Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids *via* Nitroso and Nitrone Cycloadditions

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1-Ethyl-6-fluoro-7-hydroxylamino-1,4-dihydro-4-oxoquinoline-3-carboxylic acid **7** can be either oxidized to the corresponding nitroso intermediate **8** or converted to the methylene nitrone **9**. Both intermediates form cycloaddition products with selected dienes and olefins respectively. Also, the preparation of 1-ethyl-6-fluoro-7-(hexahydro-2-methyl-5*H*-pyrrolo[3,4-*d*]isoxazol-5-yl)-3-quinolinecarboxylic acid **5** *via* a nitrone cycloaddition is presented.

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Certain structural features of the quinolone-3-carboxylic acid family contribute significantly to their antibiotic efficacy [1]. In the last 5 years several analogues have appeared that posssess excellent biological activity [2]. From this, it is apparent that the presence of a 6-fluoro on the basic quinolone nucleus is crucial for good bacteriocidal activity. However, more variety in substitution at positions 1, 7 and 8 is tolerated. In fact, most synthetic endeavors have addressed a host of substituents at these positions. Potent analogues such as Pefloxacin **1**, Ciprofloxacin **2** and CI-934 **3** have emerged as outstanding examples [3,4,5].

We are interested in preparing novel quinolone candidates for biological evaluation. In this paper we report a synthesis of 4-quinolone-3-carboxylic acids whose 7-substituent originates from either a nitroso or nitrone cycloaddition. Novel compounds with general structure **4** are presented along with the preparation of a specific nitrone cycloadduct **5**.

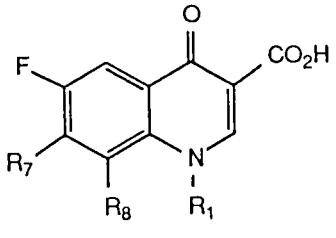
Generally, the basic methodology for the introduction of a heterocycle at the quinolone 7-position entails nucleophilic aromatic substitution on the appropriate 7-halo-4-oxoquinoline-3-carboxylic acid. One new general approach to **4** that supplements the older methods utilizes the 7-hydroxylaminoquinolone **7** as a versatile building block from which a variety of 7-substituted analogues can be synthesized. As shown in Scheme 1, the 6,7-difluoroquinolone **6** [6] reacts smoothly with hydroxylamine hydrochloride in pyridine solvent at 90°. Under these conditions, little or no reduction of the hydroxylamine to the corresponding aniline occurs [7].

This hydroxylamine **7** can either be oxidized to the nitroso intermediate **8** or converted to the methylene nitrone **9** on condensation with formaldehyde. In all cases, neither the dienophile **8** nor the 1,3-dipole **9** are isolated. Rather, they are generated in the presence of a diene or 1,3-dipolarophile, which in turn undergo cycloaddition. Those 7-(substituted)quinolones prepared from these two reactive intermediates are listed in Table 1.

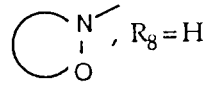
Compounds **10-12** were prepared from [4 + 2] cycloaddition of the nitroso intermediate **8** with the dienes shown. Alternatively, **13** and **14** were synthesized *via* dipolar cycloaddition of the methylene nitrone **9** with the requisite olefin [8].

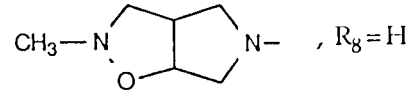
The hexahydro-2-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole moiety was introduced at C-7 by similar methodology. The most expeditious preparation of **5** was *via* the route shown in Scheme 2.

Dipolarcycloaddition of *N*-methylmethylenenitrone and *N*-trifluoroacetyl-3-pyrroline gave **15** in 45% yield. Base hydrolysis of **15** followed by nucleophilic aromatic substitution with quinolone **6** at 115° in pyridine gave **5** in 65% yield after 30 minutes.



