# Synthesis of Aminoquinolone Derivatives



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The synthesis of 3-amino-7-chloro-1-ethyl-6-fluoro-4(1*H*)-quinolinone derivatives is described. These were investigated for their antibacterial activity.

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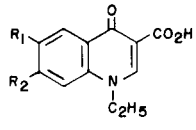
## Discussion.

There has been considerable interest for a number of years in 6,7-disubstituted-1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **1** and their derivatives as potential antibacterial agents [1]. However, little has been reported to date on the synthesis and activity of the 3-amino derivatives **2**.



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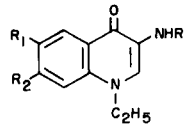


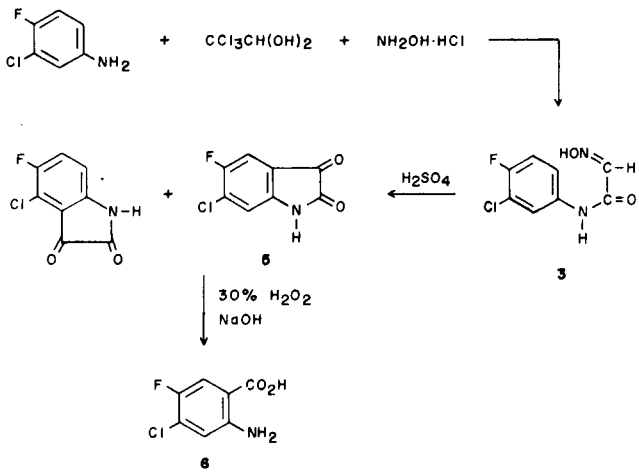
2

$R_1$ = F
$R_2$ = Cl

Our initial synthetic approach to the desired compounds **2** was *via* an analogous method used to prepare 3-nitro-4-hydroxyquinoline [2].

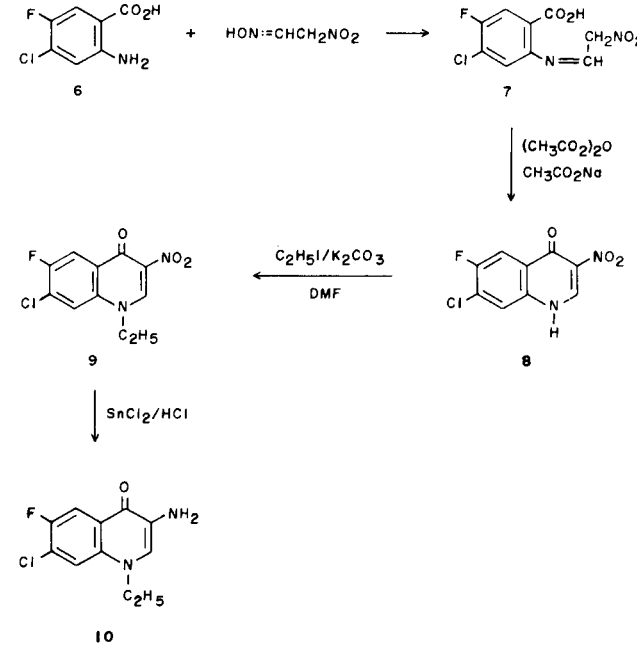
2-Amino-4-chloro-5-fluorobenzoic acid **6** (Scheme I) was obtained by reacting 3-chloro-4-fluoroaniline with chloral hydrate and hydroxylamine to the corresponding isonitrosoacetanilide **3** (Scheme I) in 75% yield [3]. Cyclization of **3** in 98% sulfuric acid gave a mixture of **4** and **5** in a ratio of 30:60. Interestingly, it was observed that oxidation [4] of the mixture with 30% hydrogen-peroxide in 2.5*N* sodium hydroxide at 80-90° followed by careful acidification results in the isolation of **6** from **5** in the mixture (Scheme I) in almost quantitative yield. The anthranilic acid derived from **4** probably remains in the filtrate and was not isolated. The nmr and mass spectra were consistent with the proposed structure of **6**.

