr (deuteriochloroform): 1.53 (t, CH_3, 3H, J = 7), 4.62 (q, CH_2, 2H, J = 7), 7.65 (t, H_6, 1H, J = 8), 8.21, 8.54 (2 d,b, H_5, H_7, 2H, J = 8), 7.72 (s, $CHCl_2$, 1H), 13.2 (s,b, 1H, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{10}Cl_2F_3NO_3$: C, 45.7; H, 2.7; N, 3.8; Cl, 19.3; F, 15.5. Found: C, 45.7; H, 2.8; N, 3.8; Cl, 19.0; F, 15.2.

2-(Dichloromethyl)-4-hydroxy-8-(trifluoromethyl-*N*-(2-thiazolyl)-3-quinolinecarboxamide (**79**).

To a solution of 2.2 g (0.022 mole) of 2-aminothiazole in 40 ml of dry methylene chloride, 10 ml of a 25% solution of tri-isobutylaluminium in hexane and 2.5 ml of methylene chloride were added dropwise at 10°. The residual solution was stirred at this temperature for 30 minutes and 1.62 g (0.0044 mole) of **8** was added. The mixture was then refluxed for 18 hours. The solvent was removed under reduced pressure and the residue was triturated with 50 ml of *N* hydrochloric acid for 30 minutes. The insoluble material was collected, washed with 10 ml of *N* hydrochloric acid and water, dissolved in 50 ml of *N* sodium hydroxide solution and then the solution was filtered and acidified to *p*H = 4 with concentrated hydrochloric acid. The resulting precipitate was filtered, dried and recrystallized from ethyl acetate to yield 0.785 g (42%) of yellow crystals, mp 204°; ir (chloroform): 3390 (NH), 1658 (C=O), 1532, 1485 cm^{-1}; pmr (DMSO-d_6): 7.37 (d, H_5 thiazole, 1H, J ~ 4), 7.73 (d, H_4 thiazole, 1H, J ~ 4), 7.70 (t, H_6 quinoline, 1H, J ~ 8), 8.23, 8.57 (2d,b, H_5, H_7 quinoline, 1H, J ~ 8), 8.72 (s, $CHCl_2$, 1H).

Anal. Calcd. for $C_{15}H_8Cl_2F_3N_3O_2S$: C, 42.7; H, 1.9; N, 9.9; Cl, 16.8; F, 13.5; S, 7.6. Found: C, 42.7; H, 1.9; N, 9.8; Cl, 16.6; F, 13.8; S, 7.6.

Method B from Scheme 2.

2-(Dichloromethyl)-8-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one (**33**).

A suspension of 17.4 g (0.085 mole) of 3-trifluoromethyl anthranilic acid (**10**) in 22 ml of dichloroacetyl chloride was gradually heated to 127° and stirred at this temperature for 0.75 hour. After cooling, the insoluble material was filtered, washed with diethyl ether and 10 ml of methyl alcohol to give 23.8 g (94%) of crystals, mp 179°.

An analytical sample was crystallized from methyl alcohol, mp 179°; ir (chloroform): 1791, 1648 (C=N), 1777 (C=O), 1150 cm^{-1} (CF_3); pmr (deuteriochloroform): 6.51 (s, $CHCl_2$, 1H), 7.6-8.6 (m aromatic, 3H).

Anal. Calcd. for $C_{10}H_4Cl_2F_3NO_2$: C, 40.3; H, 1.3; N, 4.7; Cl, 23.8; F, 19.1. Found: C, 40.2; H, 1.3; N, 4.5; Cl 23.8; F, 19.3.

2-(Dichloroacetylamino)-β-oxo-*N*-[2-(thiazolyl)]-3-(trifluoromethyl)benzenepropanamide (**55**).