1 R_1 = Et, R_7 = 4-methylpiperazine, R_8 = H
2 R_1 = cyclopropyl, R_7 = piperazine, R_8 = H
3 R_1 = Et, R_7 = 3-(N-ethylaminomethyl)-1-pyrrolidinyl, R_8 = F

4 R_1 = Et, R_7 =  , R_8 = H

5 R_1 = Et, R_7 =  , R_8 = H

SCHEME 1

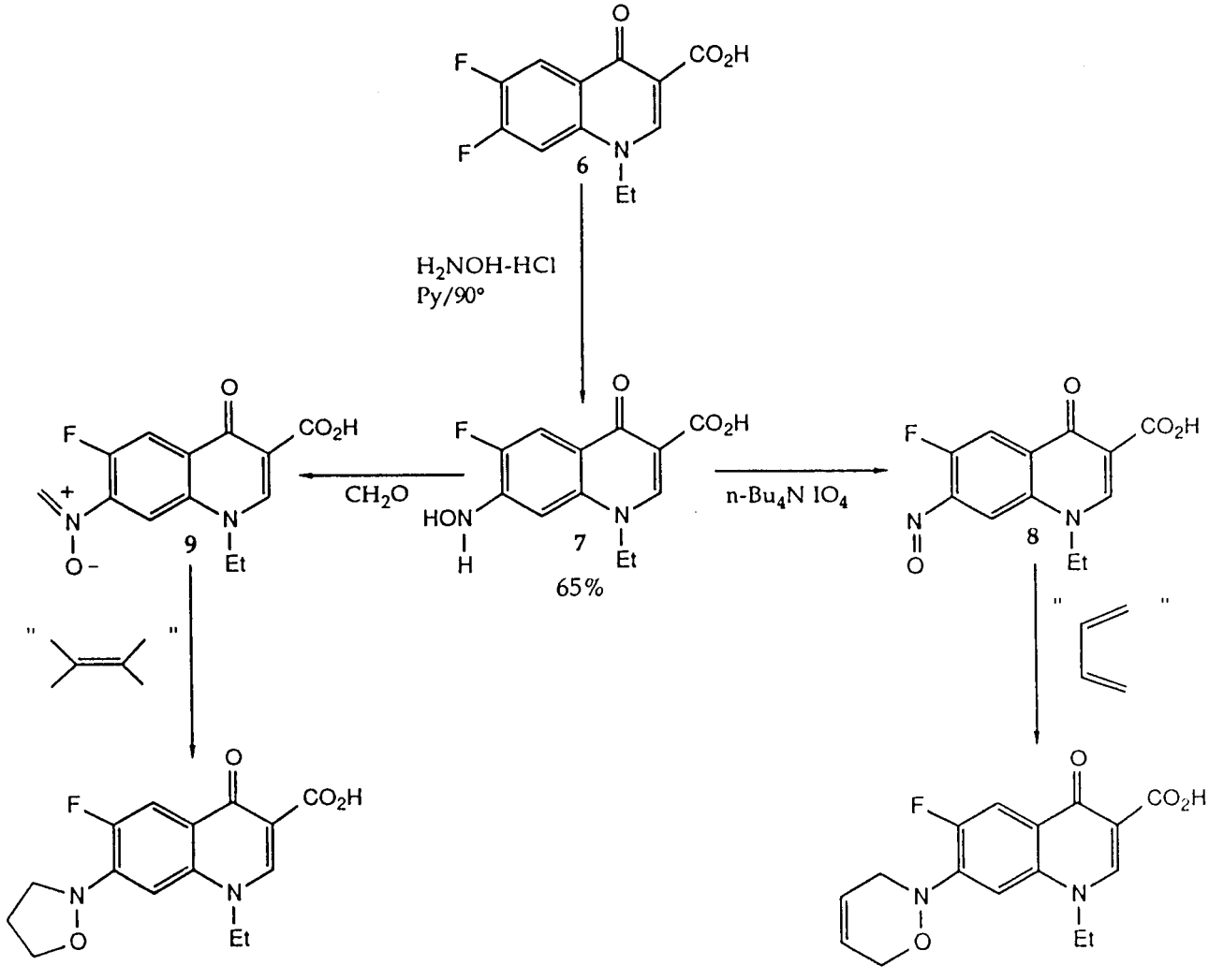
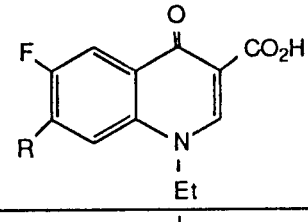
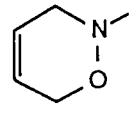
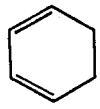
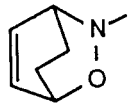
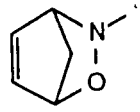
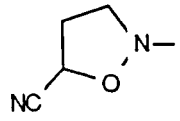
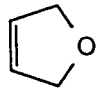
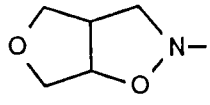


