

The Synthesis of 1-[(2-Thiazolyl)methyl]quinolones.
The Reactivity of the Methylene Bridge at Position-1 and its
Involvement in the Formation of a Stable Carbon-Nitrogen Ylid

Patrick T. Izzo* and Ving J. Lee

American Cyanamid Company, Medical Research Division, Lederle Laboratories,
Pearl River, NY 10965
Received June 11, 1987

A series of 7-chloro-1,4-dihydro-6-fluoro-1-[(2-methylthiazolyl)methyl]-4-oxoquinoline carboxylic esters **5** has been prepared. Dehydration of the intermediates 4-hydroxythiazolines **4** with trifluoroacetic anhydride resulted in the formation of a ylid **11**. Evidence for this was obtained by the X-ray analysis of the analogous product obtained in reactions carried out with 4-pyridone.

J. Heterocyclic Chem., **25**, 289 (1988).

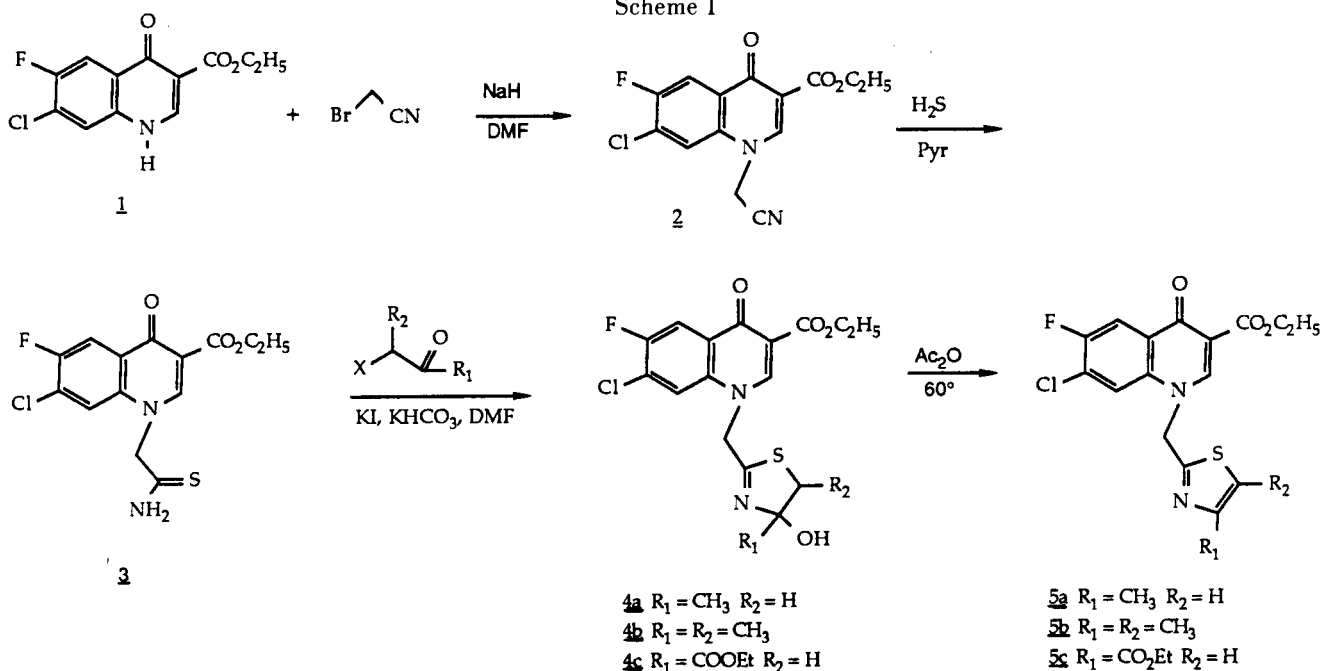
A synthetic program was undertaken in these laboratories to synthesize 1-(2-thiazolylmethyl)quinolones **5a-c**. It was envisioned that treatment of the 1-(thioacetamido)quinolone **3** with α -halogenated ketones would be a general approach to this class of compounds (Scheme I).

However, the 4-hydroxythiazoline intermediates **4** were found to be surprisingly, somewhat resistant to dehydration with acetic anhydride requiring prolonged heating at 60° and higher. Trifluoroacetic anhydride (TFAA) was then used not only for its stronger dehydrating power, but also because its (and by-product) volatility made workup easier. The product of the TFAA dehydration, however, was not the thiazole **5** but a trifluoroacetylated compound featuring an nmr spectrum in which the signal of the exocyclic methylene protons was dramatically absent. In the intermediates **2-4** as well as in **5** this signal occurred as a

two-proton singlet at δ 5.50-6.05. The appearance of a one-proton singlet at δ 7.10, however, indicated dehydration to a thiazole or some other isomeric heterocycle as suggested also by the elemental analytical data and the mass spectrum. All the remaining signals were consistent with the presence of the quinolone nucleus, the methyl and the ester groups.

Of primary interest was the site of attachment of the trifluoroacetyl group on an expected amino or hydroxyl function. Hydrolysis with dilute base cleaved the ethyl ester of the quinolone moiety but surprisingly left the trifluoroacetyl group intact. Acidic hydrolysis with dilute acid, on the other hand, cleaved both the ester and the trifluoroacetyl group. In the nmr of this product a two-proton signal reappeared at δ 6.21 and the protons were not exchangeable by deuterium oxide-perdeuteriotrifluoroacetic acid. Compar-

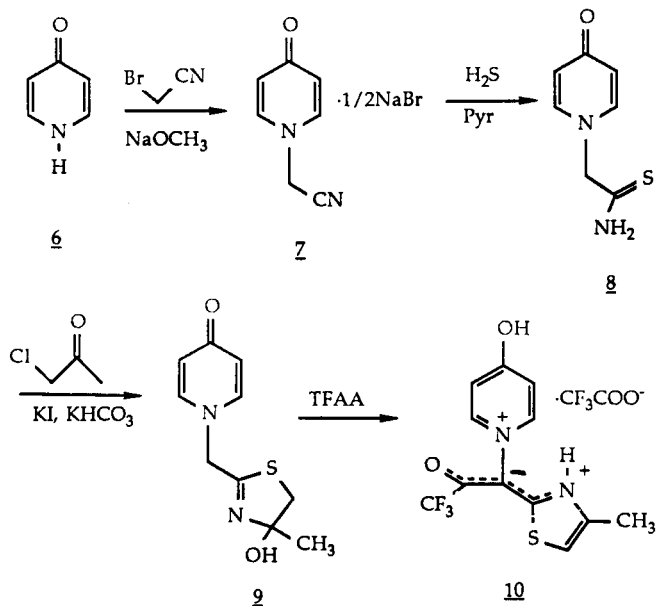
Scheme I



ing other spectral characteristics such as ir and uv as well as analytical values and mp's, this compound turned out to be identical with the acid **12**, the base-hydrolysis product of **5a** (Scheme III).