Scheme I



The synthesis of **8** (Scheme II) was achieved by the standard literature process [2]. Ethylation of **8** by treatment with ethyl iodide and anhydrous potassium carbonate in DMF gave the 7-chloro-1-ethyl-6-fluoro-3-nitro-4(1*H*)-quinolinone **9** in 80% yield. Reduction of **9** (Scheme II) with stannous chloride in hydrochloric acid yielded the amine **10** in 90% yield.

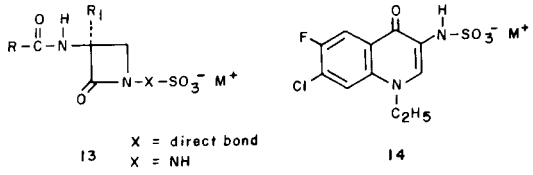
Scheme II



The amine **10** was reacted with methanesulfonylchloride and chloralhydrate to yield **11** and **12**, respectively, (Scheme III).

Monobactams and homoazamonobactams **13** have been reported to exhibit interesting antibacterial activity where by the carboxylate group of the classical β-lactam is

replaced by a sulfonic acid moiety [5]. We attempted to extend the utility of this functionality to aminoquinolinone **10** to obtain **14** and investigate the antibacterial activity.

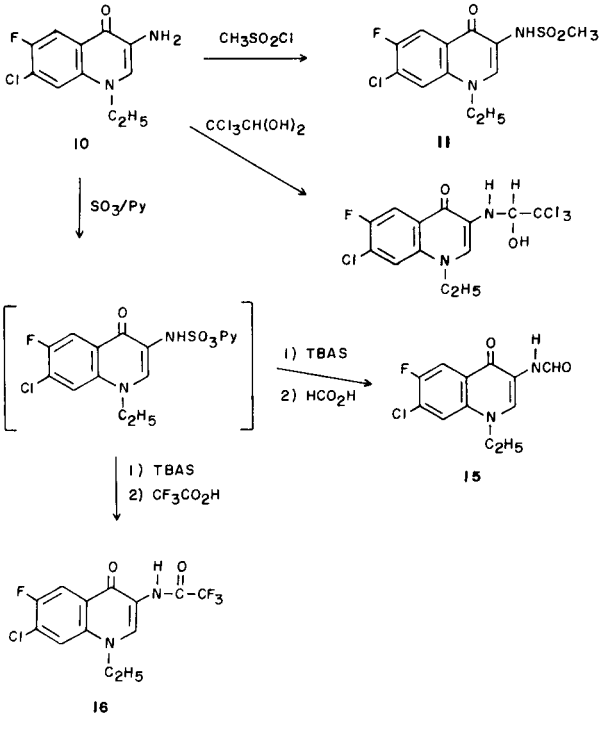


13 X = direct bond, X = NH



14

Scheme III



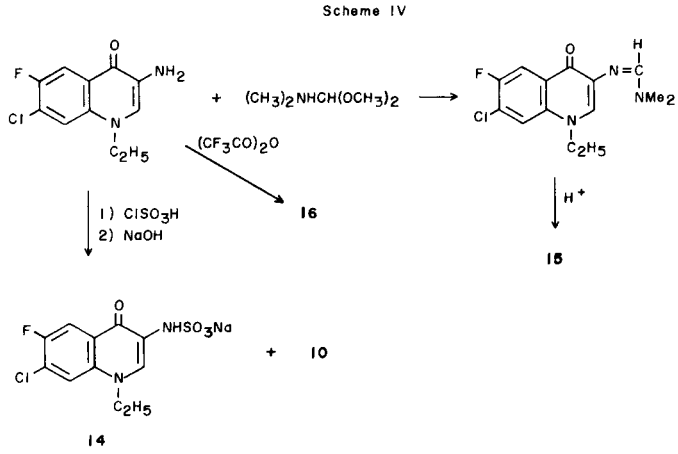
Consequently, **10** was reacted with pyridine-sulfur trioxide complex in DMF [6], but instead of **14** the formamide **15** (Scheme III) was obtained in 75% yield. The use of trifluoroacetic acid for protonation yielded corresponding trifluoroacetamide **16**, also in 75% yield.

