Studies on Quinoline Derivatives and Related Compounds. II. Synthesis of 5-Substituted 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (1)

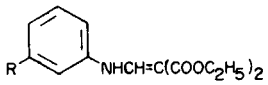
Hideo Agui, Toshiaki Komatsu and Takenari Nakagome (2)

Research Department, Pharmaceuticals Division, Sumitomo Chemical Co., 2-1, 4-Chome, Takatsukasa Takarazuka-shi, Hyogo-ken, Japan

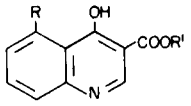
Received October 28, 1974

The cyclization of *m*-substituted anilinomethylenemalonates (**1**) in the presence of polyphosphate ester and some other cyclizing agents gave mixtures of the isomeric ethyl 5- (**2**) and 7-substituted 4-hydroxy-3-quinolinecarboxylates (**3**), which led to mixtures of the corresponding quinolinecarboxylic acids (**4** and **5**) by hydrolysis. The proportions of **4** and **5** in the mixtures were determined on the basis of their nmr spectra. Novel 5-chloro- (**8a**), 5-methyl- (**8b**) and 5-nitro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids were prepared and evaluated for antimicrobial activities. No significant activity, however, was noted.

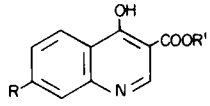
The discovery of the antibacterial activity of 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (**3**), and particularly of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**4**) spurred interest in the related quinolinecarboxylic acid derivatives. Although a number of 6-, 7-, or 8-substituted 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been prepared since then, there have been reported only two 5-substituted representatives, *i.e.*, 1-ethyl-5-fluoro- (3) and 1,4-dihydro-5-methoxy-1-methyl-4-oxo-3-quinolinecarboxylic acid (5). However, no evidence for their structures seems to have been presented in the patent litarature. Our continuing interest in this area led us to investigate the preparation of some 5-monosubstituted 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids (**8**). A search of the literature concerning the possible starting materials, 5-monosubstituted 4-hydroxy-3-quinolinecarboxylic esters, revealed that little work had been reported on their preparation. The products from thermal cyclizations of diethyl *m*-fluoroanilino- (6) and *m*-toluidinomethylenemalonates (**1b**) (7) were proved to be mixtures of isomeric ethyl 5- and 7-substituted-4-hydroxy-3-quinolinecarboxylates after converting them into the corresponding 4-hydroxyquinolines by hydrolysis and subsequent decarboxylation. In neither experiment was the 5-substituted 4-hydroxy-3-quinolinecarboxylate isolated. 5-Cyano-4-hydroxy-3-quinolinecarboxylic acid was the only product in the thermal cyclization of diethyl *m*-cyanoanilinomethylenemalonate followed by hydrolysis (8). Mapara and Desai (9) conducted cyclization of diethyl *m*-chloroanilino- (**1a**) and *m*-toluidinomethylenemalonate (**1b**) with a mixture of acetic anhydride and sulfuric acid, and obtained only the 5-isomers.



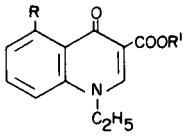
1



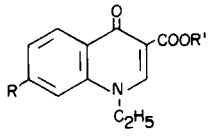
2 R' = C_2H_5
4 R' = H



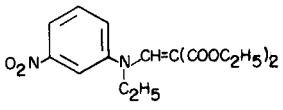
3 R' = C_2H_5
5 R' = H



6 R' = C_2H_5
8 R' = H

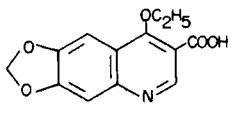


7 R' = C_2H_5
9 R' = H

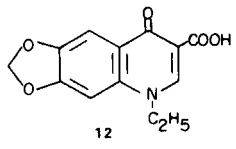


10

a R = Cl
b R = CH_3
c R = NO_2
d R = CF_3
e R = OCH_3



11



12

The first stage of the present study was to repeat the Mapara and Desai's acetic anhydride-sulfuric acid method. Diethyl *m*-chloroanilinomethylenemalonate (**1a**) was treated with acetic anhydride and sulfuric acid according to the