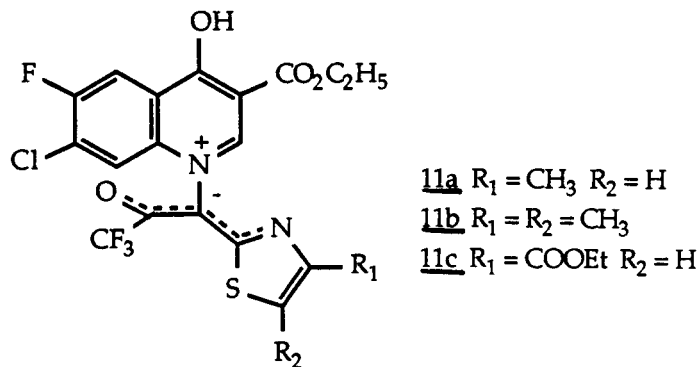
This information clearly indicated the involvement of the methylene bridge in the TFAA reaction, but the actual structure with its electronic implication remained to be elucidated. An X-ray analysis of the trifluoroacetyl compound was precluded by the repeated failure to obtain suitable crystals. Therefore, the next desirable approach was to do analogous reactions with the cognate structure, 4-pyridone **6** with the expectation that the chemistry would be similar to that observed for the quinolone and lead to a crystalline product suitable for X-ray analysis. Repetition of the synthetic sequence with 4-pyridone (Scheme II) gave analogously the hydroxythiazoline derivative **9** which on treatment with TFAA gave a trifluoroacetyl derivative **10** in good crystalline form showing the

Scheme II



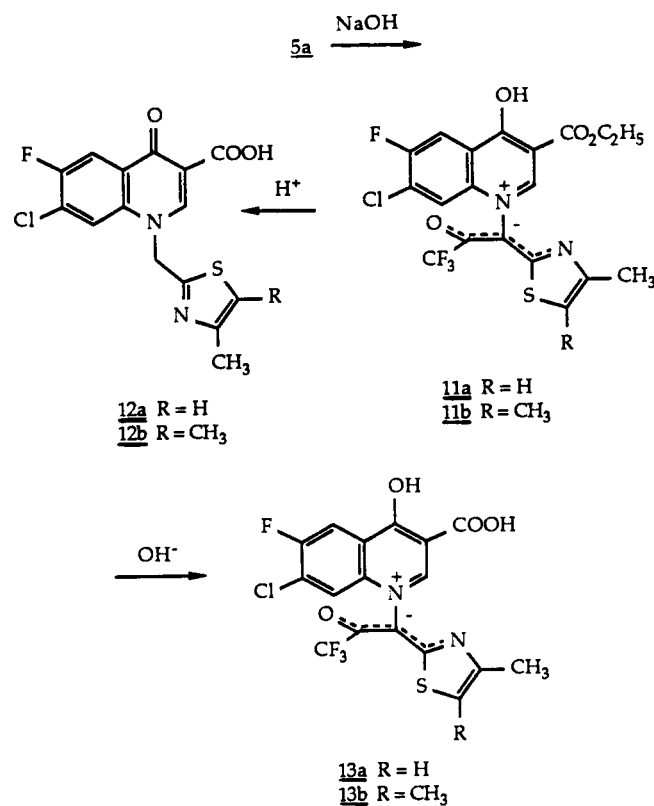
absence of methylene protons in the nmr. An X-ray determination showed a trifluoroacetylated carbon atom divested of its residual proton, a 4-hydroxypyridinium moiety, and a protonated thiazole nitrogen atom. This data together with the measurements of the various bonds involved in the expected delocalization of the negative charge, borne by an apparent trivalent carbon, indicated that the compound was the stabilized nitrogen ylid represented by structure **10** (Figure I). By analogy, therefore, one might expect that similar structures would result from the action of TFAA on the quinolones **4a-c** as depicted by formulas **11**.

The difference in the behavior of these compounds in their hydrolyses by acid and base, can now, be clearly ex-



plained. Under alkaline conditions, the base would be repelled by the negative charge delocalized on the bridge connecting the two heterocyclic moieties and no hydrolysis would occur at the site **13**. Under acidic conditions, the bridge carbanion would be protonated, thereby eliminating the stabilizing effect of charge delocalization, isolating the trifluoroacetyl group and leading to its elimination on further hydrolytic attack. The ester of the quinolone moiety is hydrolyzable by either acid or base (Scheme III).

Scheme III



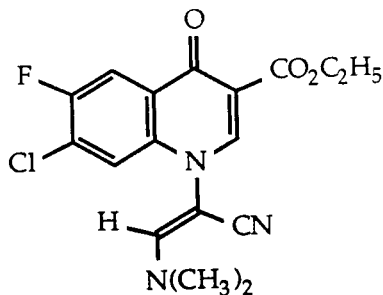
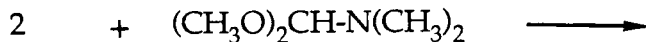
In contrast to the formation of the thiazolium trifluoroacetate salt **10**, the analogous quinoline compounds, **11a,b** did not form such a salt. This reduced basicity of the thiazole nitrogen in **11**, could be the result of the

greater electronegativity of the quinoline system compared to pyridine.

Other compounds prepared by the route shown in Scheme I were **5b** and **5c** which were generated by using 3-chloro-2-butanone and ethyl bromopyruvate respectively. In contrast with **4a-b**, treatment of **4c** with TFAA did not produce the trifluoroacetylated product **11c**, but simply dehydrated it to **5c**. Also **4c** was significantly more resistant to dehydration by acetic anhydride and TFAA than either **4a** and **b**, an unexpected behavior, as one would expect the conjugative effect of the ester group to enhance the dehydration to the aromatic thiazole.