TABLE 1

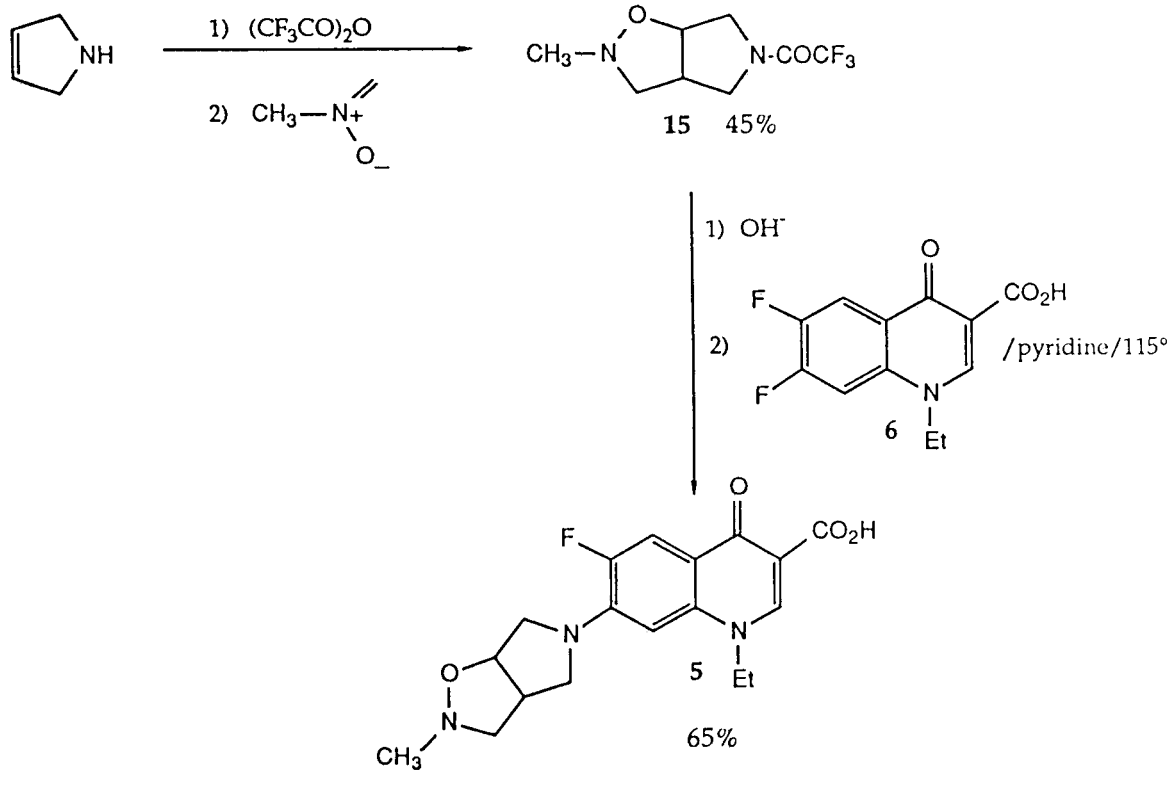
Nitroso and Nitrone Cycloadducts Resulting From Hydroxylamine 7



Compound	Olefin reacted	R	% yield	mp	Molecular Formula
10			40%	229-231°	$C_{16}H_{15}FN_2O_4$

11			42%	205°dec	$C_{18}H_{17}FN_2O_4$
12			10%	170°dec	$C_{17}H_{15}FN_2O_4$
13			72%	220°dec	$C_{16}H_{14}FN_3O_4$
14			53%	210°dec	$C_{17}H_{17}FN_2O_5$

SCHEME 2



In summary, we have found that a novel group of 7-(substituted)-4-oxoquinoline-3-carboxylic acids can be prepared through nitroso and nitrone cycloaddition chemistry. The antibacterial testing data for these compounds is forthcoming and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. The following were used for spectral characterizations: mass spectra, Varian CH-7 spectrometer, ir spectra, FT Nicolet 7199 spectrometer. The ^1H (80 MHz) and ^{13}C (75 MHz) nmr spectra were recorded either on a Varian FT80 or a Nicolet NT-300 WB spectrometer. Analtech silica gel GF plates (250 mm) were used for thin layer chromatography. Silcia gel (300-400 mesh), Merck Kieselgel 60 was employed for flash column chromatography. Solvents used were from freshly opened bottles of spectroscopy grade quality with no special drying procedure observed.

The nmr peaks were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, doublet of doublets. The ir, nmr and ms data of all compounds were consistent with assigned structures.

1-Ethyl-6-fluoro-7-hydroxylamino-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**7**).