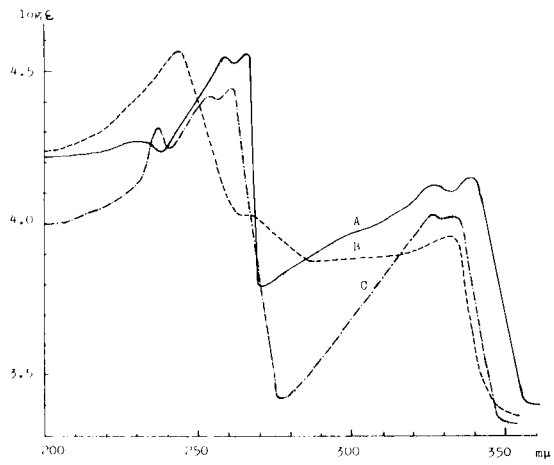


Figure 1. Uv spectra in 1% aqueous sodium carbonate of compounds. (**12**) (A); (**11**) (B); (**9a**) (C).

method of Mapara and Desai, affording a 28% yield of the cyclized product which was homogeneous by thin layer chromatography using common solvent systems; however, the nmr spectrum indicated that the product was a mixture of ethyl 5- (**2a**) and 7-chloro-4-hydroxy-3-quinolinecarboxylates (**3a**). The isomeric quinolinecarboxylates were separated into their respective pure forms, **2a**, m.p. 284-285° dec., and **3a**, m.p. 321-322° dec., on the basis of a differential solubility in dimethylformamide. Ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate (**3a**) was identical with the compound obtained by thermal cyclization of **1a** according to the method of Price and Roberts (10). The structure of **2a** was decided thus by elimination. Their nmr spectra were consistent with the assigned structures (Table II). Diethyl *m*-toluidinomethylenemalonate (**1b**) was cyclized similarly and the product, obtained in 39% yield, was shown to be an isomeric mixture by the nmr spectrum. However, the two isomers could not be separated by fractional recrystallization.

The cyclization reaction by means of acetic anhydride and sulfuric acid occurs so vigorously in an initial stage of the reaction that it is not recommended for large scale operations. With the objective of selecting a more effective cyclizing agent, the effect of other reagents on the yields and proportions of the cyclized isomers was investigated.

The anilinomethylenemalonates (**1a** and **1b**) were cyclized thermally or by using polyphosphoric acid, polyphosphate ester (PPE) or phosphorus oxychloride. The crude mixture of the quinolinecarboxylates was hydrolyzed *in situ* with aqueous sodium hydroxide and the resulting mixture of the quinolinecarboxylic acids precipitated on acidification. When phosphorus oxychloride was used, the cyclized products were the 4-chloro-3-quinolinecarboxylates, which led to the 4-hydroxy-3-quinolinecarboxylic acids by treatment with sodium acetate and acetic acid followed by hydrolysis with aqueous sodium hydroxide. The proposition of the 5- and 7-isomers shown in Table I was based upon the nmr spectral analyses.

The nmr data for the 5- and 7-substituted 4-hydroxy-3-quinolinecarboxylic acids (**4** and **5**) and their esters (**2** and **3**) are given in Table II. It is observed that a proton at C_5 appears at lower field than the other protons of the benzene ring with the exception of ethyl 4-hydroxy-4-nitro-3-quinolinecarboxylate (**5c**), in which a proton at C_8 is deshielded due to the anisotropy effect of the nitro gorup. Therefore a ratio of 5- (**4**) and 7-substituted 4-hydroxy-3-quinolinecarboxylic acids (**5**) in an isomeric mixture was

Table I

Ratios of 5- and 7-Substituted-4-hydroxy-3-quinolinecarboxylic Acids

meta Substituent	Cyclizing Agent or Solvent	Yield %	Ratio of 5-isomer (**2**):7-isomer (**3**)
Cl	Ac_2O, H_2SO_4	21	11:10
	PPE (a)	73	12:10
	PPA (b)	14	13:11
	$POCl_3$	26	13:12
	Dowtherm A	68	only 7-isomer
CH_3	Ac_2O, H_2SO_4	20	3:2
	PPE	76	8:6
	PPA	15	13:7
	$POCl_3$	67	15:11
	Dowtherm A	82	1:9
NO_2	PPE	6 (c)	1:4 (c)
CF_3	PPE	30	1:10
OCH_3	PPE	46	only 7-isomer

(a) Polyphosphate ester. (b) Polyphosphoric acid. (c) The yield and the productive ratio are those of a mixture of esters (**2c** and **3c**).