Compounds **11a-b** could also be formed directly by the action of TFAA on **5a-5b**, leading to the conclusion that the reaction is sequentially the dehydration of the intermediate thiazoline followed by the trifluoroacetylation of the exocyclic methylene.

The unusual reactivity of the exocyclic methylene at position 1 of the quinolone (See Experimental), prompted additional studies of the reaction of the intermediate cyanomethyl quinolone **2**. Treatment of **2** with dimethylformamide dimethylacetal afforded the dimethylaminomethylene adduct **15** in excellent yields. Interestingly, attempts to react **15** with nucleophilic reagents (*e.g.* hydrazines) for heterocyclic annelation were unfruitful, as were, attempts to introduce the *N*-methylpiperazinyl substituent at C-7.



15

X-Ray Structure.

Compound **10** crystallizes from ethyl acetate in the orthorhombic space group $\text{Pna}2_1$ (#33) with 4 ion pairs per unit cell.

A yellow needle crystal of $\text{C}_{14}\text{H}_{10}\text{F}_6\text{N}_2\text{O}_4\text{S}$ having approximate dimensions of $0.25 \times 0.07 \times 0.07$ mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite-monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$) and a 12 KW rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the

setting angles of 24 carefully centered reflections in the range $31 < 2\theta < 55^\circ$, corresponded to an orthorhombic cell with dimensions:

$$a = 12.642(2) \text{ \AA} \quad b = 17.414(2) \text{ \AA} \quad c = 7.835(1) \text{ \AA} \\ v = 1724.9(4) \text{ \AA}^3$$

For $Z = 4$ and $F.W. = 416.22$, the calculated density is 1.60 g/cm^3 . Based on the systematic absences of:

$$0k1: K+1 \neq 2n$$

$$h0l: h \neq 2n$$

packing considerations, a statistical analysis of intensity distribution and the successful solution and refinement of the structure, the space group was determined to be:

$$\text{Pna}2_1 \text{ (#33)}$$

The data was collected at a temperature of $23^\circ \pm 1^\circ\text{C}$ using the ω - 2θ scan technique to a maximum 2θ value of 119.0° . Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.25° with a take-off angle of 6.0° . Scans of $(1.5 + 0.30 \tan \theta)^\circ$ were made at a speed of $16^\circ/\text{min}$ (in omega). The weak reflections ($I < 10\sigma(I)$) were rescanned (maximum of 3 scans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 40 cm. The detector aperture consisted of 0.75° vertical and 1.50° horizontal manually inserted slits.

A total of 1463 reflections were collected. The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for $\text{CuK}\alpha$ is 24.8 cm^{-1} . An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.97 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.0000016).

The structure was solved by the Patterson method. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms which were bonded to carbon were included in the structure factor calculation in idealized positions ($d_C = 0.95 \text{ \AA}$), while those bonded to oxygen and nitrogen were included at different map positions. All hydrogen atoms were assigned isotropic thermal parameter which were 20% greater than the B equivalent value of the atom to which they were bonded. The final cycle of full-matrix least-squares refinement was based on 947 observed reflections ($I > 3\sigma(I)$) and 253 variable parameters and converged (largest parameter shift was 0.05 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o| = 0.050$$

$$R2 = \text{SQRT}(\Sigma w (|F_o| - |F_c|)^2 / \Sigma w F_o^2) = 0.061$$

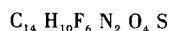
The standard deviation of an observation of unit weight was 2.05. The weighting scheme was based on counting statistics and included a factor ($p = 0.03$) to downweight the intense reflections. Plots of $\Sigma w (|F_o| - |F_c|)$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$, and various classes of indices showed no unusual trends. The largest peak on the final difference Fourier map had a height of $0.22 \text{ e}/\text{\AA}$.

Neutral atom scattering factors were taken from Cromer and Waber anomalous dispersion effects were included in F_{calc} ; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer. All calculations were performed on a VAX based TEXRAY system, a powerful laboratory computer system which included TEXSAN crystallographic software package of Molecular Structure Corporation.

B. Intensity Measurements

| | |
|-------------------------|---|
| Instrument: | Rigaku AFC6R diffractometer |
| Monochromator: | Graphite crystal, incident beam |
| Take-off angle: | 6.0° |
| Detector aperture: | 0.75 by 1.50° |
| Crystal-detector dist.: | 40 cm |
| Scan type: | ω - 2θ |
| Scan rate: | $5 - 16^\circ/\text{min}$ (in omega) |
| Scan width, deg: | $1.5 + 0.30 \tan \theta$ |
| Maximum 2θ : | 119.0° |
| No. of refl. measured: | 1463 total |
| Corrections: | Lorentz-polarization Secondary extinction (coefficient = 0.0000016) |

A. Crystal Data



$$\text{F.W. } 416.22 \quad F(000) = 840$$

$$\text{Crystal dimensions: } 0.25 \times 0.07 \times 0.07 \text{ mm}$$

$$\text{Peak width at half-height} = 0.25^\circ$$

$$\text{Cu K}\alpha \text{ radiation } (\lambda = 1.54178 \text{ \AA})$$

$$\text{Temperature} = 23 \pm 1^\circ \text{ C}$$

$$\text{Orthorhombic space group } Pna2_1$$

$$a = 12.642(2) \text{ \AA} \quad b = 17.414(2) \text{ \AA} \quad c = 7.835(1) \text{ \AA}$$

$$V = 1724.9 (4) \text{ \AA}^3$$

$$Z = 4 \quad \rho(\text{calc}) = 1.60 \text{ g/cm}^3$$

$$\mu = 24.8 \text{ cm}^{-1}$$

estimated standard deviations in the least significant figure are given in parentheses.