A solution containing **6** (1g, 3.95 mmoles) in pyridine (15 ml) and hydroxylamine hydrochloride (1.37 g, 20 mmoles) was heated at 90° in a capped pressure bottle for 9.5 hours. After cooling in ice, the bottle was opened (**Caution: pressure build-up possible**). The tlc analysis (65:25:4 chloroform:methanol:water) showed the starting material gone and the appearance of one major product along with a minor fluorescent one (the 7-amino reduced product). The reaction was diluted with 30 ml water. On removing approximately ⅓ of the solution volume on the rotovap, the product precipitated, then collected, washed sequencially with water, ethanol then ether followed by drying to give 686 mg (65%) of **7**, mp 220° dec; ^1H nmr (DMSO-d_6): δ 1.45 (t, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.2 (d, $J_{H\text{-}F}$ = 8 Hz, 1H, H_8), 7.85 (d, $J_{H\text{-}F}$ = 12 Hz, 1H, H_5), 8.90 (s, 1H), 9.25 (s, 1H), 9.8 (s, 1H); ms: (ei) m/e (relative intensity) 266 (10), 250 (25), 222 (70), 206 (100), 191 (60).

Anal. Calcd. for $C_{12}H_{11}FN_2O_4$: C, 54.14; H, 4.16; N, 10.52; F, 7.14. Found: C, 54.46; H, 4.24; N, 10.70; F, 7.15.

1-Ethyl-6-fluoro-7-(3,6-dihydro-2*H*-1,2-oxazin-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**10**).

The hydroxylamine **7** (1.5 g, 5.6 mmoles) was added in a single portion to a solution containing tetrabutylammonium periodate (4.3 g, 10 mmoles) DMF (20 ml) saturated with 1,3-butadiene. The reaction flask was capped and heated at 40° for 3 hours, then overnight at 20°. The product was collected by filtration, washed sequencially with DMF, ether and then allowed to air dry to give 0.72 g (40%). The solid **10** was recrystallized from hot DMF, mp 229-231° dec; ^1H nmr (deuteriochloroform: trifluoroacetic acid): δ 1.62 (t, 3H, CH_3), 4.07 (bs, 2H, allylic CH_2), 4.4 (q, 2H, CH_2), 4.65 (bs, 2H, allylic CH_2), 6.0 (bs, 2H, olefinic), 7.6 (d, $J_{H\text{-}F}$ = 7 Hz, H_8), 8.13 (d, $J_{H\text{-}F}$ = 12 Hz, 1H, H_5), 8.7 (s, 1H, H_2), 15.0 (s, 1H, COOH); ms: (ei) m/e (relative intensity) 318 (25), 300 (10), 274 (100), 256 (72), 220 (73), 190 (80).

Anal. Calcd. for $C_{16}H_{15}FN_2O_4$: C, 60.37; H, 4.75; N, 8.80; F, 5.97. Found: C, 60.13; H, 4.57; N, 9.01; F, 5.75.

1-Ethyl-6-fluoro-7-(2-oxo-3-azabicyclo[2.2.1]hept-5-ene-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**12**).

This compound was prepared in a similar fashion to **10** using 5 eqivalents of freshly distilled cyclopentadiene; ^1H nmr (deuteriochloroform:trifluoroacetic acid): δ 1.7 (t, 3H, CH_3), 1.91 (d, $J_{H\text{-}H}$ = 9 Hz, bridgehead H), 2.24 (d, $J_{H\text{-}H}$ = 9 Hz, brigdehead H), 4.3 (q, 2H, CH_2), 5.4 (bs, 1H, bridge H), 5.45 (bs, 1H, bridge H), 6.0 (dd, 1H, vinyl H), 6.4 (dd, 1H, vinyl H), 7.14 (d, $J_{H\text{-}F}$ = 8 Hz, H_8), 8.05 (d, $J_{H\text{-}F}$ = 12 Hz, H_5), 8.7 (s, H_2); ms: (ei) m/e (relative intensity) no molecular ion seen, 264 (10, loss of cyclopentadiene), 220 (35), 180 (50), 66 (100, cyclopentadiene).

Anal. Calcd. for $C_{17}H_{15}FN_2O_4$: C, 61.82; H, 4.58; F, 5.75; N, 8.48. Found: C, 61.46; H, 4.49; F, 5.68; N, 8.49.

1-Ethyl-6-fluoro-7-(2-oxa-3-azabicyclo[2.2.2]oct-5-en-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**11**).

