Studies on Quinoline Derivatives and Related Compounds. I. A New Synthesis of 1-Alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids.

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A novel preparative method for 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids was developed. The key process is the cyclization of *N*-alkylanilinomethylenemalonates, which was effected successfully in the presence of polyphosphoric acid, polyphosphate ester, boron trifluoride or a mixture of acetic anhydride and sulfuric acid. With phosphorus oxychloride, *N*-alkylanilinomethylenemalonates yielded 1-alkyl-4-chloro-3-carbethoxyquinolinium salts which were hydrolyzed readily to ethyl 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates or their acids. By means of this novel method several new 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids were prepared.

1-Alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been found to be effective against microorganisms, particularly gram-negative pathogens. 1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (nalidixic acid) (**1**) (2) possessing the related structure has been used for clinical purpose.

1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (oxolinic acid) (**2**) (3) has exhibited more potent antimicrobial activity in *in vitro* and *in vivo* studies (4).

The purpose of this investigation was to provide a novel and more advantageous method than that known for the synthesis of 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid derivatives from the industral standpoint. The known route to these compounds involves cyclization of substituted anilinomethylenemalonates and alkylation of the resulting 4-hydroxy-3-quinolinecarboxylates at the expense of a large excess of an alkyl halide. The present authors found that *N*-alkylanilinomethylenemalonates derived from substituted *N*-alkylanilines cyclized smoothly to afford the desired 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates in high yields by the use of suitable cyclizing agents.

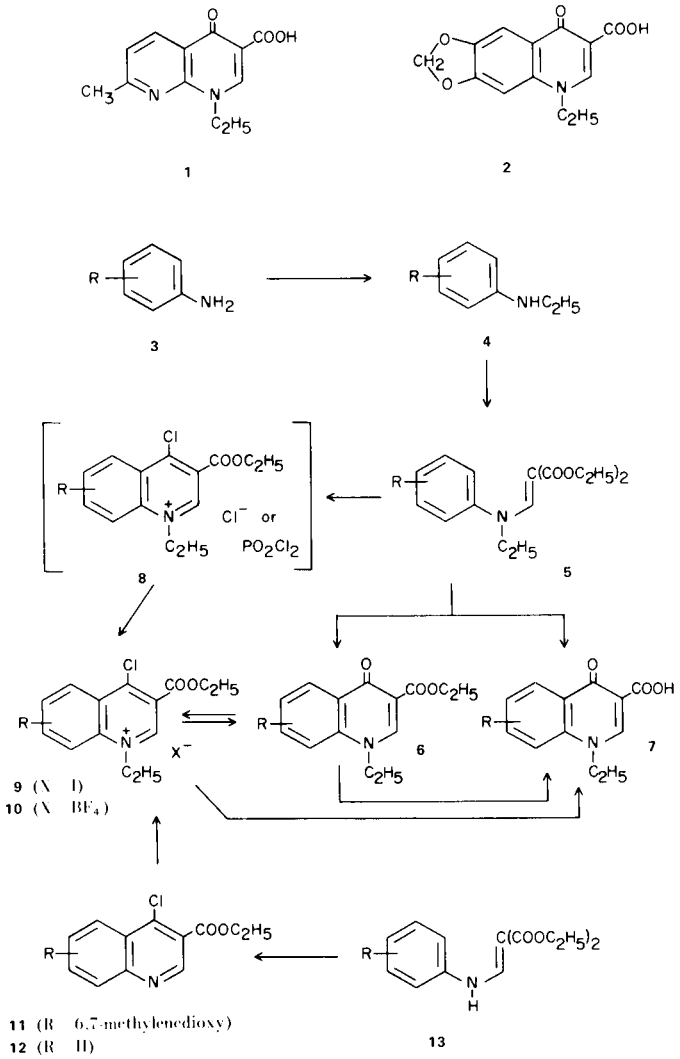
In view of the fact that the *N*-ethyl derivatives were the most active agents among other related *N*-substituted compounds in both series of nalidixic (5) and oxolinic acids (3,4), our attention was focused principally upon *N*-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates.

N-Ethylanilines employed as starting materials in this investigation were prepared by extending the Raney nickel catalyzed *N*-alkylation reaction of aniline discovered by Mozingo *et al.* (6), and developed independently by Rice and Kohn (7) and Ainsworth (8). These authors have reported the alkylation reaction of aniline with a variety of aliphatic alcohols in the presence of Raney nickel catalyst. Benzidine (7), 2,5-dimethoxyaniline (8) and α-naphthylamine have likewise been alkylated with ethanol. However, no other substituted anilines seem to have been subjected to this reaction.

The alkylation reaction was accomplished simply by refluxing a mixture of a substituted aniline, Raney nickel and an excess amount of ethyl alcohol, and the results of the ethylation of substituted anilines in the present study are summarized in Table I. *o*-Nitro and *p*-nitroanilines failed to react. α,α,α-Trifluoro-*o*-toluidine, *o*-phenetidine and *o*-ethylaniline required a large amount of the catalyst or a long reaction period. It appears that the introduction of electron withdrawing substituents into the *o*- or *p*-position to the amino group hinders the reaction. This experimental result is consistent with the report (8) that no alkylation was observed with 2-aminopyridine and 5-aminotetrazole. The existence of bulky groups at the *o*-position also decreases the reactivity, although in lesser degree. Other substituted anilines (**3e**, **3f**, **3h**, **3i**, **3k**) were ethylated smoothly to afford the corresponding *N*-ethylanilines in high yields. It was characteristic of this reaction that these secondary anilines were formed exclusively with out being accompanied by tertiary diethylanilines.