Table II

Nmr Data for 4-Hydroxy-3-quinolinecarboxylic Acids and Esters

Compound No.	C-CH_3	C-CH_2	5-CH_3	7-CH_3	7-OCH_3	H_2	H_5	H_6	H_7	H_8
2a	1.53 (t) J = 8	4.73 (q) J = 8				9.33 (bs)			7.67-8.33 (m)	
3a	1.57 (t) J = 8	4.67 (q) J = 8				9.32 (bs)	8.63 (d) J_{56} = 8	7.93 (dd) J_{65} = 8 J_{68} = 2		8.20 (d) J_{86} = 2
5a						9.45 (bs)	8.71 (d) J_{56} = 8	8.00 (dd) J_{65} = 8 J_{68} = 2		8.25 (d) J_{86} = 2
A mixture of **4a** and **5a**						9.45 (bs)	8.71 (d) J_{56} = 8		7.87-8.33 (m)	
5b				2.77 (s)		9.35 (d) J_{21} = 6	8.62 (d) J_{56} = 8	7.88 (bd) J_{65} = 8		7.97 (bs)
A mixture of **4b** and **5b**			3.13 (s)	2.77 (s)		9.33 (d) J_{21} = 8	8.60 (d) J_{56} = 8		7.07-8.37 (m)	
2c	1.57 (t) J = 8	4.75 (q) J = 8				9.50 (s)			7.92-8.58 (m)	
3c	1.58 (t) J = 8	4.79 (q) J = 8				9.56 (s)	8.94 (d) J_{56} = 8	8.70 (dd) J_{65} = 8 J_{68} = 2		9.15 (d) J_{86} = 2
A mixture of **4d** and **5d**						9.60 (s)	8.90 (d) J_{56} = 8		8.08-8.66 (m)	
5e					4.20 (s)	9.38 (d) J_{21} = 8	8.65 (d) J_{56} = 9	7.63 (bd) J_{65} = 9		7.55 (bs)

Chemical shift in δ units (ppm) in trifluoroacetic acid with TMS as internal standard. Coupling constants J in cps. Signals are designated as follows: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet.

Table III (a)

Uv Spectra of 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids.
Principal bands: λ max mμ log ϵ (in parenthesis)

Compound No.						
8a	222 (4.08)	248 (4.13)	257 (4.05)	310 (3.75)	332 (3.86)	*346 (3.77)
8b	227 (3.62)		255 (3.73)	305 (3.34)	327 (3.46)	338 (3.40)
8c	226 (4.13)	249 (4.19)	256 (4.24)	*312 (3.86)	327 (3.89)	
9a	227 (4.32)	253 (4.42)	261 (4.45)	305 (3.81)	325 (4.03)	334 (4.02)
9b	227 (4.40)	253 (4.47)	257 (4.47)		321 (4.12)	330 (4.10)
9c	*227 (4.20)		273 (4.40)	310 (3.99)		
12	222 (4.27)	258 (4.55)	267 (4.56)	*312 (4.04)	325 (4.13)	339 (4.15)
11 (b)	*225 (4.37)	243 (4.57)			*319 (4.91)	332 (4.96)

(a) Uv spectra were taken in 1% aq. sodium carbonate with a HITACHI 124 Spectrophotometer. The symbol (*) signifies an inflection. (b) Prepared by hydrolyzing ethyl 4-ethoxy-6,7-methylenedioxy-3-quinolinecarboxylate (13) with aqueous-ethanolic potassium hydroxide; colorless needles (dimethyl sulfoxide), m.p. 252° dec. *Anal.* Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.51; H, 4.05; N, 5.36.

calculated on the basis of integraged intensities of a proton at C_5 and the other protons of the benzene ring. In the nmr spectrum of a mixture of 4-hydroxy-5-methyl- (**4b**) and -7-methyl-3-quinolinecarboxylic acids (**5b**), a methyl group at C_5 is likewise deshielded by the anisotropy effect of the 4-oxo group. Similar findings have also been observed in 4-hydroxycinnoline (11). The ratio of **4b** and **5b**, therefore, was determined on the basis of integrated intensities

Table IV

MIC (μg./ml.) (a) of 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

Compound No.	*Staph. aureus* 209P	*E. coli* NIHJ	*Kleb. pneum.* 602	*Prot. mirab.* GN 2425	*Prot. vulg.* HX 19	*Pseud. aerug.* 104
8a	200	>200	>200	>200	>200	>200
8b	200	100	50	>200	100	>200
8c	>200	>200	>200	>200	>200	>200
9a	50	25	25	12.5	25	200
9b	200	6.25	25	12.5	12.5	>200
9c	50	12.5	12.5	25	12.5	200
Nalidixic Acid	100	3.13	6.25	12.5	1.56	200
Oxolinic Acid (**12**)	6.25	0.39	0.39	1.56	0.2	6.25

(a) The test organizm was inoculated into trypticase soy broth and incubated at 37° for 24 hours. Statement of a MIC value with symbol ((>)) means that no growth inhibition of the microorganism occurred with this concentration. Concentrations exceeding 200 μg./ml. have not been investigated.