To a solution of 8.65 g (0.06 mole) of *N*-(2-thiazolyl)acetamide (**11**) in 300 ml of dry tetrahydrofuran (at 0°) was slowly added 90 ml of a 15% solution of butyllithium in hexane (0.12 mole). The solution was stirred for 20 minutes at this temperature. After cooling to -70°, a solution of 9.1 g (0.03 mole) of **33** in 95 ml of tetrahydrofuran was added dropwise and the resulting mixture was stirred at -70° for an hour. After quenching with 450 ml of water and 1.2 ml of concentrated hydrochloric acid, the aqueous mixture was extracted with ethyl acetate. The organic phases were evaporated under reduced pressure and the residue washed with 100 ml of methylene chloride to give 8.50 g (64%) of crystallized **55** mp 223°. An analytical sample was crystallized from ethyl alcohol, mp 224°; ir (nujol): 3320 (OH, NH), 1694 cm^{-1} (C=O); pmr (DMSO-d_6): 6.72 (s, $CHCl_2$, 1H), 7.2-8.3 (m, aromatic, 5H), 4.21 (s, CH_2 of keto tautomer), 5.75 (S, CH of enol tautomer).

Anal. Calcd. for $C_{15}H_{10}Cl_2F_3N_3O_3S$: C, 40.8; H, 2.3; N, 9.5; Cl, 16.1; S, 7.3. Found: C, 41.1; H, 2.4; N, 9.4; Cl, 16.0; S, 7.4.

2-(Dichloromethyl)-4-hydroxy-8-(trifluoromethyl)-*N*-(2-thiazolyl)-3-quinolinecarboxamide (**79**).

To a solution of 7.5 g (0.017 mole) of **55** in 150 ml of tetrahydrofuran, was added 2.08 g (0.017 mole) of 4-*N*-dimethylaminopyridine. After stirring the yellow solution for 15 minutes, the solvent was removed under reduced pressure and the residue acidified by 100 ml of water and 17 ml of *N* hydrochloric acid and the mixture stirred for 1.5 hours. The resulting precipitate was filtered, washed with water and dried. The crude product was recrystallized from ethyl acetate to give 6.15 g (86%) of yellow crystals, mp 204° **79**.

This sample is identical with **79** prepared by method A.

2-(Chloromethyl)-8-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one (**31**).

This compound was prepared as for **33** using 6.15 g (0.03 mole) of 2-amino-3-trifluoromethylbenzoic acid and 6.3 ml (0.08 mole) of chloroacetyl chloride to yield 7.4 g (94%) of yellow crystals of **31**, mp 74-76°. An analytical sample was crystallized from petroleum ether, mp 76-78°; ir (chloroform): 1772 (C=O), 1650 cm^{-1} (C=N).

Anal. Calcd. for $C_{10}H_5ClF_3NO_2$: C, 45.6; H, 1.9; Cl, 13.5; F, 21.6; N, 5.3. Found: C, 45.6; H, 1.9; Cl, 13.7; F, 21.8; N, 5.3.

2-(Chloroacetylamino)-β-oxo-*N*-(2-thiazolyl)-3-(trifluoromethyl)benzenepropanamide (**53**).

To a solution of 4.26 g (0.03 mole) of 2-(*N*-thiazolylacetamide) in 150 ml of dry tetrahydrofuran was added (at 0°) 37 ml of a 15% solution of butyllithium in hexane. After stirring for 20 minutes and cooling to -70°, a solution of 4 g (0.015 mole) of **31** in 40 ml of tetrahydrofuran was added dropwise. After a further 15 minutes, the mixture was poured on to 300 g of ice, acidified with *N* hydrochloric acid (*p*H = 4.5) and extracted with diethyl ether. Removal of the solvent under reduced pressure yielded 7.8 g of a mixture of products (tlc). This residue was chromatographed on a column of silical gel using 50% ethyl acetate/cyclohexane.