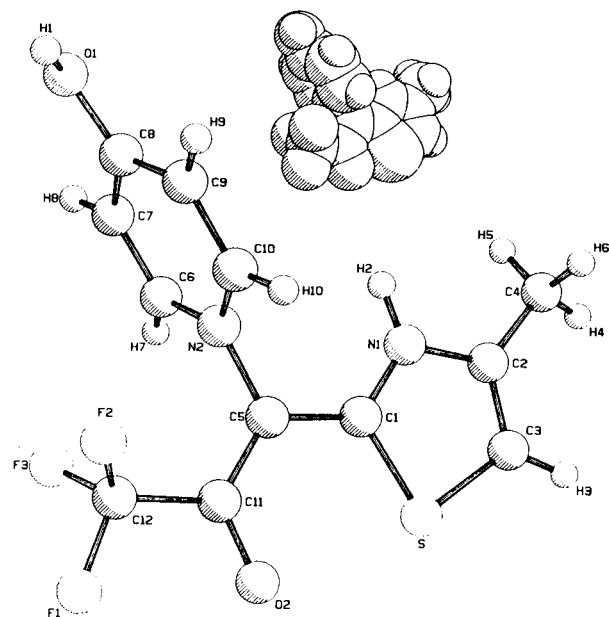


Figure 1. X-Ray Crystal Structure of Ylide 10 (trifluoroacetate anion deleted)

Table I

Intramolecular Distances (\AA) Involving the Nonhydrogen Atoms

| atom | atom | distance | atom | atom | distance |
|------|------|----------|------|------|----------|
| S | Cl | 1.72(1) | N1 | C2 | 1.38(1) |
| S | C3 | 1.74(1) | N2 | C10 | 1.35(1) |
| F1 | C12 | 1.34(1) | N2 | C6 | 1.36(1) |
| F2 | C12 | 1.31(2) | N2 | C5 | 1.46(1) |
| F3 | C12 | 1.36(2) | C1 | C5 | 1.40(1) |
| F4 | C14 | 1.22(2) | C2 | C3 | 1.34(1) |
| F5 | C14 | 1.24(2) | C2 | C4 | 1.47(1) |
| F6 | C14 | 1.52(3) | C5 | C11 | 1.37(1) |
| F7 | C14 | 1.46(3) | C6 | C7 | 1.36(1) |
| O1 | C8 | 1.30(1) | C7 | C8 | 1.38(1) |
| O2 | C11 | 1.26(1) | C8 | C9 | 1.35(2) |
| O3 | C13 | 1.26(1) | C9 | C10 | 1.37(1) |
| O4 | C13 | 1.18(1) | C11 | C12 | 1.55(2) |
| N1 | C1 | 1.33(1) | C13 | C14 | 1.53(2) |

Table II

Intramolecular Distances (\AA) Involving the Hydrogen Atoms

| atom | atom | distance | atom | atom | distance |
|------|------|----------|------|------|----------|
| O1 | H1 | 1.060 | C4 | H5 | 0.953 |
| N1 | H2 | 1.137 | C6 | H7 | 0.953 |
| C3 | H3 | 0.950 | C7 | H8 | 0.955 |
| C4 | H6 | 0.945 | C9 | H9 | 0.951 |
| C4 | H4 | 0.953 | C10 | H10 | 0.947 |

The structure and atom numbering of the molecule are shown in Figure 1. Tables I and II contain the intramolecular distances involving the nonhydrogen and hydrogen atoms and Tables III and IV contain bond angles involving the nonhydrogen and hydrogen atoms. The distances are in angstroms and the angles are in degrees. The

Table III

Intramolecular Bond Angles (°) Involving the Nonhydrogen Atoms

| atom | atom | atom | angle | atom | atom | atom | angle |
|------|------|------|----------|------|------|------|--------|
| C1 | S | C3 | 90.2(5) | O2 | C11 | C5 | 123(1) |
| C1 | N1 | C2 | 116.0(9) | O2 | C11 | C12 | 118(1) |
| C10 | N2 | C6 | 120.0(8) | C5 | C11 | C12 | 119(1) |
| C10 | N2 | C5 | 121.3(8) | F2 | C12 | F1 | 110(1) |
| C6 | N2 | C5 | 118.7(8) | F2 | C12 | F3 | 107(1) |
| N1 | C1 | C5 | 125.5(9) | F2 | C12 | C11 | 115(1) |
| N1 | C1 | S | 110.4(8) | F1 | C12 | F3 | 105(1) |
| C5 | C1 | S | 124.1(7) | F1 | C12 | C11 | 110(1) |
| C3 | C2 | N1 | 111(1) | F3 | C12 | C11 | 110(1) |
| C3 | C2 | C4 | 128(1) | O4 | C13 | O3 | 129(1) |
| N1 | C2 | C4 | 121(1) | O4 | C13 | C14 | 116(1) |
| C2 | C3 | S | 112.1(9) | O3 | C13 | C14 | 115(1) |
| C11 | C5 | C1 | 120.9(8) | F4 | C14 | F5 | 124(1) |
| C11 | C5 | N2 | 121.4(9) | F4 | C14 | F7 | 91(2) |
| C1 | C5 | N2 | 117.7(8) | F4 | C14 | F6 | 83(2) |
| N2 | C6 | C7 | 119.0(9) | F4 | C14 | C13 | 118(1) |
| C6 | C7 | C8 | 122(1) | F5 | C14 | F7 | 82(2) |
| O1 | C8 | C9 | 125(1) | F5 | C14 | F6 | 89(2) |
| O1 | C8 | C7 | 118(1) | F5 | C14 | C13 | 118(1) |
| C9 | C8 | C7 | 117(1) | F7 | C14 | F6 | 163(2) |
| C8 | C9 | C10 | 121(1) | F7 | C14 | C13 | 101(2) |
| N2 | C10 | C9 | 120(1) | F6 | C14 | C13 | 96(2) |

Table IV

Intramolecular Bond Angles (°) Involving the Hydrogen Atoms

| atom | atom | atom | angle | atom | atom | atom | angle |
|------|------|------|--------|------|------|------|--------|
| H1 | O1 | C8 | 109.25 | H5 | C4 | C2 | 109.52 |
| H2 | N1 | C1 | 102.58 | H7 | C6 | N2 | 120.08 |
| H2 | N1 | C2 | 140.81 | H7 | C6 | C7 | 120.93 |
| H3 | C3 | C2 | 124.16 | H8 | C7 | C6 | 118.32 |
| H3 | C3 | S | 123.69 | H8 | C7 | C8 | 119.50 |
| H6 | C4 | H4 | 109.62 | H9 | C9 | C8 | 119.91 |
| H6 | C4 | H5 | 109.63 | H9 | C9 | C10 | 118.81 |
| H6 | C4 | C2 | 110.18 | H10 | C10 | N2 | 119.75 |
| H4 | C4 | H5 | 108.94 | H10 | C10 | C9 | 119.91 |
| H4 | C4 | C2 | 108.93 | | | | |

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Fisher oil-bath apparatus and are uncorrected. Infra red (ir) spectra were recorded by a Nicolet 20 SXB FT-IR spectrometer and taken on potassium bromide discs. Proton magnetic resonance spectra (^1H nmr) were taken on methyl sulfoxide-d₆ solution with tetramethylsilane (TMS) as internal

standard by means of a Varian 80 MHz instrument. Mass spectra were taken with a Varian Mat CH7 mass spectrometer, and the single crystal X-ray analysis was performed by the crystallographic staff of the Molecular Structure Corporation, College Station, Texas. Microanalyses were performed by the Lederle Laboratories Analytical Department.