of the C_5- and C_7-methyl groups. From the results shown in Table I, it was assumed that PPE was the most effective reagent for obtaining the 5-substituted quinolinecarboxylate among those examined in the present study. PPE was used, therefore, for the cyclization of diethyl *m*-nitroanilino- (**1c**) (8), *m*-trifluoromethylanilino- (**1d**) (6) and *m*-anisidinomethylenemalonates (**1e**) (12) in order to study the effect of the substituents on the direction of ring closure. The position of ring closure seems likely to be influenced largely by steric hindrance caused by the substituent, as shown in Table I. Thus, when the substituent was the trifluoromethyl group, the 7-isomer (**5d**) predominated, and with a methoxy group the 5-isomer was not detected in the product. These results were in contrast with those in the cyclization of the anilinomethylenemalonate substituted with a chloro or a methyl residue, described above.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids, the potential antimicrobials, were prepared in the following manner. 5-Chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**8a**) was prepared by treating **2a** with ethyl iodide and potassium carbonate in dimethylformamide followed by hydrolysis. The mixture of **2b** and **3b** obtained by cyclization of diethyl *m*-toluidinomethylenemalonate (**1b**) was hydrolyzed with aqueous sodium hydroxide to give a mixture of **4b** and **5b** which was ethylated in a similar manner to yield a mixture of isomeric 1-ethyl-1,4-dihydro-5-methyl- (**8b**) and -7-methyl-4-oxo-3-quinolinecarboxylic acids (**9b**). Fractional recrystallization from methanol gave the 5-isomer (**8b**) in 18% and the 7-isomer (**9b**) in 13% yield, respectively. Ethylation and hydrolysis steps could be reversed withoug significant difference in results.

It has been known that *N*-alkylation occurs in preference to *O*-alkylation in the alkylation of 4-hydroxy-3-quinolinecarboxylates (1,4,13). The alkylated compounds (**8a-b** and **9a-b**) in the present study were shown to be *N*-ethyl rather than *O*-ethyl compounds by the comparison of their uv spectra with those of 4-ethoxy-6,7-methylenedioxy-3-quinolinecarboxylic acid (**11**) and 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**12**). As Table III and Figure 1 show, the spectra of **8a-b** and **9a-b** closely resemble that of **12**, thus confirming the *N*-ethyl-4-quinolone structure.

Although ethyl 4-hydroxy-5-nitro- (**2c**) and -7-nitro-3-quinolinecarboxylates (**3c**) were separated by fractional recrystallization of the cyclization product of diethyl *m*-nitroanilinomethylenemalonate (**1c**), the yield of **2c** from **1c** was only 1%. An alternative pathway, therefore, was tried to obtain 1-ethyl-1,4-dihydro-5-nitro-4-oxo-3-quinolinecarboxylic acid (**8c**). *N*-Ethyl-*m*-nitroaniline (14) was condensed with diethyl ethoxymethylenemalonate in a conventional manner (1) to afford a 30% yield of diethyl *N*-ethyl-*m*-nitroanilinomethylenemalonate (**10**), which was cyclized in the presence of PPE. The cyclized product, shown to be a mixture of isomeric quinoline esters (**6c** and **7c**) by the nmr spectral study, was separated by column chromatography to ethyl 1-ethyl-1,4-dihydro-5-nitro- (**6c**) and -7-nitro-4-oxo-3-quinolinecarboxylates (**7c**). The yields, however, were not significantly improved (**6c** in 3%, and **7c** in 5% yield). Alkaline hydrolysis of these quinoline esters gave 1-ethyl-1,4-dihydro-5-nitro- (**8c**) and -7-nitro-4-oxo-3-quinolinecarboxylic acids (**9c**), respectively.

5- And 7-substituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids prepared in the present study were tested for antibacterial activities on some microorganisms and compared with nalidixic and oxolinic acids. The susceptibility of the microorganisms to the compounds was

determined by a 2-fold serial dilution method used by Turner *et al.* (15), and expressed as minimum inhibitory concentration (MIC) in μg/ml. As seen in Table IV, the 5-substituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids exhibited only slight or no activity in the test, while the 7-substituted derivatives were more active than their isomers. These compounds, however, were still less active than nalidixic and oxolinic acids.

EXPERIMENTAL (16)

Ethyl 5-Chloro- (**2a**) and 7-Chloro-4-hydroxy-3-quinolinecarboxylates (**3a**).