In addition to these *N*-ethylanilines (**4d-i**, **4k-l**) obtained in this manner, *N*-ethylaniline (**4a**), *N*-ethyl-*o*- (**4b**) and -*p*-toluidine (**4c**), and *N*-ethyl-α-naphthylamine (**4j**) were allowed to react with diethyl ethoxymethylenemalonate

SCHEME I



(EMME) (9), and diethyl *N*-ethylanilinomethylenemalonates (**5a-k**) were obtained in good yields with the exception of **4l** which did not react under conventional reaction conditions. The failure of compound **4l** to react might be attributed to the lesser electron density at the nitrogen atom.

Then the thermal cyclization of malonates **5a** (**5**, R = H) and **5i** (**5**, R = 6,7-methylenedioxy) in Dowtherm was attempted, no cyclization taking place.

The use of polyphosphoric acid (PPA) as a cyclizing agent, however, was found to be fruitful, and gave ethyl 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**6a**) from **5a** and **6i** from **5i** in 76 and 79% yields, respectively (10). The two quinolones (**6a** (10a) and **6i** (3)) are known compounds and were identical with the samples prepared by the reported procedure (3). The esters (**6a** and **6i**) were hydrolyzed readily to the carboxylic acids (**7a** and **7i**). When cyclization with PPA was conducted at an elevated temperature the acid (**6a**) was obtained in decreased yield. An attempted synthesis of compound **6a** in one stage by heating *N*-ethylaniline (**4a**) with EMME in the presence of PPA failed.

Polyphosphate ester (PPE) and boron trifluoride could replace PPA successfully in the same cyclizations. Cyclization of **5a** with a mixture of acetic anhydride and sulfuric acid, which has been used by Bandiwala and Desai (11) for the preparation of 2-substituted-4-quinolinols, followed by alkaline hydrolysis gave a moderate yield of **7a**. Heating **5a** with phosphorus pentoxide in boiling benzene resulted in the partial cleavage of the malonate, *N*-ethylaniline being separated in addition to some (17%) of the cyclized ester (**6a**). Other variations of cyclizing agents, for example zinc chloride in acetic anhydride and acetic acid or a melt of aluminium chloride, had virtually no effect.

When the malonate **5i** was heated with phosphorus oxychloride, cyclization took place smoothly to give a quinolinium salt (**8i**). This intermediate was converted to the iodide (**9i**) and isolated for characterization. The same compound was prepared also by the action of phosphorus oxychloride on **6i** or by quaternization of compound **11** with ethyl iodide. Compound **11** was prepared

SCHEME II

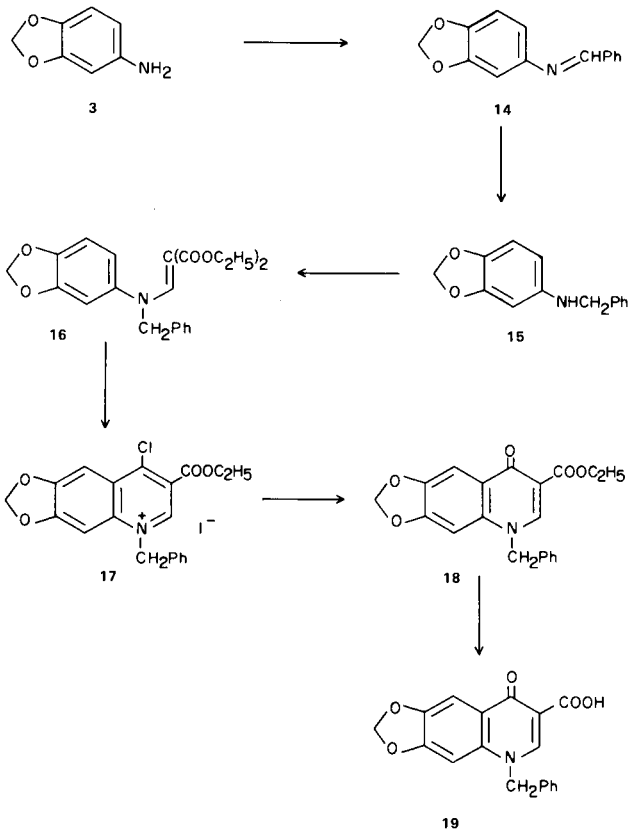


TABLE I

Raney Nickel Catalyzed *N*-Alkylation of Anilines with Ethanol

Starting material					*N*-Ethylaniline	
Substituent	Amount, g. (mole)	Raney Ni, g.	Ethanol, ml.	Reflux time, hr.	Compound No.	Yield, %
2-Ethyl	15.2 (0.125)	8 (a)	50	55	**4d**	80 (b)
2-Methoxy	37 (0.3)	10	100	9	**4e** (c)	80
4-Methoxy	35 (0.28)	15	100	5.5	**4f** (d)	90
2-Ethoxy	41 (0.3)	10	100	30	**4g** (e)	46 (b)
3,4-Dimethoxy	31 (0.3)	7	75	6	**4h** (f)	88
3,4-Methylene-dioxy	123 (0.9)	30	500	8	**4i**	96
3-Trifluoro-methyl	24 (0.15)	6	50	19	**4k**	88
2-Trifluoro-methyl	24 (0.15)	20 (g)	50	95	**4l**	11 (b)
2-Nitro	41 (0.3)	10	100	14		
4-Nitro	5 (0.036)	4	50	54		

(a) Raney nickel was divided into two portions. The second 4 g. portion was added 30 hours after the reaction started. (b) The reaction was interrupted, and the desired *N*-ethylaniline was separated from the remaining primary aniline by silica gel column chromatography using carbon tetrachloride as the eluent. (c) Lit. (14). (d) Lit. (15 and 16). (e) Lit. (17). (f) Lit. (18). (g) Each 5 g. portion of Raney nickel was added at 5 hour intervals over the period of initial 20 hours.