Ethyl 7-Chloro-1-cyanomethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **2**.

To a stirred suspension of 8.1 g (30 mmoles) of ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-quinolinecarboxylate **1** [1] in 150 ml of dimethylformamide was added 1.2 g of a 60% sodium hydride-oil dispersion (30 mmoles sodium hydride). The mixture was stirred at ambient temperature for 30 minutes or until all the solid dissolved. Bromoacetonitrile (4.3 g, 36 mmoles) was then added in one portion. An instantaneous reaction took place, the solution turning a deeper color. After 18 hours at room temperature, the solution was concentrated *in vacuo* to about half volume and diluted with water. The resultant, light brown precipitate, was collected, washed first by slurrying in water and then in alcohol and finally dried *in vacuo* to yield 8.4 g (90%) of off-white product, mp 237-238°; ir: ν max 1720, 1618 cm^{-1} ; ^1H nmr: δ 1.30 (t, $\text{OCH}_2\text{-CH}_3$), 4.25 (q, $\text{OCH}_2\text{-CH}_3$), 5.70 (s, CH_2CN), 8.06 (1H, d, $^3J_{\text{H-F}} = 9.3$ Hz, 5-H), 8.25 (1H, d, $^4J_{\text{H-F}} = 5.9$ Hz, 8-H), 8.83 (1H, s, 2-H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{ClFN}_2\text{O}_3$: C, 54.47; H, 3.27; Cl, 11.48; N, 9.07. Found: C, 54.04; H, 3.06; Cl, 11.61; N, 8.95.

Ethyl 1-(2-Amino-2-thioxoethyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **3**.

A slow stream of hydrogen sulfide gas was bubbled through a magnetically stirred suspension of 5 g (16 mmoles) of the nitrile **2** in 220 ml of pyridine at ambient temperature for 1.5 hours. The flask was stoppered and allowed to stand at ambient temperature for 18 hours. The precipitated, colorless, crystalline product was filtered, washed several times with ethanol and dried in a vacuum oven, mp 267-268° dec, 4 g (73%); ir: ν max 2780-3300, 1718, 1615 cm^{-1} ; ^1H nmr: δ 1.29 (t, $\text{OCH}_2\text{-CH}_3$), 4.25 (q, $\text{OCH}_2\text{-CH}_3$), 5.35 (2H, s), 7.71 (1H, d, $^4J_{\text{H-F}} = 5.60$ Hz, 8-H), 8.03 (1H, d, $^3J_{\text{H-F}} = 9.60$ Hz, 5-H), 8.67 (1H, s, 2-H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{ClFN}_2\text{O}_3\text{S}$: C, 49.07; H, 4.04; Cl, 10.34; N, 8.17; S, 9.36. Found: C, 49.21; H, 3.44; Cl, 10.39; N, 8.13; S, 9.04.

Ethyl 7-Chloro-1,4-dihydro-1-[(4,5-dihydro-4-hydroxy-4-methyl-2-thiazolyl)methyl]-6-fluoro-4-oxo-3-quinolinecarboxylate **4a**.

To a stirred solution of 1 g (3 mmoles) of the thioamide **3** in 20 ml of dimethylformamide (warmed briefly to effect complete solution) was added 0.5 g (3 mmoles) of potassium iodide, 0.6 g (6 mmoles) of potassium bicarbonate, and 0.31 g (3 mmoles + 20% excess) of redistilled chloroacetone. The solution turned at first red and then a lemon yellow. Stirring at ambient temperature was continued for 3 hours, and then most of the solvent was removed at reduced pressure at about 60°. Addition of water to the viscous concentrate caused the separation of a colorless, crystalline solid which was filtered, washed with water and dried. Recrystallization from ethanol (*ca.* 50 ml) gave a colorless, crystalline product, mp 165-167° dec; 1 g (83%); ir: ν max 3400, 2990, 3060, 1728 cm^{-1} ; ^1H nmr: δ 1.31 (6H, t, $\text{OCH}_2\text{-CH}_3$, CH_3), 3.28 (2H, q, CH_2 of the thiazoline), 4.17 (2H, q, $\text{OCH}_2\text{-CH}_3$), 5.52 (2H, s, exocyclic CH_2), 7.82 (1H, d, $^4J_{\text{H-F}} = 5.60$ Hz, 8-H), 8.05 (1H, d, $^3J_{\text{H-F}} = 8.80$ Hz, 5-H), 8.76 (1H, s, 2-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{ClFN}_2\text{O}_3\text{S}$: C, 51.20; H, 4.04; Cl, 8.89; N, 7.02; S, 8.02. Found: C, 51.58; H, 3.90; Cl, 9.03; N, 6.68; S, 8.06.

Ethyl 7-Chloro-1,4-dihydro-6-fluoro-1-[(4-methyl-2-thiazolyl)methyl]-4-oxo-3-quinolinecarboxylate **5a**.

A solution of 0.5 g (1.25 mmoles) of **4a** in 15 ml of acetic anhydride was stirred and heated at 65-70° for 18 hours. Evaporation of the solvent at reduced pressure and recrystallization of the residue from ethanol (15 ml) gave a colorless, crystalline product, mp 191-192°, 0.35 g (73%); ir: ν max 1720, 1610 cm^{-1} ; ^1H nmr: δ 1.30 (3H, t, $\text{OCH}_2\text{-CH}_3$), 2.33 (3H, s, CH_3), 4.25 (2H, q, $\text{OCH}_2\text{-CH}_3$), 6.06 (2H, s, exocyclic CH_2), 7.32 (1H, s, thiazole H), 8.07 (1H, d, $^3J_{\text{H-F}} = 8.80$ Hz, 5-H), 8.23 (1H, s, $^4J_{\text{H-F}} = 4.00$ Hz, 8-H),

8.97 (1H, s, 2-H).