To a stirred mixture containing 7 ml. of acetic anhydride and 3.96 g. (0.02 mole) of *m*-chloroanilinomethylenemalonate (**1a**) (10) was added in one portion 4 ml. of concentrated sulfuric acid, whereupon the temperature spontaneously rose to about 100°. Stirring was continued for about 5 minutes and the resulting dark brown solution was poured into ice water. The precipitate was collected by filtration, washed consecutively with water, ethanol and chloroform, and dried, yielding 1.39 g. (28%) of a crude mixture consisting of **2a** and **3a**. This product was recrystallized from *ca.* 30 ml. of dimethylformamide to give a white solid which still contained **2a** and **3a**. The mother liquor was evaporated *in vacuo* and the residue washed with chloroform and recrystallized from dimethylformamide to give pale yellow needles of ethyl 5-chloro-4-hydroxy-3-quinolinecarboxylate (**2a**), yield 0.1 g. (2%), m.p. 284-285° dec., (lit. (9) 271°).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.26; H, 4.00; N, 5.56; Cl, 14.07. Found: C, 57.46; H, 3.81; N, 5.45; Cl, 14.28.

The mixture of **2a** and **3a** obtained after one recrystallization was recrystallized further four times from dimethylformamide to afford 0.22 g. (5%) of ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate (**3a**) as colorless needles, m.p. 321-322° dec., undepressed on admixture with the sample prepared according to the method of Price and Roberts (10). The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.26; H, 4.00; N, 5.56; Cl, 14.07. Found: C, 57.20; H, 3.74; N, 5.45; Cl, 14.37.

Cyclization of *m*-Substituted Anilinomethylenemalonates.

m-Substituted anilinomethylenemalonates were cyclized by the following procedures. A crude cyclized product led directly to a mixture of isomeric carboxylic acids (or single carboxylic acid in a few instances) which was readily separable from a reaction mixture. The yield of product and the ratio of the carboxylic acids are listed in Table I.

A. With Acetic Anhydride and Sulfuric Acid.

An anilinomethylenemalonate (**1a** or **1b**, 0.02 mole) was treated with acetic anhydride and sulfuric acid in the same manner as described above. The reaction mixture was poured into ice water and the resulting solution was neutralized to *p*H 7 by the addition of 30% aqueous sodium hydroxide. An insoluble solid was collected by filtration, washed with water and dissolved in 50 ml. of 10% potassium hydroxide. The alkaline solution was stirred and heated at 90-100° for 2 hours, treated with charcoal and filtered. The filtrate was acidified to *p*H 1-2 by the addition of 6 *N* hydrochloric acid and cooled. The precipitate, found to be a mixture of 5- and 7-substituted quinolinecarboxylic acids by the nmr spectrum, was filtered, washed with water and dried *in vacuo*.

B. With Polyphosphate Ester (PPE).

A mixture containing 15 g. of phosphorus pentoxide, 15 ml. of anhydrous ether and 30 ml. of chloroform was gently refluxed until the solution was clear (*ca.* 30 hours), and filtered through glass wool to remove a small amount of insoluble material (16).

To the resulting oily solution of PPE was added an anilinomethylenemalonate (**1a-e**, 0.02 mole). The reaction mixture was stirred and heated at 90-100° for 2 hours. After cooling, the oily mixture was poured into ice water, the precipitated solid filtered and washed with water. The cyclization products obtained herein were subjected to alkaline hydrolysis in the same manner described above except for the product from **1c** (see Table I).

C. With Polyphosphoric Acid (PPA).

A mixture containing an anilinomethylenemalonate (**1a** or **1b**, 0.02 mole) and 20 g. of PPA was stirred and heated at 100-110° for 2 hours. After cooling the pale orange syrupy material was mixed with ice water and processed in the same manner as described above.

D. With Phosphorus Oxychloride.

A mixture containing an anilinomethylenemalonate (**1a** or **1b**, 0.02 mole) and 50 ml. of phosphorus oxychloride was refluxed for 4 hours. The excess phosphorus oxychloride was distilled off under reduced pressure, the syrupy residue was poured into ice water and made alkaline by the addition of saturated aqueous sodium bicarbonate. The mixture was shaken three times with chloroform, the combined chloroform layers separated, washed with 5% aqueous sodium bicarbonate and then with water, dried over magnesium sulfate and evaporated. The resulting syrup was dissolved in 50 ml. of acetic acid and sodium acetate (2.45 g.) was added. The mixture was refluxed for 4 hours and the acetic acid removed *in vacuo*. To the residue was added 30 ml. of 5% aqueous potassium hydroxide and 5 ml. of methanol, and the mixture was refluxed for 2 hours. The resulting solution was treated with charcoal and acidified to *p*H 1-2 by the addition of 6 *N* hydrochloric acid, whereupon a mixture of isomeric quinolinecarboxylic esters deposited out, which was collected by filtration, washed with water and dried *in vacuo*.