TABLE II

Diethyl *N*-Ethylarylaminomethylenemalonates

Compound No.	Arylamino	Molecular Formula	Elemental Analysis					
			Calcd., %			Found, %		
			C	H	N	C	H	N
5a	Anilino (a)	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	65.78	7.39	5.04
b	*o*-Toluidino	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.75	7.38	4.45
c	*p*-Toluidino	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.45	7.38	4.73
d	*o*-Ethylanilino	$C_{18}H_{25}NO_4$	67.69	7.89	4.39	67.35	7.91	4.30
e	*o*-Anisidino	$C_{17}H_{23}NO_5$	63.53	7.21	4.36	63.41	7.49	4.39
f	*p*-Anisidino	$C_{17}H_{23}NO_5$	63.53	7.21	4.36	63.32	6.95	3.92
g	*o*-Phenetidino	$C_{18}H_{25}NO_5$	64.46	7.51	4.18	64.17	7.35	4.07
h	3,4-Dimethoxy-anilino	$C_{18}H_{25}NO_6$	61.52	7.17	3.99	61.33	7.24	4.13
i	3,4-Methylene-dioxyanilino	$C_{17}H_{21}NO_6$	60.88	6.31	4.18	60.69	6.08	4.03
j	α-Naphthylamino	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	69.98	6.92	3.85
k	α,α,α-Trifluoro-*m*-toluidino	$C_{17}H_{20}NO_4F_3$	56.87	5.62	3.90	56.66	5.44	3.72

(a) M.p. 47-48° (lit. 50° (19)). Other diethyl *N*-ethylarylaminomethylenemalonates are liquid.

TABLE III

4-Chloro-3-carboethoxy-1-ethylquinolinium Iodides

Compd. No.	Substituent R	M.p., °C	Appearance	Yield, %	Molecular Formula		Analysis, % C	H	N	Cl
8a	None	145-146 dec.	red prisms	75	$C_{14}H_{15}ClINO_2$	Calcd.	42.89	3.86	3.57	9.07
						Found	42.65	3.94	3.48	8.84
b	8-Methyl	145 dec.	red prisms	80	$C_{15}H_{17}ClINO_2$	Calcd.	44.40	4.22	3.45	
						Found	44.31	4.38	3.29	
d	8-Ethyl	112 dec.	red rods	70	$C_{16}H_{19}ClINO_2$	Calcd.	45.80	4.57	3.34	8.47
						Found	45.78	4.51	3.46	8.34
e	8-Methoxy	152 dec.	yellow needles	52	$C_{15}H_{17}ClINO_3$	Calcd.	42.70	4.03	3.32	8.41
						Found	42.73	4.04	3.37	8.20
f	6-Methoxy	183 dec.	orange scales	45	$C_{15}H_{17}ClINO_3$	Calcd.	42.70	4.03	3.32	8.41
						Found	42.50	4.05	3.35	8.46
g	8-Ethoxy	122-123 dec.	red needles	80	$C_{16}H_{19}ClINO_3$	Calcd.	44.10	4.36	3.22	8.15
						Found	43.98	4.47	3.28	7.88
i	6,7-Methylene-dioxy	188 dec.	orange rhombs	88	$C_{15}H_{15}ClINO_4$	Calcd.	41.36	3.48	3.21	8.14
						Found	41.26	3.40	3.41	8.08

TABLE IV

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylates

Comp. No.	Substituents	Method (a)	M.p., °C	Recrystn. Solvent	Molecular Formula		Analysis, % C	H	N
6a	None	A,B,C	110-111 (b)	AcOEt-petr. ether	$C_{14}H_{15}NO_3$	Calcd.	68.55	6.16	5.71
						Found	68.27	6.19	5.95
b	8-Methyl	A,C	128-129	MeCN	$C_{15}H_{17}NO_3$	Calcd.	69.48	6.61	5.40
						Found	69.67	6.35	5.55
c	6-Methyl	C (c)	189-190	AcOEt	$C_{15}H_{17}NO_3$	Calcd.	69.48	6.61	5.40
						Found	69.66	6.64	5.42
d	8-Ethyl	C	133-135	benzene	$C_{16}H_{19}NO_3$	Calcd.	70.31	7.01	5.13
						Found	70.12	6.95	5.05
e	8-Methoxy	C	105-106	$CHCl_3$-petr. ether	$C_{15}H_{17}NO_4$	Calcd.	65.44	6.22	5.09
						Found	65.60	6.22	5.13
f	6-Methoxy	A,C	146-148	AcOEt	$C_{15}H_{17}NO_4$	Calcd.	65.44	6.22	5.09
						Found	65.77	5.90	4.81
g	8-Ethoxy	C	88-89	AcOEt	$C_{16}H_{19}NO_4$	Calcd.	66.42	6.62	4.84
						Found	66.48	6.69	4.73
h	6,7-Dimethoxy	C (c)	154.5-156 (f)	MeCN	$C_{16}H_{19}NO_5 \cdot H_2O$	Calcd.	59.43	6.55	4.33
						Found	59.56	6.51	4.32
i	6,7-Methylenedioxy	A,B,C	179-180 (d)	AcOEt					
j	7,8-Benzo (e)	A	136-137	MeOH-H_2O	$C_{17}H_{17}NO_3$	Calcd.	72.06	6.05	4.94
						Found	72.14	5.91	4.81

(a) Method A: Cyclization with PPA. Method B: Cyclization with PPE. Method C: Hydrolysis of 4-chloroquinolinium salts with aqueous sodium bicarbonate. (b) Lit. m.p. 104-105° (10a). (c) The intermediate quinolinium salt was not isolated. (d) Lit. m.p. 177-178° (3). (e) Ethyl 1,4-dihydro-4-oxo-3-benzo[*h*]quinolinecarboxylate. (f) Anhydrous compound, m.p. 184.5-185.5°. *Anal.* Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.73; H, 6.20; N, 4.46.