The structures of **15** and **16** were confirmed by alternate synthesis (Scheme IV).

The reaction of **10** with chlorosulfonic acid yielded **14** (Scheme IV) in 30% yields along with the starting amine. The infrared spectrum of **14** showed strong $SO_2$ absorption at 1225 $cm^{-1}$ and at 800 $cm^{-1}$. The nmr was also consistent with the proposed structure.

The fast atom bombardment (FAB) mass spectra are also consistent with the assignment for structure **14**. Sodium and proton adduct molecular ions of **14** were observed. The exact mass data for the former ion confirms the elemental composition for **14**. Under the FAB ex-

Scheme IV



perimental conditions, the $Na^+$ of **14** is exchanged with protons from the FAB matrix to produce the proton adduct ion of the sulfamic acid form of **14**. This assignment was confirmed by exact mass FAB measurements. Also observed were ions assigned to the sodium and proton adducts of **10**. It is not possible to experimentally differentiate by FAB MS the latter three decomposition ions from impurities present in the sample. However, microanalysis confirms the fact that these ions arose as FAB decomposition ions. The exchange of $[NaSO_3]^+$ with protons is a common FAB decomposition process observed in the FAB mass spectra of monobactams [7], sulfated carbohydrates [8] and sulfonated azo dyes. [9].

The above compounds did not exhibit any promising antibacterial activity.

## EXPERIMENTAL

All melting points were taken on Mel-Temp apparatus, and are not corrected. Samples for elemental analysis were dried over phosphorus pentoxide under high vacuum for two hours. Infrared spectra were measured on a Perkin-Elmer model spectrophotometer (Model 217). The nmr spectra were determined with a Varian Model FT-80 spectrometer. Chemical shifts are in ppm relative to internal tetramethylsilane. Electron impact (EI) mass spectra were recorded on a Finnegan-MAT CH-7. Low resolution fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS-50 and exact mass FAB data were obtained on a VG ZAB-HF equipped with an articulated FAB probe. FAB matricies used were thioglycerol and dithiothreitol/dithioeritritol (5:1 w:w).

*N*-(3-Chloro-4-fluorophenyl)-2-(hydroxyimino)acetamide **3**.

It was prepared according to the method of Yen and Buu-Hoi [3] with some modifications.

A solution of 4-fluoro-3-chloroaniline (18 g, 0.12 mole) in concentrated hydrochloric acid (30 ml) was stirred for 12 hours. Hydroxylamine hydrochloride (22 g, 0.32 mole) in water (150 ml) was added into the above solution of the hydrochloride. This was added to a solution of chloral hydrate (18 g, 0.11 mole) and sodium sulfate decahydrate (260 g, 0.81 mole) in 200 ml of water at 90-95° over 20 minutes. The mixture was refluxed for three hours. The solid obtained after cooling was recrystallized from water to yield 20 g (75%) of **3**, mp 175-180°; ir (potassium bromide): $\nu$ max 3400, 3000, 2800, 1680, 1500, 820, 700 $cm^{-1}$; $^1H$ nmr (DMSO-$d_6$): $\delta$ 12.24 (s, 1H), 10.4 (s, 1H), 7-7.3 (m, arH, 2H); ms:

216 ($m^+$).

*Anal.* Calcd. for $C_8H_6ClFN_2O_2$: C, 44.34; H, 2.77; N, 12.93; Cl, 16.49; F, 8.77. Found: C, 44.47; H, 2.76; N, 12.86; Cl, 16.49; F, 8.78.

6-Chloro-5-fluoro-1*H*-indole-2,3-dione **5**.