E. Thermal Cyclization in Dowtherm A.

An anilinomethylenemalonate (**1a** or **1b**, 0.02 mole) was cyclized thermally in boiling Dowtherm A and the product was hydrolyzed according to the method of Price and Roberts (10).

From **1a**, 3.04 g. (68%) of 7-chloro-4-hydroxy-3-quinolinecarboxylic acid (**5a**) was obtained, m.p. 275-276° dec. (lit. (10) 273-274° dec.). That the product was not contaminated with the 5-chloro isomer was confirmed by the nmr spectrum.

From **1b**, 3.33 g. (82%) of a mixture of 4-hydroxy-5-methyl- (**4b**) and 4-hydroxy-7-methyl-3-quinolinecarboxylic acid (**5b**) having a melting point of 263-264° dec., was obtained. Recrystallization from dimethylformamide gave 1.76 g. (43%) of pure **5b**, m.p. 271-272° dec. (lit. (9) 263° dec.).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.90; H, 4.53; N, 6.79.

5-Chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**8a**).

A mixture containing 0.2 g. of ethyl 5-chloro-4-hydroxy-3-quinolinecarboxylate (**2a**), 0.138 g. of powdered potassium carbonate, 0.624 g. of ethyl iodide and 30 ml. of dimethylformamide was stirred and heated at 100-110° for 4 hours. The reaction was followed by *tlc* using a mixture of chloroform and methanol (10:1) as solvent. After the reaction was completed, the excess reagent

and solvent were removed *in vacuo*. To the residue was added 20 ml. of 10% aqueous potassium hydroxide and 5 ml. of methanol. The mixture was refluxed for one hour. After cooling, the solution was acidified to *p*H 1 by the addition of concentrated hydrochloric acid. The resulting solid was collected by filtration, washed with water and recrystallized from aqueous dimethylformamide, yielding 0.1 g. (50%) of the acid (**8a**) as colorless needles, m.p. 270-272° dec; nmr spectrum (trifluoroacetic acid): 1.83 δ (CH_3, t), 2.98 δ ($C\text{-}CH_2$, q), 8.02-8.04 δ (ring protons), 9.48 δ (C-2 proton, s).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.23; H, 4.00; N, 5.56. Found: C, 57.16; H, 3.94; N, 5.49.

7-Chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**9a**).

The quinolinecarboxylic acid (**5a**) was ethylated by means of ethyl iodide in the same manner as for the preparation of the 5-chloro isomer (**8a**). Recrystallization of the product from dimethylformamide gave colorless needles of **9a**, yield 77%, m.p. 275-276° (lit. (2) 274°); nmr spectrum (trifluoroacetic acid): 1.83 δ (CH_3, t), 4.95 δ ($C\text{-}CH_2$, q), 8.02 δ (C-6 proton, q), 8.27 δ (C-8 proton, d), 8.78 δ (C-5 proton, d), 9.50 δ (C-2 proton, s).

1-Ethyl-5-methyl- (**8b**) and -7-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**9b**).

The isomeric mixture (1.0 g.) of **4b** and **5b** prepared by cyclization of *m*-toluidinomethylenemalonate (**1b**) with PPE followed by hydrolysis, was added to a stirred mixture containing 1.36 g. of powdered potassium carbonate, 3.12 g. of ethyl iodide and 20 ml. of dimethylformamide. The resulting mixture was stirred and heated at 100-110° for 5 hours, during which time the reaction was followed by *tlc* using a mixture of chloroform and methanol (10:1) as solvent. After the reaction was completed, the excess reagent and solvent were removed *in vacuo*. To the residue was added 30 ml. of 10% aqueous potassium hydroxide. The mixture was refluxed for one hour. The solution was acidified to *p*H 1 by the addition of 6 *N* hydrochloric acid. The precipitate was collected by filtration, washed with water and dried to give 0.94 g. (83%) of a white solid. This solid consisting of the acids (**8b** and **9b**) was digested with 50 ml. of hot methanol, and the mixture filtered while hot. The insoluble material was recrystallized from dimethylformamide to give 0.15 g. (13%) of 1-ethyl-1,4-dihydro-7-methyl-4-oxo-3-quinolinecarboxylic acid (**9b**) as colorless prisms, m.p. 280-282° (lit. (3) 285°, (5) 285-286°; nmr spectrum (trifluoroacetic acid): 1.83 δ (CH_3, t), 2.83 δ (CH_3, s), 4.96 δ ($C\text{-}CH_2$, q), 7.94 δ (C-6 proton, q), 8.10 δ (C-8 proton, d), 8.72 δ (C-5 proton, d), 9.42 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.57; N, 6.05.