TABLE V

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids

Compd. No.	Substituent	M.p., °C	Recrystn. Solvent	Molecular Formula	Analysis Calcd., % C	H	N	Found, % C	H	N
7a	None	251-252 (a)	DMF-H_2O (b)	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.54	5.12	6.70
b	8-Methyl	202-205	DMF	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.67	5.40	6.00
c	6-Methyl	218.5-219.5	DMF-H_2O	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.66	5.52	5.80
d	8-Ethyl	193-194	DMF	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.77	6.34	5.76
e	8-Methoxy	261-262.5	DMF	$C_{13}H_{13}NO_4$	63.15	5.30	5.67	63.13	5.24	5.71
f	6-Methoxy	218.5-219	DMF-H_2O	$C_{13}H_{13}NO_4$	63.15	5.30	5.67	63.44	4.90	5.59
g	8-Ethoxy	199-200	DMF-H_2O	$C_{14}H_{15}NO_4$	64.36	5.79	5.36	64.38	5.69	5.36
h	6,7-Dimethoxy	255.5-256	MeOH	$C_{14}H_{15}NO_5$	60.64	5.45	5.05	60.78	5.29	5.11
i	6,7-Methylenedioxy	318 dec. (c)	DMF							
j	7,8-Benzo (d)	235.5-236	$CHCl_3$	$C_{15}H_{13}NO_3$	70.58	5.13	5.49	70.78	4.89	5.26

(a) Lit. m.p. 248-249° (10a). (b) DMF = dimethylformamide. (c) Lit. m.p. 313-314° (3). (d) 1-Ethyl-1,4-dihydro-4-oxo-3-benzo[*h*]-quinolinecarboxylic acid.

by the reaction of the malonate **13** (12) with phosphorus oxychloride. Quaternization of compound **11** with triethyloxonium fluoroborate (13) yielded the quinolinium fluoroborate (**10i**).

The analogous treatment of unsubstituted and substituted *N*-ethylanilinomethylenemalonic esters with phosphorus oxychloride gave various quinolinium iodides, listed in Table III, mostly in satisfactory yields. Only the malonate **5k** resisted cyclization, presumably because of the deactivating effect by the trifluoromethyl group on the positions where ring closure might occur. These quinolinium salts were readily hydrolyzed to the corresponding carboxylic acids (**7**) or their ethyl ester (**6**) depending upon the reaction conditions. These conversions into the quinolinecarboxylates proved the structures of the quinolinium salts. These transformations are shown in Scheme I.

1-Benzyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium iodide (**17**) was prepared similarly by a sequence of reactions shown in Scheme II. Hydrolysis of **17** with aqueous sodium bicarbonate gave the quinolone ester (**18**), which was converted to the known acid (**19**) (3) by treatment with aqueous sodium hydroxide.

The 1-alkyl-4-chloro-3-carboethoxyquinolinium salts prepared in this study are promising intermediates and their nucleophilic substitution reactions will be reported in the near future.

EXPERIMENTAL (20)

General Procedure for the Preparation of *N*-Ethylanilines.

A mixture containing an aniline, Raney nickel (21) and 99% ethanol was stirred and heated under reflux. The reaction was followed by tlc using isopropyl ether, chloroform or carbon tetrachloride as solvent and heating was continued until the primary aniline disappeared. The nickel catalyst was filtered and washed several times with ethanol. The filtrate and washings were combined, the alcohol removed under reduced pressure and the residue distilled through a 6 cm. Vigreux column *in vacuo*. The results of experiments were summarized in Table I. In the experiments with *N*-ethyl-*o*-phenetidine, *N*-ethyl-*o*-ethylaniline and *N*-ethyl-α,α,α-trifluoro-*o*-toluidine, a significant amount of the primary amine remained even after prolonged heating, and the pure secondary amine was separated by silica gel column chromatography using carbon tetrachloride as eluent. That *N*-ethylanilines obtained in this manner were not contaminated with primary or tertiary amines was confirmed by their nmr spectra and tlc. Most *N*-ethylanilines prepared are unstable in air and stored under nitrogen. *N*-ethyl-*o*-ethylaniline, *N*-ethyl-α,α,α-trifluoro-*o*-toluidine and *N*-ethyl-3,4-methylenedioxyaniline are novel compounds.

A. *N*-Ethyl-*o*-ethylaniline (**4d**).

This compound had b.p. 78-79°/5 mm; n_D^{25} 1.5362; NMR spectrum (deuteriochloroform), 6.34-7.23 δ (ring-H, m), 3.27 δ (NH, s), 3.13 δ (N-CH_2, q), 2.42 δ (C-CH_2, q), 1.25 δ (CH_3, t), 1.20 δ (CH_3, t).

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.68; H, 10.15; N, 9.26.

B. *N*-Ethyl-*o*-anisidine (**4e**).

This compound had b.p. 60-63°/0.1 mm (lit. (14) 117°/3 mm); NMR spectrum (deuteriochloroform), 6.38-7.18 δ (ring-H, m), 3.92 δ (NH, s), 3.80 δ (OCH_3, s), 3.13 δ ($N\text{-}CH_2$, q), 1.23 δ (CH_3, t).

C. *N*-Ethyl-*p*-anisidine (**4f**).

This compound had b.p. 95-99°/3.5 mm (lit. (15) 135-140°/20 mm, lit. (16) 130°/12 mm); n_D^{25} 1.5451 (lit. (15) n_D^{20} 1.5444); NMR spectrum (deuteriochloroform), 6.42-6.95 δ (ring-H, m), 3.70 δ (OCH_3, s), 3.25 δ (NH, s), 3.23 δ ($N\text{-}CH_2$, q), 1.19 δ (CH_3, t).