It was prepared according to the method of Yen and Buu-Hoi [3]. The isonitroso compound (21.6 g, 0.10 mole) was added portion-wise and with stirring, to sulfuric acid (75 ml), the temperature being kept at 60-70°, then raised to 80° for 60 minutes. On cooling the reaction, product was poured on crushed ice and the yellow precipitate of the mixture of **4** and **5** was collected. The solids were purified by chromatography on silica gel using chloroform:methanol mixture (9:1) when **4** eluted to yield 5.5 g (30%), followed by **5** 11.5 g (63%); $^1$H nmr (DMSO-$d_6$): for **4** $\delta$ 11.14 (broad, 1H, NH), 7.8 (m, arH-6, 1H), 7.4 (m, arH-7, 1H); mp 202-205, ms: 199 ($M^+$); $^1$H nmr (DMSO-$d_6$): for **5** $\delta$ 11.14 (s, 1H, NH), 7.82 (d, arH-4, 1H, $J_{HF}$ = 8 Hz), 7.52 (d, arH-7, 1H, $J_{HF}$ = 6 Hz); ms: 199 ($M^+$); mp 260-265°.

*Anal.* Calcd. for **5** $C_8H_3ClFNO_2$: C, 48.12; H, 1.5; N, 7.0; Cl, 17.8; F, 9.52. Found: C, 48.06; H, 1.54; N, 6.89; Cl, 17.76; F, 9.35.

2-Amino-4-chloro-5-fluorobenzoic Acid **6** [4].

A solution of **4** and **5** (20 g, 0.10 mole) in 2.5 *N*-sodium hydroxide (175 ml) was treated drop-wise with 30% hydrogen peroxide (30 ml), warmed to 80-90° for two hours and filtered. The acid precipitated by concentrated hydrochloric acid, was filtered, redissolved in 2.5*N* sodium hydroxide (100 ml) and re-acidified with concentrated hydrochloric acid to *p*H-4 at 15-20° to yield 10 g (84%) of **6**. The solid was recrystallized from xylene in quantitative yield, mp 225-230°; ir (potassium bromide): $\nu$ max 3400, 3500, 1700, 1580, 1300, 800 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 9 (brd, N-H), 7.5 (d, arH-6, 1H, $J_{HF}$ = 8 Hz), 7 (d, arH-3, 1H, $J_{HF}$ = 6 Hz); ms: 189 ($M^+$).

*Anal.* Calcd. for $C_7H_5ClFNO_2$: C, 44.32; H, 2.64; N, 7.4; Cl, 18.73; F, 10.02. Found: C, 44.32; H, 2.42; N, 7.41; Cl, 18.43; F, 9.82.

4-Chloro-5-fluoro-2-[(2-nitroethylidene)amino]benzoic Acid **7**.

It was prepared according to the method of Bachman and Welton [2], crystallized from ethanol as bright yellow needles in 75% yield, mp 215-220°; ir (potassium bromide): $\nu$ max 3200, 1700, 1600, 1500, 1200, 800 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 7 (d, 2H, -$CH_2$), 7.8 (t, 1H, -CH), 8.2 (d, arH-3, 1H, $J_{HF}$ = 6.2 Hz), 8.5 (d, arH-6, 1H, $J_{Hf}$ = 8 Hz), ms: 260 ($M^+$).

*Anal.* Calcd. for $C_9H_6ClFN_2O_4$: C, 41.45; H, 2.3; N, 10.74; F, 7.3; Cl, 13.62. Found: C, 41.72; H, 2.35; N, 10.78; F, 7.13; Cl, 13.52.

7-Chloro-6-fluoro-3-nitro-4(1*H*)-quinolinone **8**.

It was prepared by the method of Bachman and Welton [2]. Crystallized from DMF as white needles in 50% yield, mp >300°; ir (potassium bromide): $\nu$ max 3100, 1640, 1500, 1300, 780 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 9.5 (s, 1H), 8.3 (d, arH-5, 1H, $J_{HF}$ = 8 Hz), 8.1 (d, arH-8, 1H, $J_{HF}$ = 6 Hz); ms: 242 ($M^+$).