The methanolic filtrate was allowed to stand overnight at room temperature. The precipitate was collected by filtration and recrystallized from *ca.* 100 ml. of hot methanol, yielding 0.1 g. of the first crop consisting of **8b** and **9b** and 0.2 g. (18%) of the second crop consisting of 1-ethyl-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic acid (**8b**) as colorless needles, m.p. 216-218°: nmr spectrum (trifluoroacetic acid): 1.80 δ (CH_3, t), 3.13 δ (CH_3, s), 4.91 δ ($C\text{-}CH_2$, q), 7.63-8.23 δ (ring protons), 9.35 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.68; H, 5.69; N, 5.97.

Ethyl 4-Hydroxy-5-nitro- (**2c**) and -7-nitro-3-quinolinecarboxylates (**3c**).

A mixture containing 6.16 g. of *m*-nitroanilinomethylenemalonate (8) and 20 g. of PPE (17) was stirred and heated at 110° for 4 hours. After cooling, the mixture was poured into ice water. The brown solid that separated out was filtered, washed with water and then with ethanol. Recrystallization from aqueous dimethylformamide gave 0.32 g. (6%) of white solid consisting of **2c** and **3c** in a ratio of 1 to 2, as determined by the nmr spectrum. Second recrystallization from dimethylformamide (*ca.* 50 ml.) yielded 0.21 g. (4%) of pure ethyl 4-hydroxy-7-nitro-3-quinolinecarboxylate (**3c**) as colorless needles, m.p. 344° dec. (lit. (8) > 300°).

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.19; H, 4.04; N, 10.78.

The second dimethylformamide filtrate was concentrated to a small volume, diluted with a small amount of water and cooled. The deposited crystals were collected by filtration, washed with water and dried, yielding 0.06 g. (1%) of ethyl 4-hydroxy-5-nitro-3-quinolinecarboxylate (**2c**), m.p. 320° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.01; H, 3.78; N, 10.47.

Ethyl *N*-Ethyl-*m*-nitroanilinomethylenemalonate (**10**).

A mixture containing 0.89 g. of *N*-ethyl-*m*-nitroaniline (14), 1.16 g. of diethyl ethoxymethylenemalonate was stirred and heated at 110-120° until the evolution of ethanol ceased (6 hours). The disappearance of the *N*-ethylaniline was confirmed by tlc using isopropyl ether as solvent. The resulting syrup was washed with *n*-hexane which was removed by decantation. The residue was dissolved in chloroform and the solution passed through a silica gel column for chromatography. Evaporation of the solvent from the eluate afforded 0.72 g. (30%) of the pure malonate (**10**) as a yellow viscous liquid.

Anal. Calcd. for $C_{16}H_{20}N_2O_6$: C, 57.19; H, 6.00; N, 8.34. Found: C, 56.76; H, 5.85; N, 8.22.

Cyclization of Ethyl *N*-Ethyl-*m*-nitroanilinomethylenemalonate (**10**).

Ethyl 1-Ethyl-1,4-dihydro-5-nitro- (**6c**) and -7-nitro-4-oxo-3-quinolinecarboxylates (**7c**).

A mixture containing 7.56 g. of the malonate (**10**), and 20 g. of PPE (17) was stirred and heated for 6 hours. After cooling, the mixture was poured into 30 ml. of ice water and extracted with chloroform. The chloroform layer was separated, washed with water, and dried over sodium sulfate. The filtered solution was evaporated, the residue (7.13 g.) triturated with 100 ml. of ethanol and filtered to give 1.5 g. of yellow powder, m.p. 183-197°.

This was dissolved in chloroform-ethanol (9:1) mixture and passed through a silica gel column for decolorization. Evaporation of the solvent left 1.07 g. of a yellow solid which was again dissolved in chloroform and the solution poured on a silica gel column for chromatography. The initial fraction eluted with chloroform, gave 0.18 g. (3%) of a yellow solid having a melting point of 201-202°. Recrystallization from ethanol gave 0.15 g. of ethyl 1-ethyl-1,4-dihydro-5-nitro-4-oxo-3-quinolinecarboxylate (**6c**) as yellow scales, m.p. 201-202°; nmr spectrum (trifluoroacetic acid): 1.57 δ (CH_3, t), 1.83 δ (CH_3, t), 4.78 δ ($C\text{-}CH_2$, q), 5.12 δ ($C\text{-}CH_2$, q), 8.05-8.78 δ (ring protons), 9.60 δ (C-2 proton, s).