D. *N*-Ethyl-*o*-phenetidine (**4g**).

This compound had b.p. 86-89°/0.7-0.8 mm (lit. (17) 150°/5 mm); NMR spectrum (deuteriochloroform), 6.23-6.93 δ (ring-H, m), 3.95 δ (OCH_2, q), 3.57 δ (NH, s), 3.05 δ ($N\text{-}CH_2$, q), 1.37 δ (CH_3, t), 1.23 δ (CH_3, t).

E. *N*-Ethyl-3,4-dimethoxyaniline (**4h**).

This compound had b.p. 116-119°/2.5 mm (lit. (18) 145-151°/8 mm); NMR spectrum (deuteriochloroform), 5.97-6.92 δ (ring-H, m), 3.77 δ (OCH_3, s), 3.48 δ (NH, s), 3.07 δ ($N\text{-}CH_2$, q), 1.17 δ (CH_3, t).

F. *N*-Ethyl-3,4-methylenedioxyaniline (**4i**).

This compound had b.p. 101-103°/1 mm; n_D^{27} 1.5666; NMR spectrum (deuteriochloroform), 5.87-6.80 δ (ring-H, m), 5.80 δ ($O\text{-}CH_2\text{-}O$, s), 3.38 δ (NH, s), 3.03 δ ($N\text{-}CH_2$, q), 1.15 δ (CH_3, t).

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.43. Found: C, 65.60; H, 6.71; N, 8.21.

G. *N*-Ethyl-α,α,α-trifluoro-*o*-toluidine (**4k**).

This compound had b.p. 53-54°/5 mm, n_D^{27} 1.4763; NMR spectrum (deuteriochloroform), 6.47-7.58 δ (ring-H, m), 4.17 δ (NH, s), 3.21 δ ($N\text{-}CH_2$, q), 1.30 δ (CH_3, t).

Anal. Calcd. for $C_9H_{10}F_3N$: C, 57.19; H, 5.33; N, 7.41. Found: C, 57.30; H, 5.32; N, 7.39.

H. *N*-Ethyl-α,α,α-trifluoro-*m*-toluidine (**4l**).

This compound had b.p. 56-60°/0.8-1 mm (lit. (14) 82°/4 mm); $n_D^{27.5}$ 1.4760 (lit. (14) n_D^{24} 1.4770); NMR spectrum (deuteriochloroform), 6.53-7.43 δ (ring-H, m), 3.65 δ (NH, broad s), 3.09 δ ($N\text{-}CH_2$, q), 1.20 δ (CH_3, t).

General Preparation of Diethyl *N*-Ethylanilinomethylenemalonates (**5a-k**).

In addition to the *N*-ethylanilines (**4d-i**, **4k-l**) prepared as above, commercial *N*-ethylaniline (**4a**), *N*-ethyl-*o*- (**4b**) and *N*-ethyl-*p*-toluidine (**4c**), and *N*-ethyl-α-naphthylamine (**4j**) served as the starting materials.

A stirred mixture containing equimolar amounts of an *N*-ethylaniline and diethyl ethoxymethylenemalonate was heated at 120-140° until the evolution of ethanol ceased. The disappearance of the *N*-ethylaniline was confirmed by tlc using chloroform or isopropyl ether as solvent. The time required for *o*-anisidine and *o*-phenetidine was 12 hours; for all others 2 to 4 hours was sufficinet. The condensation was unsuccessful for *N*-ethyl-α,α,α-trifluoro-*o*-toluidine which was recovered unchanged after heating at 130-140° for 12 hours. Yields were almost quantitative, and the crude products were pure enough for the next step. For analytical purposes the samples were purified by elution through a silica gel column using chloroform or isopropyl ether as the eluent. Except for diethyl *N*-ethylanilinomethylenemalonate which melted at 47-48°, all other malonates are viscous oils and novel compounds. Their analytical data are listed in Table II.

Cyclization of Diethyl *N*-Ethylanilinomethylenemalonate (**5a**).

A. With Polyphosphoric Acid (PPA).

To 4 g. of 85% *ortho*-phosphoric acid was added portionwise 6 g. of phosphorus pentoxide below 80° with external cooling and stirring. The resultant mixture was heated at 60-70° for 1 hour to give a clear solution of PPA. To this solution of PPA was added 3 g. of diethyl *N*-ethylanilinomethylenemalonate and the resulting mixture was stirred and heated at 110-120° for 15 minutes. After cooling, the orange yellow sirupy material was mixed with ice water and the solution was adjusted to *p*H 5 by the addition of aqueous sodium hydroxide solution. Oil that separated gradually crystallized upon standing in a refrigerator. The crystals were filtered, washed with water and dried, weighing 1.9 g. (76%). Recrystallization from ethyl acetate-petroleum ether gave 1.5 g. (60%) of ethyl 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**6a**) as colorless prisms, m.p. 110-111° (lit. (10) 104-105°); NMR spectrum (deuteriochloroform), 8.58 δ (C_2-H, s), 7.19-7.83 δ (ring-H, m), 4.35 δ ($N\text{-}CH_2$ or $O\text{-}CH_2$, q), 4.26 δ ($N\text{-}CH_2$ or $O\text{-}CH_2$, q), 1.61 δ (CH_3, t), 1.40 δ (CH_3, t). When the cyclization was carried out at 170-180° for 40 minutes, the product was 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**7a**), m.p. 250-251°, yield 48%. The analytical sample was recrystallized from acetonitrile or dimethylformamide to give colorless needles, m.p. 251-252° (lit. (10a) 248-249°).

B. With Polyphosphate Ester (PPE).

A mixture containing 30 g. of phosphorus pentoxide, 30 ml. of anhydrous ether and 60 ml. of chloroform was gently refluxed for 35 hours and filtered to remove a small amount of insoluble material. To the resulting solution of PPE was added 6.8 g. of the malonate (**5a**) and the solution was heated on an oil bath to remove the chloroform. After the volatile solvent was distilled the temperature was raised to 100-110° and heating was continued for 3 hours. After cooling, the solution was poured into ice water which was made alkaline by the addition of 10% aqueous sodium hydroxide solution. The mixture was shaken with chloroform and the chloroform layer separated, washed with water and dried over magnesium sulfate. The filtered solution was evaporated, and the residual oil was crystallized from ethyl acetate-petroleum ether to give 4.1 g. (72%) of the ester (**6a**), m.p. 110-111°, as colorless prisms.