The hydroxylamine **7** (2.5 g, 9.4 mmoles) was dissolved in 50 ml of DMF. To this was added 10 ml of 1,3-cyclohexadiene followed by tetrabutylammonium periodate (17.3 g, 40 mmoles). The resultant reaction mixture was stirred at 20° for 23 hours. The precipitated product was collected by filtration, washed with DMF then ether and air dried to give 2.13 g. Recrystallization from hot DMF gave 1.35 g of **11** (42%), mp 205° dec; ^1H nmr (deuteriochloroform:trifluoroacetic acid): δ 1.65 (m, 5H, CH_3, CH_2), 2.4 (m, 2H, CH_2), 4.65 (q, 2H, CH_2), 5.1 (bs, 2H, bridgehead H's), 6.3 (t, $J_{H\text{-}H}$ = 7 Hz, 1H, vinyl H), 6.7 (t, $J_{H\text{-}H}$ = 7 Hz, 1H, vinyl H), 7.2 (d, $J_{H\text{-}F}$ = 8 Hz, H_8), 8.05 (d, $J_{H\text{-}F}$ = 12 Hz, H_5), 9.05 (s, H_2); ms: (ei) m/e (relative intensity) 344 (8), 300 (5), 220 (40), 206 (27), 190 (60), 80 (80), 78 (100).

Anal. Calcd. for $C_{18}H_{17}FN_2O_4$: C, 62.79; H, 4.98; N, 8.14; F, 5.52. Found: C, 62.46; H, 4.84; N, 8.34; F, 5.59.

1-Ethyl-6-fluoro-7-(4-cyano-3-isoxazolidinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**13**).

A suspension containing the hydroxylamine **7** (1 g, 3.76 mmoles), acrylonitrile (5 ml, 75 mmoles) and paraformaldehyde (1.0 g) in DMF (10 ml) was heated in a capped bottle at 90° for 15 hours. After cooling, water (30 ml) was added. The product was collected by filtration and recrystallized from DMF/water to give 900 mg (72%) of **13**, mp 220° dec; ^1H nmr (DMSO-d_6): δ 1.4 (t, 3H, CH_3), 2.5 (bs, DMSO), 2.75 (q, 2H, CH_2), 3.3 (s, H_2O), 3.8 (m, 2H, CH_2), 4.55 (q, 2H, CH_2), 5.6 (t, 1H, CHNC), 7.6 (d, $J_{H\text{-}F}$ = 8 Hz, H_8), 8.05 (d, $J_{H\text{-}F}$ = 12 Hz, H_5), 9.05 (s, H_2); ms: (ei) m/e (relative intensity) 331 (10), 304 (15), 287 (55), 260 (95), 206 (100); ir (potassium bromide): 2250 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}FN_3O_4$: C, 58.01; H, 4.26; N, 12.68; F, 5.74. Found: C, 58.19; H, 4.20; N, 12.61; F, 5.75.

1-Ethyl-6-fluoro-7-(tetrahydrofuro[3,4-*d*]isoxazol-2(3*H*)-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (**14**).

A suspension containing **7** (1 g, 3.76 mmoles), 2,5-dihydrofuran (2 ml, 26 mmoles) and paraformaldehyde (0.5 g) and DMF (10 ml) was heated at 140° in a capped bottle for 2 hours. On workup, the DMF was removed *in vacuo* leaving a solid residue. This residue was triturated with hot ethanol. The collected triturates were reduced in volume to crystallize 0.69 g (53%) of **14**, mp 210° dec; ^1H nmr (deuteriochloroform:trifluoroacetic acid): δ 1.37 (t, 3H, CH_3), 2.50 (s, 1H, CH), 3.25 (m, 1H, CHO), 3.5 (m, 3H), 3.8 (d, 1H, J = 9.5 Hz), 3.95 (m, 2H), 4.47 (q, 2H, CH_2-N), 4.9 (dd, 1H, J = 3.5 Hz), 7.45 (d, 1H, H_8, $J_{F\text{-}H}$ = 6.7 Hz), 7.83 (d, 1H, H_5, J = 12 Hz), 8.90 (s, 1H, H_2); ms: (ei) m/e (relative intensity) 348 (30), 304 (100), 218 (33).

Anal. Calcd. for $C_{17}H_{17}N_2FO_5$: C, 58.62; H, 4.92; N, 8.04; F, 5.45. Found: C, 58.40; H, 5.05; N, 7.98; F, 5.41.

Hexahydro-2-methyl-5-trifluoroacetyl-2*H*-pyrrolo[3,4-*d*]isoxazole (**15**).