The first fraction gave 1.5 g (24%) of **14**. An analytical sample was crystallized from acetonitrile, mp 236-238°; pmr (DMSO-d_6): 3.35 (s, CH_2CO, 2H), 4.22 (s, CH_2Cl, 2H), 7.10 (t, H_6 quinoline, 1H, J = 8), 7.93, 8.16 (2d, H_5 and H_7 quinoline, 2H, J = 8), 7.30, 7.57 (2d, H_4 and H_5 thiazole, J = 4); ir (nujol): 3370 (NH), 1732, 1670 cm^{-1} (C=O); cmr 89.7 (C_2), 111.9 (C_{4a}), 134.3 (C_5), 118.4 (C_6), 133.2 (C_7), 114.1 (C_8J_{CF} = 31), 142.2 (C_{8a}), 123.5 (CF_3, J_{CF} = 272), 157.3, 137.5, 113.7 (C_2, C_4, C_5 thiazole), 41.3 (CH_2Cl), 47.5 (CH_2CO), 159.8 and 165.7 (C=O); ms (150): 356, 244, 100, 142, 127, 264, 270, 246, 250, 360, 256, 405 (M); uv (ethanol-hydrochloric acid): 227 (23000), 265 (14500), 339 (4200).

Anal. Calcd. for $C_{15}H_{11}ClF_3N_3O_3S$: C, 44.4; H, 2.7; N, 10.4; Cl, 8.7; S, 7.9. Found: C, 44.5; H, 2.8; N, 10.4; Cl, 8.9; S, 7.9.

The second fraction gave 1 g (16%) of **53** mp 192-194°; pmr (DMSO-d_6): 4.3 (s, CH_2, 2H), 5.77 (s, enol, 1H), 7.2-8.2 (m aromatics, 5H); ir (nujol): 1635, 1670 cm^{-1} (C=O); ms (160): 351, 100, 244, 127, 230, 182, 264, 405 (M); uv (ethanol-hydrochloric acid): 272 (9500), 312 (2000).

Anal. Calcd. for $C_{15}H_{11}ClF_3N_3O_3S$: C, 44.4; H, 2.7; N, 10.4; Cl, 8.7; S, 7.9. Found: C, 44.8; H, 2.7; N, 10.2; Cl, 8.9; S, 8.2.

2-(Chloromethyl)-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (**77**).

The product was prepared as for **79** using 0.405 g of **53** and 0.122 g of dimethylaminopyridine to yield 0.247 g (64%) of **77**, mp, 218°; ir (nujol): 1660, 1649 cm^{-1} (C=O); pmr (DMSO-d_6): 5.51 (s, CH_2Cl, 2H), 7.34 (d, H_5 thiazole, 1H, J = 4), 7.65 (d, H_4 thiazole, 1H, J = 4), 7.73 (t, H_6 quinoline, 1H, J = 8), 8.29-8.65 (2d,b, H_5 and H_7 quinoline, 2H, J = 8).

Anal. Calcd. for $C_{15}H_9ClF_3N_3O_2S$: C, 46.5; H, 2.3; N, 10.8; Cl, 9.1; S, 8.3. Found: C, 46.3; H, 2.4; N, 10.6; Cl, 9.4; S, 8.4.

2-Ethenyl-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (**74**).

To a suspension of 0.144 g (0.003 mole) of sodium hydride (50% oil dispersion) in 7.5 ml of dimethylformamide was slowly added 1.15 g (0.003 mole) of **50** (prepared as for **55**) in 12 ml of dimethylformamide. The reaction was brought to reflux. After cooling, the mixture was poured into water and acidified with *N* hydrochloric acid (*p*H = 4.5). The precipitate was filtered and crystallized from acetonitrile to yield 0.604 g (55%) of **74**, mp 236°; pmr (DMSO-d_6): 5.7-6.4 (m, CH_2=, 2H), 7.3-7.8 (m, CH=, 1H), 7.35 (d, H_5 thiazole, 1H, J = 4), 7.63 (d, H_4 thiazole, 1H, J = 4), 8.22, 8.65 (2d,b, H_5 H_7 quinoline, J = 8), 7.66 (t, H_6 quinoline, J = 8).

Anal. Calcd. for $C_{16}H_{10}F_3N_3O_2S$: C, 52.6; H, 2.8; N, 11.5; F, 15.6; S, 8.8. Found: C, 52.7; H, 2.8; N, 11.8; F, 15.2; S, 8.6.