C. With Boron Trifluoride.

A mixture containing 3.0 g. of the malonate (**5a**) and 20 ml. of boron trifluoride etherate was refluxed for 3 hours. After cooling, a deposited solid was filtered, washed with a small amount of ether and added to 50 ml. of 5% aqueous potassium hydroxide. The mixture was refluxed for 2.5 hours, acidified to *p*H 4 by the addition of 6 *N* hydrochloric acid and cooled with ice. The white precipitate was filtered, washed with water and dried to give 1.64 g. (74%) of the acid (**7a**), m.p. 250°.

D. With Acetic Anhydride and Sulfuric Acid.

To a mixture containing 14 ml. of acetic anhydride and 5 g. of the malonate (**5a**) was added 7 ml. of concentrated sulfuric acid with cooling so that the inner temperature did not exceed 80°. The resulting mixture was stirred at room temperature for 15 minutes, poured into ice water and made alkaline by the addition of 30% aqueous sodium hydroxide. The mixture was heated at 90-95° on a water bath for 1 hour, and processed in the same manner as above, yielding 2 g. (54%) of the acid (**7a**).

E. With Phosphorus Pentoxide.

To a stirred mixture containing 3 g. of the malonate (**5a**) and 60 ml. of anhydrous benzene was added 11.5 g. of phosphorus pentoxide. The resulting mixture was refluxed for 4 hours, cooled and poured into ice water. The aqueous layer was separated, made alkaline with aqueous sodium hydroxide, extracted with chloroform and the chloroform extract was dried over magnesium sulfate. Evaporation of the chloroform *in vacuo* left 0.35 g. (28%) of a yellow oily material. The infrared spectrum of the product was identical with that of *N*-ethylaniline.

The benzene layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent left 1.36 g. of yellow oil which was dissolved in chloroform and the solution poured on a silica gel column for chromatography. The initial fraction eluted with chloroform, gave a yellow oily material which was not further investigated. The following fraction eluted with chloroform-ether (1:1) mixture afforded 0.4 g. (17%) of the ester (**6a**), m.p. 109-110°.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**7a**).

The authentic sample of **7a** was prepared by the reaction of ethyl 4-hydroxy-3-quinolinecarboxylate, sodium hydride and ethyl iodide in dimethylformamide followed by alkaline hydrolysis, according to the procedure of Kaminsky and Meltzer (3) for the preparation of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**7i**), m.p. 249-251°, yield 70%.

No depression of the m.p. was observed when admixed with the sample prepared by cyclization of **5a** (Method A-E). Infrared spectra of the samples were also identical.

Cyclization of Diethyl *N*-Ethyl-3,4-methylenedioxyanilinomethylenemalonate (**5i**).

A. With PPA.

A mixture containing 5.7 g. of diethyl *N*-ethyl-3,4-methylenedioxyanilinomethylenemalonate (**5i**) and 17 g. of PPA was heated at 90-95° for 1 hour, cooled and mixed with 50 g. of ice water. The *p*H of the pale yellow solution was adjusted to 4 by the addition of 30% aqueous sodium hydroxide and deposited crystals were filtered, washed with water and dried to give 3.94 g. (79%) of the crude ester, m.p. 173-177°. This was purified by recrystallization from acetone to yield 2.8 g. (57%) of ethyl 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**6i**) as colorless needles, m.p. 179-180°, undepressed on admixture with a sample prepared according to the procedure of Kaminsky and Meltzer (3). When the reaction mixture was mixed with water, made alkaline with sodium hydroxide and hydrolyzed without isolating the ester, a 83% yield of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**7i**), m.p. 318° dec., was obtained after acidification of the reaction mixture.

B. With PPE.

Five g. of the malonate (**5i**) was treated with PPE prepared from 25 g. of phosphorus pentoxide, 25 ml. of anhydride ether and 50 ml. of chloroform in the same manner as for cyclization of **5a**. The reaction mixture was subjected to alkaline hydrolysis without isolating the ester (**6i**) and 3.51 g. (90%) of the acid (**7i**) was obtained, m.p. 317° dec. Recrystallization from dimethylformamide gave colorless prisms, m.p. 318° dec.; NMR spectrum (deuteriotrifluoracetic acid), 9.30 δ (2-CH, s), 7.98 δ (ring-H, s), 7.60 δ (ring-H, s), 6.43 δ (O-CH_2-O, s), 4.87 δ (N-CH_2, q), 1.78 δ (CH_3, t).

C. With Boron Trifluoride.

A mixture containing 5 g. of the malonate (**5i**) and 20 ml. of boron trifluoride etherate was refluxed for 8 hours. The ether was removed *in vacuo* and the residue mixed with 50 ml. of 5% aqueous sodium hydroxide and heated at 90-95° for 5 hours. The dark brown solution was treated with charcoal, filtered and the filtrate acidified with 6 *N* hydrochloric acid to *p*H 3. The acid (**7i**) that precipitated was collected by filtration, washed with water and dried, m.p. 311° dec., yield 3.25 g. (85%). Recrystallization from dimethylformamide gave colorless prisms, m.p. 318° dec.

The acid (**7i**) prepared by Methods A-C were identified by mixed melting point determination and comparison of their infrared spectra.

Cyclization of Diethyl *N*-Ethylanilinomethylenemalonates with Phosphorus Oxychloride.