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.58; H, 4.72; N, 9.43.

The following fraction eluted with chloroform-methanol (98:2) mixture afforded 0.33 g. (5%) of ethyl 1-ethyl-1,4-dihydro-7-nitro-4-oxo-3-quinolinecarboxylate (**7c**) upon evaporation of the solvent, m.p. 221-223°. Recrystallization from ethanol gave 0.3 g. of yellow needles, m.p. 224-226°; nmr spectrum (trifluoroacetic acid): 1.57 δ (CH_3, t), 1.85 δ (CH_3, t), 4.78 δ ($C\text{-}CH_2$, q), 5.13 δ

($C\text{-}CH_2$, q), 8.78 δ (C-6 proton, q), 9.10 δ (C-5 proton, d), 9.23 δ (C-8 proton, d), 9.63 δ (C-2 proton, s).

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.73; H, 4.84; N, 9.61.

1-Ethyl-1,4-dihydro-5-nitro-4-oxo-3-quinolinecarboxylic Acid (**8c**).

A mixture containing 0.1 g. of the ester (**6c**) and 5 ml. of 10% aqueous sodium hydroxide was refluxed for 2 hours. After cooling, the solution was acidified to *p*H 1-2 by the addition of *N* hydrochloric acid. The precipitate was filtered, washed with water and recrystallized from dimethylformamide, yielding 0.06 g. (67%) of the acid (**8c**) as colorless needles, m.p. 265-267° dec.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84; N, 10.86. Found: C, 54.78; H, 4.08; N, 10.37.

1-Ethyl-1,4-dihydro-7-nitro-4-oxo-3-quinolinecarboxylic Acid (**9c**).

The ester (**7c**) (0.08 g.) was hydrolyzed in the same procedure given above. Recrystallization of the product from dimethylformamide afforded 0.05 g. (69%) of the acid (**9c**) as orange needles, m.p. 287-289° dec., (lit. (3) 277-278°).

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84; N, 10.86. Found: C, 54.83; H, 4.09; N, 10.44.

REFERENCES

(1) H. Agui, T. Mitani, M. Nakashita and T. Nakagome, *J. Heterocyclic Chem.*, 8, 357 (1971).

(2) Author to whom inquiries concerning this paper should be directed.

(3) N. Barton, A. F. Crowther, W. Hepworth, D. N. Richardson and G. W. Driver, British Patent 830, 832 (1960): *Chem. Abstr.*, 55, 7442e (1961).

(4) D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968).

(5) M. Nakanishi, T. Yokobe, A. Tsuda, Japanese Patent 10549 (1969); *Chem. Abstr.*, 71, 91331p (1969).

(6) H. R. Snyder, H. E. Freier, P. Kovacic and E. M. van Heyningen, *J. Am. Chem. Soc.*, 69, 371 (1947).

(7) R. M. Roberts, *J. Org. Chem.*, 14, 277 (1949).

(8) C. C. Price, H. R. Snyder, O. H. Bullit, Jr. and P. Kovacic, *J. Am. Chem. Soc.*, 69, 374 (1974).

(9) R. K. Mapara and C. M. Desai, *J. Indian Chem. Soc.*, 31, 951 (1954).

(10) C. C. Price and R. M. Roberts, *J. Am. Chem. Soc.*, 68, 1204 (1946).

(11) J. M. Bruce, P. Knowles and L. S. Besford, *J. Chem. Soc.*, 4044 (1964).

(12) W. M. Lauer, R. T. Arnold, B. Tiffany and J. Tinker, *J. Am. Chem. Soc.*, 68, 1268 (1946).

(13) T. Nakagome, H. Agui, T. Mitani, and M. Nakashita, *German Offen* 2,103,805; *Chem. Abstr.*, 75, 98458b (1971).

(14) E. Nölting and Th. Stricker, *Ber.*, 19, 546 (1886).

(15) F. J. Turner, S. M. Ringel, J. M. Martin, P. J. Storino, J. M. Daly and B. S. Schwartz, "Antimicrobial Agents and Chemotherapy," 475-479 (1968).

(16) All melting points are uncorrected. The nuclear magnetic resonance spectra were taken in the solvent indicated with a Varian T60 Spectrometer and compared with TMS as an internal standard. In thin layer chromatography silica gel on plastic sheet (Spotfilm^R fluorescent, Tokyo Kasei Kogyo Co. Ltd.) was used throughout this work unless otherwise stated.

(17) L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1967, p. 892.