A commerical sample of 3-pyrroline (10 g) contaminated with 25% of pyrrolidine was dissolved in a mixture of pyridine (15 ml) and ether (30 ml) then reacted with trifluoroacetic anhydride (22 ml) which was added dropwise over a period of one hour. The reaction mixture was stirred at room temperature for one additional hour and the pyridiniumtrifluoroacetate salt was filtered. The filtrate was evaporated to an oily residue which was distilled (36°/3.5 mm) to give 14 g of a 75/25 3-pyrroline/pyrrolidine trifluoroacetate mixture; ^1H nmr (deuteriochloroform): δ 1.95 (m, pyrrolidine impurity), 3.6 (pyrrolidine impurity), 4.4 (m, 4H), 5.7 (s, 2H, vinyl); ir (neat) cm^{-1}: 3160, 2960, 2900, 1700; ms: (ei) m/e (relative intensity) 165 (M^+, 98).

To a solution containing this 3-pyrroline/pyrrolidine trifluoroacetate

mixture (10 g) sodium acetate (3.7 g, 0.045 mole) and formaldehyde (4.7 ml, 0.06 mole, 38%) in ethanol (60 ml) was added *N*-methylhydroxylamine hydrochloride (3.8 g, 0.045 mole) in water (2 ml) and ethanol (13 ml) over 3 hours. The reaction mixture was refluxed overnight, cooled and then filtered. The filtrate was concentrated to approximately 10 ml volume, diluted with 30 ml water and the *p*H was adjusted to 7.0 with sodium bicarbonate. The product was extracted (ethyl acetate) then distilled (104°/2 mm) to give 5 g of **15** as a colorless oil (45%); ^{1}H nmr (deuteriochloroform): δ 2.7 (s, 3H, CH_3), 3.1-4.1 (m, 7H), 4.4 (m, 1H, CHO); ir (neat): cm^{-1} 2970, 2980, 2960, 1690.

Anal. Calcd. for $C_8H_{11}F_3N_2O_2$: C, 42.85; H, 4.94; F, 25.42; N, 12.49. Found: C, 42.66; H, 4.94; F, 25.49; N, 12.42.

1-Ethyl-6-fluoro-7-(hexahydro-2-methyl-5*H*-pyrrolo[3,4-*d*]isoxazol-5-yl)-3-quinolinecarboxylic Acid (**5**).

Dowex 1-X4 (Cl^-) resin was slurried in 10*N* sodium hydroxide, then transferred to a 2 cm OD column to form a 28 cm deep resin bed. The column was washed with water until neutral *p*H. The solution of **15** (5 g) in water (10 ml) was slowly passed through the column. The column was then washed with water until neutral *p*H. Column effluent cuts with *p*H = 10-11 were collected then evaporated to give 2.8 g (97%) of an oil which was hexahydro-2-methyl-2*H*-pyrrolo[3,4-*d*]isoxaxole and used crude in the reaction with **6**.

A suspension of **6** (2.53 g, 0.01 mole) and crude hexahydro-2-methyl-2*H*-pyrrolo[3,4-*d*]isoxazole (2.56 g, 0.02 mole) in pyridine (10 ml) was heated at 115° for 30 minutes under a nitrogen atmosphere. The light suspension was filtered hot and the product crystallized from the filtrate on cooling. The product was filtered, washed with pyridine and dried to give 2.34 g of **5** (65%), mp 210-212°; ^{1}H nmr (trifluoroacetic acid): δ 1.75 (t, 3H, CH_3), 3.5 (s, 3H, CH_3-N), 2.75-5.1 (m, 10H), 5.65 (m, 1H, CHO), 7.1 (d, 1H, H_8, $J_{H\text{-}F}$ = 8 Hz), 8.3 (d, 1H, H_5, $J_{H\text{-}F}$ = 12 Hz), 9.25 (s, 1H, H_2).

Anal. Calcd. for $C_{16}H_{20}FN_3O_4$: C, 59.82; H, 5.57; F, 5.25; N, 11.62. Found: C, 59.49; H, 5.55; F, 5.35; N, 11.65.

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[7] At temperatures greater than 100° substantial amounts of the corresponding 7-aminoquinolone derivative contaminates the reaction mixture.

[8] In all cases the product collected was only that which had precipitated at the end of the specified reaction time. The mother liquor in these reactions always contained additional product.

In entry 12 of Table 1, the dimerization of cyclopentadiene was most likely responsible for the lower isolated product yield.