*Anal.* Calcd. for $C_9H_4ClFN_2O_3$: C, 44.55; H, 1.65; N, 11.50; Cl, 14.6; F, 7.83. Found: C, 44.44; H, 1.71; N, 11.31; Cl, 14.52; F, 7.63.

7-Chloro-1-ethyl-6-fluoro-3-nitro-4(1*H*)-quinolinone **9**.

A mixture of **8** (4 g, 0.016 mole), potassium carbonate (6.46 g, 0.047 mole), ethyl iodide (7 ml, 0.087 mole) and DMF (25 ml) was heated at 80-90° with stirring for 14 hours. The mixture was evaporated to dryness, washed with water and filtered. Recrystallization from DMF yielded brown prisms in 90% yield, mp 280-285°; ir (potassium bromide): $\nu$ max 1640, 1500, 1300, 800 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 9.2 (s, 1H), 8.4 (d, arH-5, 1H, $J_{HF}$ = 8 Hz), 8.2 (d, arH-8, 1H, $J_{HF}$ = 6.3 Hz), 4.2 (q, 2H-$CH_2$), 1.2 (t, 3H, -$CH_3$); ms: 270 ($M^+$).

*Anal.* Calcd. for $C_{11}H_8ClFN_2O_3$: C, 48.88; H, 2.96; N, 10.37; F, 7.03; Cl, 13.14. Found: C, 48.86; H, 2.94; N, 10.34; F, 7.03; Cl, 13.10.

3-Amino-7-chloro-1-ethyl-6-fluoro-4(1*H*)-quinolinone **10**.

To a solution of stannous chloride (2.5 g, 0.011 mole) in concentrated hydrochloric acid (25 ml) at 90-95° was added **9** (1 g, 0.0037 mole) and heated for 3 hours. The reaction mixture was cooled to 5-10°, basified to *p*H-14 with 20% sodium hydroxide solution. The solid obtained was filtered and recrystallized from benzene to yield 0.87 g (97%) of **10**, mp 160-165°; ir (potassium bromide): $\nu$ max 3400, 3300, 1580, 1360, 1210, 900 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 8.2 (d, arH-5, 1H, $J_{HF}$ = 8 Hz); 8 (d, arH-8, 1H, $J_{HF}$ = 6 Hz), 7.7 (s, 1H), 4.2 (q, 2H, $CH_2$), 1.2 (t, 3H, -$CH_3$); ms: 240 ($M^+$).

*Anal.* Calcd. for $C_{11}H_{10}ClFN_2O$: C, 54.88; H, 4.15; N, 11.6; F, 7.9; Cl, 14.8. Found: C, 54.80; H, 4.10; N, 11.52; F, 7.86; Cl, 14.74.

*N*-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl)methanesulfonamide **11**.

A mixture of **10** (0.250 g, 0.001 mole), methanesulfonyl chloride (0.09 ml, 0.0012 mole) triethylamine (0.11 ml, 0.001 mole) and benzene (10 ml) was heated on a steam bath for six hours. The solid obtained was filtered and recrystallized from DMF to yield **11**, 0.3 g (90%), mp >300°; ir (potassium bromide): $\nu$ max 3200, 1580, 1420, 1360, 1000 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): $\delta$ 8.7 (br, s, N-H), 8.2 (d, arH-5, 1H, $J_{HF}$ = 8 Hz), 8 (d, arH-8, 1H, $J_{HF}$ = 6 Hz), 7.6 (s, 1H), 4.2 (q, 2H, $CH_2$), 2.8 (s, 3H, $CH_3$), 1.2 (t, 3H, -$CH_3$); ms: 318 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{12}ClFO_3N_2S$: C, 45.2; H, 3.8; N, 8.8; S, 10.04; F, 5.96; Cl, 11.16. Found: C, 45.1; H, 3.7; N, 8.6; S, 10.00; F, 5.82; Cl, 11.08.