N-[1,4-Dihydro 1-[2-[4-hydroxy 3-[(2-thiazolylamino)carbonyl]-8-(trifluoromethyl)-2-quinolinyl]ethyl]-4-pyridinylidene]-*N*-methylmethanaminium Hydroxide Inner Salt (**15**).

To a solution of 4.1 g (0.0107 mole) of **50** in 100 ml of tetrahydrofuran was added 1.3 g (0.0107 mole) of 4-*N*-dimethylamino pyridine. After stirring for 4 hours, and concentrating the solution to 300 ml, the precipitate was filtered and crystallized from 200 ml of ethyl alcohol to yield 4.8 g (63%) of **15**, mp 252°; pmr (DMSO-d_6): 3.10 (s, N-$(CH_3)_2$, 6H), 3.88 (t, CH_2, 2H, J = 6), 4.72 (t, CH_2, 2H, J = 6), 7.08 (d, H_5 thiazole, J = 4), 7.45 (d, H_4 thiazole, 1H, J = 4), 7.33 (t, H_8 quinoline, 1H, J = 8), 7.91-8.50 (2 d,b, H_5 and H_7 quinoline, 2H, J = 8), 6.8-8.4 (m pyridine 4H); uv (ethanol and ethanol-sodium hydroxide): 290 (44500), 326 (15500), 332 (15500), 349 (11200); (ethanol-hydrochloric acid): 295 (40500), 327 (15500), ms (240): 266, 246, 121, 122, 281, 365 (M).

Anal. Calcd. for $C_{23}H_{20}F_3N_5O_2S$: C, 56.7; H, 4.1; N, 14.4; F, 11.7; S, 6.6. Found: C, 56.6; H, 4.1; N, 14.3; F, 11.6; S, 6.6.

4-Hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-2-(2-(trifluoromethyl)-phenyl)-3-quinolinecarboxamide (**76**).

To a stirred suspension of 0.912 g (0.02 mole) of sodium hydride (50% oil dispersion) in 45 ml of dimethylformamide was added a solution of **52** (prepared as for **55**) in the same solvent. The yellow solution was refluxed for two hours and after cooling poured into 250 ml of water and acidified with *N* hydrochloric acid (*p*H = 4). The precipitate was collected and recrystallized twice from acetonitrile to give 3.3 g (30%) of white crystals of **76**, mp 275°; pmr (DMSO-d_6): 7.23 (d, H_5 thiazole, 1H, J = 4), 7.60 (d, H_4 thiazole, 1H, J = 4), 8.36, 8.80 (2 d,b H_5, H_7 quinoline, J = 8), 7.6-8.0 (m, aromatic, 5H); ms: (160) 384, 364, 483 (M), 357, 309, 385, 288, 239.

Anal. Calcd. for $C_{21}H_{11}F_6N_3O_2S$: C, 52.2; H, 2.3; N, 8.7; F, 23.6; S, 6.6. Found: C, 51.9; H, 2.2; N, 8.8; F, 23.6; S, 6.8.

The mother liquors were evaporated and the residue was chromatographed on a column of silica gel using ethyl acetate as solvent to yield **20** (18%) mp 116°; pmr (deuteriochloroform): 6.38 (s, H_3 quinoline, 1H), 8.62 (d, H_7 quinoline, 1H, J ~ 8), 7.3-8.0 (m, aromatic, 6H), 8.4 (s, b, exchangeable deuterium oxide); ms: (120) 357 (M), 309, 290, 356 (M + H), 308, 310, 337, 338.

Anal. Cacld. for $C_{17}H_9F_6NO$: C, 57.1; H, 2.5; N, 3.9; F, 31.9. Found: C, 57.0; H, 2.5; N, 3.9; F, 31.8.

2-(1,1-Dimethylethyl)-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (**75**).

Compounds **75** and **19** were prepared following the same procedure as for **76** and **20** using 3.1 g (0.075 mole) of **51** in 10 ml of dimethylformamide with 0.36 g of sodium hydride dispersion. The crude product was purified by chromatography to yield 0.4 g of **75** (14%), mp, 222° and 0.3 g of **19** (15%), mp 125°.