Anal. Calcd. for $C_{17}H_{14}ClFN_2O_3S$: C, 53.62; H, 3.71; N, 7.36; S, 8.42. Found: C, 53.51; H, 3.58; N, 7.26; S, 8.31.

7-Chloro-3-ethoxycarbonyl-6-fluoro-4-hydroxyquinolinium 3,3,3-Trifluoro-1-(4-methyl-2-thiazolyl)-2-oxopropylide **11a**.

A suspension of 1 g (2.5 mmoles) of **4a** in 100 ml of trifluoroacetic anhydride was heated under reflux for 24 hours. The starting compound slowly dissolved, but before complete solution was achieved a new, white, fine, solid began to precipitate and continued doing so during the heating period. At the end the mixture was cooled and filtered affording 1 g (80%) of a cream-colored product, mp 301-303° dec. Recrystallization from 5% aqueous dimethylformamide (20 ml) gave 0.650 g of a colorless product, mp 303-304° (dec); ir: ν max 2720-3160, 1720, 1697 cm^{-1} ; 1H nmr: δ 1.28 (3H, t, OCH_2-CH_3), 2.25 (3H, s, CH_3 of the thiazole), 4.24 (2H, q, OCH_2-CH_3), 7.10 (1H, s, thiazole H), 7.82 (1H, d, $^2J_{H-F} = 5.6$ Hz, 8-H), 8.05 (1H, d, $^3J_{H-F} = 8.80$ Hz, 5-H), 8.78 (1H, s, 2-H), 13.57 (OH); MW 476; ms: (m/e) 475 (M^+).

Anal. Calcd. for $C_{19}H_{13}F_4ClN_2O_4S$: C, 47.97; H, 2.54; F, 15.97; Cl, 7.45; N, 5.89; S, 6.73. Found: C, 47.52; H, 2.69; F, 15.81; Cl, 7.38; N, 6.36; S, 7.01.

4-Oxo-1(4*H*)-pyridineacetonitrile-Sodium Bromide Complex **7**.

To a stirred and cooled (ice bath) solution of 9.5 g (0.1 mole) of 4-pyridone **6** in 100 ml of dimethylformamide was added 5.4 g (0.1 mole) of sodium methoxide (or an equivalent amount of sodium hydride). The reaction was vigorous and rapid. After 10-15 minutes, 12 g (0.1 mole) of freshly-distilled bromacetonitrile was added and the reaction mixture was stirred at room temperature for 4 hours. The precipitated solid was washed with ethanol by trituration. Recrystallization from a large volume of acetonitrile and concentrating gave 8 g of crystalline solid. Recrystallizations (2 \times) from ethanol (ca. 150 ml each) afforded 4.8 g (27%) of a yellow, crystalline compound, exhibiting a constant mp of 246-248°; ir: ν max 2920, 1640, 1580 cm^{-1} ; 1H nmr: δ 5.19 (2H, s), 6.16 (2H, d, J = 7.7 Hz), 7.74 (2H, d, J = 7.7 Hz); ms (m/e) 134 (M^+).

Anal. Calcd. for $C_7H_8N_2O \cdot 0.55NaBr$: C, 44.11; H, 3.17; N, 14.69; Br, 23.00; Na, 6.61. Found: C, 44.15; H, 3.38; N, 14.51; Br, 22.65; Na, 6.40.

2-(4-Oxo-1(4*H*)-pyridinyl)-ethanethioamide **8**.

A slow stream of hydrogen sulfide was bubbled through a stirred suspension of 1.5 g (8 mmoles) of **7** in 35 ml of pyridine for 45 minutes at ambient temperature. The flask was stoppered and allowed to stand for 18 hours. The nearly colorless solid was filtered and recrystallized from a methanol-ether mixture (1:1, ca. 40 ml) affording 925 mg (70%) of an orange, crystalline product, mp 198-200° (dec); ir: ν max 2200-3400, 1620, 1520 cm^{-1} ; 1H nmr: δ 4.76 (2H, s), 6.06 (2H, d, J = 7.7 Hz), 7.51 (2H, d, J = 7.7 Hz).

Anal. Calcd. for $C_8H_8N_2OS$: C, 50.00; H, 4.80; N, 16.66; S, 19.05. Found: C, 50.28; H, 4.90; N, 16.50; S, 18.90.

4-Hydroxypyridinium 3,3,3-Trifluoro-1-(4-methyl-2-thiazolyl)-2-oxopropylide Mono(trifluoroacetate Salt) **10**.

To a stirred solution of 1.7 g (10 mmoles) of **8** in 55 ml of dimethylformamide was added 1.7 g (10 mmoles) of potassium iodide, 1 g (10 mmoles) of potassium bicarbonate and 1 g (10 mmoles) of chloroacetone. The reaction was stirred at ambient temperature for 18 hours, the solvent was removed *in vacuo* and the brown liquid, residue was treated three times with toluene followed by distillation *in vacuo* each time. The residue was 2 g of a brown liquid. NMR indicated this to be the expected hydroxythiazoline **9**. Without further purification, this material was suspended in 10 ml of trifluoroacetic anhydride and stirred overnight. The excess TFAA (and trifluoroacetic acid) was evaporated *in vacuo*, leaving a dark liquid residue, which on treatment with ethyl acetate, filtering and cooling over several hours afforded a 1.9 g (46%) of a brown, crystalline product, mp 228-230° dec. Further recrystallizations from ethyl acetate did not alter the mp; ir: ν max 2600-3200, 1720, 1620 cm^{-1} ; 1H nmr: δ 2.26 (3H, s, CH_3), 7.01 (1H, s, thiazole-H), 7.10 (2H, d, J = 6.96 Hz), 8.44 (2H, d, J = 6.96 Hz).