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-3[(2,2,2-trichloro-1-hydroxyethyl)-amino]-4(1*H*)-quinolinone **12**.

A mixture of **10** (0.1 g, 0.00042 mole), chloralhydrate (0.08 g, 0.00048 mole) and benzene was heated on a steam bath for fourteen hours. The solvent was evaporated and the residue crystallized from DMF to yield **12** 0.13 g (81%), mp >300°; ir (potassium bromide): $\nu$ max 1640, 1600, 1260, 820, 780 $cm^{-1}$; $^1$H nmr (deuteriotrifluoroacetic acid): $\delta$ 8.2 (d, arH-5, 1H), 7.9 (d, arH-8, 1H), 7.6 (s, 1H), 4.7 (s, CH), 4.2 (q, 2H, $CH_2$), 1.2 (t, 3H, $CH_3$).

*Anal.* Calcd. for $C_{13}H_{11}Cl_4FN_2O_2$: C, 40.20; H, 2.8; N, 7.21; Cl, 36.5; F, 4.9. Found: C, 40.6; H, 2.4; N, 7.31; Cl, 36.32; F, 5.02.

*N*-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl)formamide **15**.

To a solution of **10** (0.500 g, 0.002 mole) in DMF (10 ml) was added to sulfur trioxide-pyridine (0.86 g, 0.0054 mole). The mixture was stirred at room temperature for twenty hours and poured into water (20 ml) containing potassium hydrogen phosphate (1.4 g, 0.01 mole). To the aqueous layer was added tetrabutyl ammonium hydrogensulfate (0.9 g, 0.0026 mole) followed by extractions with methylene chloride (3 x 20 ml). The extract was dried (sodium sulfate) and evaporated to yield crude solid which was further used without any purification.

To the above residue was added 99% formic acid (5 ml) and allowed to stand in an ice box for twelve hours. Dilution with water yielded **15**, 0.380 g (68%) which was recrystallized from ethanol, mp 260-265°; ir (potassium bromide): $\nu$ max 3200, 1620, 1600, 1400, 1300, 1210, 1000, 800 $cm^{-1}$; $^1$H nmr (deuteriotrifluoroacetic acid): $\delta$ 9.2 (s, 1H), 8.5 (s, 1H), 8.33 (d, arH-5, 1H, J = 8 Hz), 8.22 (d, arH-8, 1H, J = 6 Hz), 4.2 (q, 2H, $CH_2$), 1.2 (t, 3H, $CH_3$); ms: 268 ($M^+$).

*Anal.* Calcd. for $C_{12}H_{10}ClFN_2O_2$: C, 53.73; H, 3.73; N, 10.45; Cl, 13.25, F, 7.0. Found: C, 53.65; H, 3.71; N, 10.42; Cl, 13.21; F, 6.94.

*N*-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl)-2,2,2-trifluoro acetamide **16**.

To the crude product obtained by the reaction of **10** (0.5 g, 0.002 mole) with sulfur trioxide-pyridine (0.86 g, 0.0054 mole) see above procedure), was added to trifluoroacetic acid (5 ml) and allowed to stand in an ice box for twelve hours. Dilution with water yielded **16**, 0.41 g (61%) which was recrystallized from DMF, mp >300°; ir (potassium bromide): $\nu$ max 3300, 1700, 1600, 1500, 1200, 900 $cm^{-1}$; $^1$H nmr (deuteriotrifluoroacetic acid): $\delta$ 10.5 (s, 1H), 8.26 (s, 1H), 8.1 (d, arH-5, 1H, $J_{HF}$ = 8 Hz), 8 (d, arH-8, 1H, $J_{HF}$ = 6 Hz), 4.2 (q, 2H, $CH_2$), 1.2 (t, 3H, $CH_3$).