Compound **75** pmr (DMSO-d_6): 1.42 (s, *t*-Bu, 9H), 7.38 (d, H_5 thiazole, 1H, J ~ 4), 7.63 (d, H_4 thiazole, J = 4), 7.77 (t, H_6 quinoline, 1H, J = 8), 8.27, 8.68 (2 d, b, H_5, H_7 quinoline, 2H, J = 8).

Anal. Calcd. for $C_{18}H_{16}F_3N_3O_2S$: C, 54.7; H, 4.1; N, 10.8; F, 14.4; S, 8.1. Found: C, 54.6; H, 4.1; N, 10.5; F, 14.5; S, 8.2.

Compound **19** had pmr (deuteriochloroform): 1.43 (s, *t*-Bu, 9H), 6.47 (d, exchangeable deuterium oxide, s, H_3, 1H, J ~ 1.5), 7.47 (t, H_6 quinoline, 1H, J = 8), 7.76-8.68 (2 d, b, H_5, H_7, 2H, J = 8), ms: (50), 269 (M), 254, 234, 227, 206, 207.

2-(1-Chloroethyl)-4-hydroxy-*N*-(2-thiazolyl)-8-(trifluoromethyl)-3-quinolinecarboxamide (**86**).

This compound was prepared as for **79** with an 81% yield using 1.5 g (0.036 mole) of **62** in 21 ml of tetrahydrofuran and 0.439 g of 4-dimethylaminopyridine at room temperature, mp 192°; pmr (DMSO-d_6): 6.61 (q, CHCl, 1H, J = 6.5), 1.93 (d, CH_3, 3H, J = 6.5), 7.67 (d, H_4 thiazole, 1H, J = 4), 7.32 (d, H_5 thiazole, 1H, J = 4), 7.70 (t, H_6 quinoline, 1H, J = 8), 8.62-8.23 (2 d, b, H_5 and H_7 quinoline, 2H, J = 8).

Anal. Calcd. for $C_{16}H_{11}ClF_3N_3O_2S$: C, 47.8; H, 2.8; N, 10.5; Cl, 8.8; S, 8.0. Found: C, 47.6; H, 2.8; N, 10.4; Cl, 8.9; S, 8.1.

1,3-Dihydro-3-methyl-1-((2-thiazolyl)imino)-5-(trifluoromethyl)-furo[3,4-*b*]-quinolin-9-ol (**24**).

A solution of 5 g (0.012 mole) of **62** and 1.46 g (0.012 mole) of 4-dimethylaminopyridine in 70 ml of dry tetrahydrofuran was refluxed for an hour. The resulting precipitate was filtered and stirred for 45 minutes in 70 ml of water and 12 ml of *N* hydrochloric acid. The yellow crystals were collected to give 2.36 g (54%) of **24**, mp 260°. The product was dissolved in dimethylformamide and precipitated by ethyl ether to give an analytically pure sample, mp 260°; nmr (DMSO-d_6): 1.72 (d, CH_3, J = 7), 5.95 (q, CH, J = 7), 7.62 (d, H_5, thiazole, J = 3.5), 7.32 (d, H_4 thiazole, J = 3.5), 7.4, 8.7 (m aromatic 3H); uv (ethanol-hydrochloric acid): 319 (21000), 352 (32000), 363 (24500); (ethanol-sodium hydroxide): 270 (8000), 304 (25500), 317 (27500), 365 (24000), 381 (20000); ms: (150), 365 (M), 266, 286, 100, 366 (M + H), 218, 350.

Anal. Calcd. for $C_{16}H_{10}F_3N_3O_2S$: C, 52.6; H, 2.8; N, 11.5; F, 15.6; S, 8.8. Found: C, 52.1; H, 2.8; N, 11.5; F, 15.4; S, 8.7.

Acknowledgement.

The authors wish to thank N. Moine for the microanalysis and V. Delaroff, R. Smolik, B. Khemis, C. Lang, J. Fabian, N. Dupuy and D. Jovanovic for running and interpreting spectra; C. Fromentin for very able technical assistance and E. Bricard for her help in the preparation of this manuscript.

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