A mixture containing 10 g. of a diethyl *N*-ethylanilinomethylenemalonate and 50 ml. of phosphorus oxychloride was refluxed for 3-5 hours. Excess phosphorus oxychloride was distilled under reduced pressure and the residue was poured into ice water. Excess potassium iodide (*ca.* 10 g.) was added to the resulting clear solution. The crystals that separated out were collected by filtration, washed with water and then with acetone or a mixture of acetone and water and dried *in vacuo* to give a 1-ethyl-4-chloro-3-carboethoxyquinolinium salt. The product obtained in this manner was usually analytically pure. If necessary, this was recrystallized from acetone or acetone-water.

In the cyclization of diethyl *N*-ethyl-6,7-methylenedioxyanilinomethylenemalonate, the reaction temperature between 70-80° was found optimal. 1-Ethyl-4-chloro-3-carboethoxyquinolinium salts obtained by this method are listed in Table III.

1-Ethyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium Iodide (**9i**) from Ethyl 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**6i**).

A mixture containing 15 g. of the ester (**6i**), 60 ml. of phosphorus oxychloride was stirred and heated at 75° for 3 hours. Worked up in the same manner as stated above, 20.6 g. (90%) of **8i** was obtained as orange rhombs, m.p. 188° dec. The infrared spectrum of the product was identical with that of a sample prepared from **5i**.

Ethyl 4-Chloro-6,7-methylenedioxy-3-quinolinecarboxylate (**11**) (12).

A mixture containing 30 g. of diethyl 3,4-methylenedioxyanilinomethylenemalonate (**5i**) and 150 ml. of phosphorus oxychloride was heated at 95-100° for 4 hours. The excess phosphorus oxychloride was removed *in vacuo*, the residue poured into ice water and made alkaline with sodium carbonate. An insoluble material was collected by filtration, washed with water and dried *in vacuo* at 70°, to give 26.5 g. (97%) of the crude product, m.p. 103-108°. Recrystallization from ethanol yielded yellow rhombs, m.p. 109-110° (lit. (12) m.p. 107-108°), yield 31 g. (85%); NMR spectrum (deuteriochloroform), 8.94 δ (2-C-H, s), 7.43 δ (ring-H, s), 7.23 δ (ring-H, s), 5.60 δ (O-CH_2-O, s), 4.47 δ (CH_2, q), 1.45 δ (CH_3, t).

Anal. Calcd. for $C_{13}H_{10}ClNO_4$: C, 55.86; H, 3.60; N, 5.01; Cl, 12.68. Found: C, 55.69; H, 3.33; N, 5.00; Cl, 12.63.

Quaternization of Ethyl 4-Chloro-6,7-methylenedioxy-3-quinolinecarboxylate (**11**).

A.

A mixture containing 2 g. of ethyl 4-chloro-6,7-methylenedioxy-3-quinolinecarboxylate (**11**) and 20 ml. of ethyl iodide was refluxed for 28 hours. After cooling, yellow crystals that separated out were collected by filtration, washed with acetone and dried to give 2.28 g. (73%) of 1-ethyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium iodide (**9i**), m.p. 188° dec., undepressed on admixture with the sample prepared by cyclization of **5i**. The infrared spectra of the two samples were identical.

B.

To a stirred mixture containing 4.95 g. (0.0177 mole) of **11**, 20 ml. of dichloroethane and 5 ml. of chloroform was added 3.8 g. (0.02 mole, 1.13 equivalents) of triethyloxonium fluoroborate (13). The resulting slurry was heated at 50° for 15 minutes and allowed to stand in a refrigerator for 48 hours. During this period colorless prisms depostied, which were collected by filtration, washed with dichloroethane and dried *in vacuo* to yield 5.4 g. (77%) of 1-ethyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium fluoroborate (**10i**). Recrystallization from acetone-ether afforded colorless prisms, m.p. 153-155°, yield 4.3 g. (62%); NMR spectrum (dimethylsulfoxide-d_6), 9.0 δ (2-CH, s), 7.57 δ (ring-H, s), 7.63 δ (ring-H, s), 6.33 δ (O-CH_2-O, s), 4.54 δ (N-CH_2, q), 4.40 δ (O-CH_2, q), 1.47 δ (CH_3, t), 1.37 δ (CH_3, t).

Anal. Calcd. for $C_{15}H_{15}BClF_4NO_4$: C, 45.57; H, 3.79; N, 3.54; Cl, 8.98. Found: C, 45.65; H, 3.76; N, 3.43; Cl, 8.98.

4-Chloro-3-carboethoxy-1-ethylquinolinium Fluoroborate (**10a**).

To a stirred mixture of 4.7 g. (0.02 mole) of ethyl 4-chloro-3-quinolinecarboxylate (**12**) (22), 20 ml. of dichloroethane and 10 ml. of chloroform was added 3.8 g. (0.02 mole) of triethyloxonium fluoroborate. The resulting slurry was heated at 50° for 30 minutes when all the solid went into solution. The solution was kept in a refrigerator for 48 hours, but no precipitate was formed.

The solvent was removed *in vacuo*, the residue mixed with dichloroethane, and the solvent was again concentrated. Ether was added to the residue which crystallized upon standing and the crystalline solid was collected by filtration and dried *in vacuo*, giving 6.43 g. (92%) of the crude quinolinium salt, m.p. 100-103°. The analytical sample was prepared by recrystallization from acetone-ether, colorless scales, m.p. 117-118°; NMR spectrum (deuteriochloroform), 9.42 δ (2-CH, s), 8.13-8.50 δ (ring-H, m), 5.20 δ (N-CH_2, q), 4.54 δ (O-CH_2, q), 1.72 δ (CH_3, t), 1.44 δ (CH_3, t).

Anal. Calcd. for $C_{14}H_{15}BClF_4NO_2$: C, 47.81; H, 4.27; N, 3.94; Cl, 10.10. Found: C, 47.72; H, 4.35; N, 3.86; Cl, 9.94.