Anal. Calcd. for $C_{14}H_{10}F_6N_2O_4S$: C, 40.42; H, 2.42; F, 27.40; N, 6.73; S, 7.69. Found: C, 40.52; H, 2.45; F, 27.23; N, 6.70; S, 7.65.

Alkaline Hydrolysis of **11a**. 3-Carboxy-7-chloro-6-fluoro-4-hydroxyquinolinium 3,3,3-Trifluoro-1-(4-methyl-2-thiazolyl)-2-oxopropylide **13a**.

To a suspension of 218 mg (0.5 mmole) of **11a** in 10 ml of 1-propanol was added 1 ml of 1*N* sodium hydroxide (1 mmole). The solid dissolved to a clear yellow solution which was then heated at reflux for 2 hours. The solution was cooled, neutralized with 1 ml of 1*N* hydrochloric acid and evaporated to dryness. The white, solid residue was extracted with 10-15 ml of methanol and filtered. Addition of a few drops of anhydrous hydrochloric acid/methanol caused the precipitation of a colorless, crystalline solid which was collected and dried; mp 321-322° dec, 150 mg (63%); ir: ν max 2800-3120, 1750, 1730, 1608 cm^{-1} ; 1H nmr: δ 2.24 (3H, s, CH_3), 7.07 (1H, s, thiazole H), 7.85 (1H, d, $^2J_{H-F} = 6.4$ Hz, 8-H), 8.33 (1H, d, $^3J_{H-F} = 8.8$ Hz, 5-H), 9.00 (1H, s, 2-H), 12.9 (COOH); mw 448.9, ms: (m/e) 448 (M^+).

Anal. Calcd. for $C_{17}H_9ClF_6N_2O_4S$: C, 45.50; H, 2.02; F, 16.93; N, 6.24; S, 7.14. Found: C, 45.43; H, 1.99; F, 16.70; N, 6.29; S, 7.18.

Acid Hydrolysis of **11a**. 7-Chloro-1,4-dihydro-6-fluoro-1[(4-methyl-2-thiazolyl)methyl-4-oxo-3-quinolinecarboxylic Acid] **12a**.

To a stirred suspension of 400 mg (0.84 mmoles) of **11a** in 5 ml of 1-propanol was added 2 ml of 6*N* hydrochloric acid. The mixture was heated at reflux for 6 hours, remaining heterogeneous during this period. It was, then, cooled and filtered. The colorless solid was washed with water, and recrystallized from 1-propanol to afford 250 mg (84%) of product, mp 267-268°; ir: ν max 3055, 1720, 1618 cm^{-1} ; 1H nmr: δ 2.28 (3H, s, CH_3), 6.21 (2H, s, $-CH_2-$), 7.32 (1H, s, thiazole H), 8.18 (1H, d, $^2J_{H-F} = 9.93$ Hz, 5-H), 8.48 (1H, d, $^3J_{H-F} = 6.0$ Hz, 8-H), 9.30 (1H, s, 2-H), 14.56 (1H, s, COOH); ms: (m/e) 352 (M^+), 308 ($M^+ - CO_2$).

Anal. Calcd. for $C_{15}H_{10}ClFN_2O_4S$: C, 51.07; H, 2.86; F, 5.39; N, 7.94; S, 9.09. Found: C, 50.89; H, 2.79; F, 5.38; N, 7.63; S, 9.10.

Alkaline Hydrolysis of **5a**.

A mixture of 371 mg (1 mmole) of **5a**, 15 ml of ethanol and 1 ml of 2.5*N* sodium hydroxide was heated at reflux for 3.5 hours. The solvent was evaporated *in vacuo* and the white solid residue was taken up in water. The aqueous solution was filtered. The filtrate was acidified with a few drops of 6*N* hydrochloric acid affording a colorless, powdery solid. Recrystallization from acetonitrile (50 ml) gave 190 mg (54%) of crystalline product (mp 264-266°) identical in every respect with 7-chloro-1,4-dihydro-6-fluoro-1-[4-methyl-2-thiazolyl]methyl-4-oxo-3-quinolinecarboxylic acid (**12a**).

Ethyl 7-Chloro-1,4-dihydro-1[(4,5-dihydro-4-hydroxy-4,5-dimethyl-2-thiazolyl)methyl]-6-fluoro-4-oxo-3-quinolinecarboxylate **4b**.

To a stirred solution of 2 g (6 mmoles) of the thioamide **3** in 40 ml of dimethylformamide was added 0.7 g (6 + 10% excess mmoles) of 3-chloro-2-butanone, 1 g (6 mmoles) of potassium iodide and 1.2 g (12 mmoles) of potassium bicarbonate. Stirring at ambient temperature was continued for 18 hours. Most of the solvent was removed *in vacuo* and replaced by water whereupon a sticky material separated out. The partially crystalline material, was recrystallized from aqueous ethanol (20 ml) affording 1.3 g (52%) of colorless, crystalline product, mp 164-166° dec. For analytical purposes, a small sample was recrystallized from a mixture of ethyl acetate and ethanol to give the colorless, crystalline compound, mp 174-176° dec; ir: ν max 3000-3280, 1720, 1670 cm^{-1} .

Anal. Calcd. for $C_{18}H_{18}ClFN_2O_4S$: C, 52.37; H, 4.39; Cl, 8.59; F, 4.60; N, 6.78; S, 7.77. Found: C, 52.24; H, 4.29; Cl, 8.68; F, 4.83; N, 6.83; S, 7.55.

7-Chloro-3-ethoxycarbonyl-6-fluoro-4-hydroxy-quinolinium 3,3,3-Trifluoro-1-(4,5-dimethyl-2-thiazolyl)-2-oxopropylide **11b**.

A suspension of 95 mg (0.23 mmole) of **4b** in 15 ml of trifluoroacetic anhydride was heated at reflux for 18 hours. Evaporation to dryness and recrystallization of the solid residue from ethanol (20 ml) gave a yellow, crystalline product, mp 315° dec, 30 mg (27%); ir: ν max 2980-3160,

1720, 1610 cm^{-1} ; ^1H nmr: δ 1.26 (3H, t, $\text{OCH}_2\text{-CH}_3$), 2.12 (3H, s, $\text{R}_2 = \text{CH}_3$), 2.28 (3H, s, $\text{R}_1 = \text{CH}_3$), 4.21 (2H, q, $\text{OCH}_2\text{-CH}_3$), 7.50 (1H, d, $^4\text{J}_{\text{H-F}} = 6.1$ Hz, 8-H), 8.08 (1H, d, $^3\text{J}_{\text{H-F}} = 7.6$ Hz, 5-H), 8.56 (1H, s, 2-H), 12.75 (1H, s, OH).