*Anal.* Calcd. for $C_{13}H_9ClF_4N_2O_2$: C, 46.43; H, 2.68; N, 8.33; Cl, 10.56; F, 22.6. Found: C, 46.41; H, 2.62; N, 8.30; Cl, 10.51; F, 22.42.

A mixture of **10** (0.6 g, 0.0024 mole), chloroform (20 ml) and trifluoroacetic anhydride (0.34 ml, 0.0024 mole) was refluxed for four hours. The

solvent was evaporated, the residue extracted in water and neutralized to yield **16** in 80% yield.

*N'*-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl)-*N,N*-dimethylformimidamide **17**.

A mixture of **10** (0.15 g, 0.00062 mole) and *N,N*-dimethylformamide dimethyl acetal (3 ml, 0.025 mole) was heated on a steam bath for four hours. The solvent was evaporated and the residue recrystallized from benzene to yield **17**, 0.15 g (83%), mp 120-125°; $^1$H nmr (DMSO-$d_6$): δ 8.8 (s, 1H), 8.4 (d, arH-5, 1H, $J_{HF}$ = 8 Hz), 8.2 (d, arH-8, 1H, $J_{HF}$ = 6 Hz), 8 (s, 1H, -CH), 4.2 (q, 2H, -C*H*$_2$), 2.8 (d, -N, $(CH_3)_2$), 1.2 (t, 3H, $CH_3$); ms: 295 ($M^+$).

*Anal.* Calcd. for $C_{14}H_{15}ClFN_3O$: C, 56.8; H, 5.07; N, 14.21; Cl, 12.01; F, 6.42. Found: C, 56.6; H, 5.02; N, 14.10; 12.10; F, 6.22.

Hydrolysis of **17**.

A mixture of **17** (0.1 g, 0.00034 mole) in acetic acid (2 ml) was stirred at room temperature for three hours. Neutralized with 2% potassium hydroxide solution and the solid recrystallized from ethanol to yield **15** in quantitative yield.

(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl)sulfamic Acid Monosodium Salt **14**.

Chlorosulfonic acid (0.07 ml, 0.0011 mole) was added to a solution of **10** (0.6 g, 0.0025 mole) in chloroform (10 ml) at 0-5°. The reaction mixture was gradually raised to room temperature over two hours and stirred for twenty hours. The product that isolated was filtered, reslurried in water (15 ml) and basified to *p*H 10 with drop-wise addition of 20% sodium hydroxide solution. The precipitated amine **10** was filtered off, the filtrate saturated with sodium chloride and allowed to stand overnight in an ice box. The sodium salt of **14** isolated in 30% yield which was recrystallized from 95% ethanol; ir (potassium bromide): ν max 3400, 3200, 1600, 1520, 1225, 1050, 800 cm$^{-1}$; $^1$H nmr (deuterium oxide): δ 6.98 (d, 2H, J = 8.7 Hz), 6.94 (d, 1H, J = 6 Hz), 6.91 (s, 1H), 4.1 (q, 2H, -$CH_2$), 1.3 (t, 3H, -$CH_3$); ms: 342 ($M^+$).

*Anal.* Calcd. for $C_{11}H_9ClFN_2O_4SNa$: C, 38.5; H, 2.6; N, 8.2; F, 5.54; Cl, 10.4; S, 9.34; Na, 6.17. Found: C, 38.42; H, 2.51; N, 8.16; F, 5.50; Cl, 10.31; S, 9.30; Na, 6.2.

Ms: (FAB) 365 (s, 1Cl, $[M+Na]^+$), 343 (s, 1Cl, $[M+H]^+$), 321 (s, 1Cl, $[M-Na+2H]^+$), 263 (vs, 1Cl, $[M+Na-SO_3Na+H]^+$), 241 (vs, 1Cl, $[M-SO_3Na+2H]^+$). Exp. 364.9734; Theo. $C_{11}H_9ClFN_2O_4SNa_2$, Δ = 1.7 mmu. Exp. 321.0101; Theo. $C_{11}H_{11}ClFN_2O_4S$, Δ = 1.1 mmu.

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