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{ClF}_4\text{N}_2\text{O}_4\text{S}$: C, 48.94; H, 3.08; F, 15.48; N, 5.71; S, 6.53. Found: C, 48.80; H, 3.06; F, 15.25; N, 5.67; S, 6.80.

Ethyl 7-Chloro-1-[(4-ethoxycarbonyl-4,5-dihydro-4-hydroxy-2-thiazolyl)methyl]-1,4-dihydro-6-fluoro-4-oxoquinolinecarboxylate **4c**.

To a stirred solution of 1 g (3 mmoles) of the thioamide **3** in 20 ml of dimethylformamide was added 0.6 g (6 mmoles) of potassium bicarbonate and 0.7 g (9.6 mmoles) of ethyl bromopyruvate. The solution, which turned lemon yellow was stirred at ambient temperature for 18 hours. Addition of water (20 ml) caused the precipitation of a solid which was recrystallized from ethanol (20 ml) to afford 574 mg (44%) of a brown, crystalline product mp 171-174 $^\circ$; ir: ν max 3000, 3320, 1730, 1700, 1620 cm^{-1} ; ^1H nmr: δ 1.06, 1.29 (6H, 2t, $\text{OCH}_2\text{-CH}_3$'s), 3.40 (2H, s, thiazoline H's), 3.91-4.29 (4H, m, $\text{OCH}_2\text{-CH}_3$'s), 5.69 (2H, s, exocyclic CH_2), 7.10 (1H, s, OH), 7.84 (1H, d, $^4\text{J}_{\text{H-F}} = 5.9$ Hz, 8-H), 8.03 (s, d, $^3\text{J}_{\text{H-F}} = 9.4$ Hz, 5-H), 8.81 (1H, s, 2-H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{ClFN}_2\text{O}_6\text{S}$: C, 49.95; H, 3.97; Cl, 7.76; N, 6.13; S, 7.02. Found: C, 49.80; H, 3.94; Cl, 7.72; N, 6.01; S, 6.93.

Ethyl 7-Chloro-1-[(4-ethoxycarbonyl-2-thiazolyl)methyl]-1,4-dihydro-6-fluoro-4-oxoquinolinecarboxylate **5c**.

A suspension of 200 mg (0.44 mmole) of **4c** in 5 ml of trifluoroacetic anhydride was stirred at ambient temperature for 7 days. Removal of the solvent *in vacuo* gave a mixture of products. The reaction was continued by dissolving this material in acetic anhydride (10 ml) and heating the solution at 65-70 $^\circ$ for 24 hours. Removal of the solvent *in vacuo* left a solid residue which, after recrystallization, from ethanol (7 ml) afforded 135 mg (70%) of pale yellow, crystalline product, mp 174-176 $^\circ$; ir: ν max 1720, 1700, 1610 cm^{-1} ; ^1H nmr: δ 1.26 (6H, t, $\text{OCH}_2\text{-CH}_3$'s), 4.25 (4H, q, $\text{OCH}_2\text{-CH}_3$'s), 6.10 (2H, s, exocyclic CH_2), 8.03 (1H, d, $^3\text{J}_{\text{H-F}} = 10.4$ Hz, 5-H), 8.20 (1H, d, $^4\text{J}_{\text{H-F}} = 7.2$ Hz, 8-H), 8.5 (1H, s, thiazole H), 8.96 (1H, s, 2-H); ms: (m/e) 439 (M $^+$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{ClFN}_2\text{O}_5\text{S}$: C, 52.00; H, 3.68; Cl, 8.08; N, 6.38; S, 7.31. Found: C, 51.91; H, 3.61; Cl, 8.00; N, 6.14; S, 7.40.

Acid Hydrolysis of **11b**. 7-Chloro-1,4-dihydro-6-fluoro-1-[4,5-dimethyl-2-thiazolyl)methyl]-4-oxoquinolinecarboxylic Acid (**12b**).

In a reaction similar to that performed in the hydrolysis of **11a**, 235 mg (0.48 mmole) of **11b** gave 150 mg (85%) of **12b**, mp 235-237 $^\circ$ dec.

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{ClFN}_2\text{SO}_3$: C, 52.39; H, 3.30; F, 5.18; N, 7.64. Found: C, 51.97; H, 3.28; F, 5.12; N, 7.26.

Ethyl 7-Chloro-1[1-cyano-2-(dimethylamino)ethenyl]-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate **15**.

A mixture of 0.85 g (2.7 mmoles) of **2** and 10 ml of dimethylformamide dimethylacetal was heated in an oil bath at 120 $^\circ$ for 0.5 hours. The starting material dissolved after a few minutes and a colorless, crystalline solid appeared right after. The suspension was cooled, filtered and the solid recrystallized from 40 ml of ethanol to give 566 mg (58%) of a colorless, crystalline product, mp 224-226 $^\circ$; ir: ν max 3000, 2200, 1730, 1700 cm^{-1} ; ^1H nmr: δ 1.29 (3H, t, OCH_2CH_3), 3.19 (6H, s, 2CH_3 's), 4.24 (2H, q, OCH_2CH_3), 7.58 (1H, s, =CH-), 7.96 (1H, d, $^3\text{J}_{\text{H-F}} = 9.4$ Hz, 5-H), 8.06 (1H, d, $^4\text{J}_{\text{H-F}} = 6.6$ Hz, 8-H), 8.52 (1H, s, 2-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{ClFN}_3\text{O}_3$: C, 56.13; H, 4.16; Cl, 9.74; N, 11.55. Found: C, 56.00; H, 4.02; Cl, 9.80; N, 11.45.

Acknowledgements.

The authors wish to thank Mr. K. Angyal for the mass spectrometry determination and Mr. G. Morton for very valuable assistance in the interpretation of the nmr's.

REFERENCES

- [1] H. Koga, A. Itoh, S. Murayama, S. Suzue, and T. Irikawa, *J. Med. Chem.*, **23**, 1358 (1980).