Hydrolysis of 4-Chloro-3-carboethoxy-1-ethylquinolinium Salts.

Method A.

A mixture containing 5 g. of a 4-chloro-3-carboethoxy-1-ethylquinolinium iodide (**9**) or fluoroborate (**10**) and 50 ml. of 5% aqueous sodium bicarbonate was heated at 85-95° for 15 to 30 minutes and cooled. The separated ethyl 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate was filtered or extracted with chloroform. Purification was accomplished by recrystallization. Silica gel treatment was effective for decolorization. Yields of 80-100% was obtained. The esters are listed in Table IV.

Method B.

A mixture containing 5 g. of a 4-chloro-3-carboethoxy-1-ethylquinolinium iodide (**9**) or fluoroborate (**10**) and 50 ml. of 5% aqueous sodium hydroxide was heated at 85-90° for half an hour. The clear solution was acidified to *p*H 3 by the addition of 6 *N* hydrochloric acid and cooled. The deposited 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid was collected by filtration, washed with water and dried at 80-100°, yield, 90-100%. An analytical sample was obtained by recrystallization from dimethylformamide or dimethylformamide and water. The acids are listed in Table V.

N-Benzylidene-3,4-methylenedioxyaniline (**14**).

A mixture containing 13.7 g. (0.1 mole) of 3,4-methylenedioxyaniline, 10.6 g. (0.1 mole) of benzaldehyde and 50 ml. of methanol was refluxed for 24 hours. Evaporation of the methanol *in vacuo* gave 20.9 g. (93%) of dark liquid of **14**; NMR spectrum (deuteriochloroform), 8.40 δ (N=CH, s), 6.80-8.00 δ (ring-H, m), 5.91 δ (O-CH_2-O, s). This material was purified by elution through a silica gel column using chloroform as the eluent.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.62; H, 4.78; N, 6.05.

N-Benzyl-3,4-methylenedioxyaniline (**15**).

To a stirred mixture containing 10.25 g. (0.046 mole) of *N*-benzylidene-3,4-methylenedioxyaniline (**14**) and 100 ml. of methanol was added portionwise 2.0 g. (0.051 mole) of sodium borohydride with external ice cooling. After the addition was completed, the mixture was stirred under ice cooling for 3 hours, at room temperature for 2 hours and heated under reflux for 0.5 hour. The reaction mixture was concentrated *in vacuo*, the residue dissolved in water (*ca.* 50 ml.), and extracted with ether. The ethereal extracts were separated, washed with water, dried over magnesium sulfate and evaporated to give 8.84 g. (86%) of **15** as dark liquid; NMR spectrum (deuteriochloroform), 5.90-7.51 δ (ring-H, m), 5.70 δ (O-CH_2-O, s), 4.23 δ (N-CH_2, s), 3.67 δ (NH, broad s). For analytical purpose, this material was purified by passing it through a silica gel column using chloroform as eluent.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.07; H, 5.77; N, 6.17. Found: C, 74.00; H, 5.59; N, 6.08.

Diethyl *N*-Benzyl-3,4-methylenedioxyanilinomethylenemalonate (**16**).

A mixture containing 6.81 g. (0.03 mole) of *N*-benzyl-3,4-methylenedioxyaniline (**15**) and 6.48 g. (0.03 mole) of diethyl ethoxymethylenemalonate was stirred and heated at 110° for 12 hours. After cooling, the reaction mixture was washed with *ca.* 100 ml. of *n*-hexane to remove a small amount of the unreactive starting materials. The insoluble liquid of diethyl *N*-benzyl-3,4-methylenedioxyanilinomethylenemalonate (**16**) (11.36 g., 95%) was pure and used for the next step. A part of the product was purified by passing it through a silica gel column for an analytical sample; NMR spectrum (deuteriochloroform), 7.83 δ (C=CH, s), 6.33-7.44 δ (ring-H, m), 5.93 δ (O-CH_2-O, s), 4.87 δ (N-CH_2, s) 4.20 δ (CO_2CH_2, q), 1.23 δ (CH_3, t), 1.07 δ (CH_3, t).

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.85; H, 5.83; N, 3.55.

1-Benzyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium Iodide (**17**).

A solution of 10.77 g. (0.0296 mole) of diethyl *N*-benzyl-3,4-methylenedioxyanilinomethylenemalonate (**16**) dissolved in 60 ml. of phosphorous oxychloride was refluxed for 7 hours. After the reaction was completed, excess phosphorus oxychloride was evaporated *in vacuo*. The resulting brown syrup was dissolved in water (*ca.* 100 ml.) and filtered. Potassium iodide (20 g.) was added to the filtrate, and the yellow precipitate that separated out was collected by filtration, washed repeatedly with water, then with acetone and dried *in vacuo*. There was obtained 8.14 g. (67%) of 1-benzyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium

iodide (**17**), m.p. 188° dec.

Anal. Calcd. for $C_{20}H_{17}ClINO_4$: C, 48.23; H, 3.43; N, 2.81; Cl, 7.11; I, 25.43. Found: C, 48.08; H, 3.46; N, 2.60; Cl, 6.91; I, 25.13.

Ethyl 1-Benzyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**18**).

A mixture containing 2.5 g. of the quinolinium iodide (**17**), 3 g. of sodium bicarbonate and 60 ml. of water was stirred and heated under reflux for 15 minutes. After cooling the insoluble solid was collected by filtration, washed with water and dried. There was obtained 1.73 g. (99%) of crude ethyl 1-benzyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**18**), which was recrystallized from chloroform to yield 1.5 g. (85%) of colorless needles, m.p. 183-184°; NMR spectrum (dimethylsulfoxide-d_6), 8.73 δ (2-CH, s), 8.33 δ (ring-H, s), 7.07-7.73 δ (ring-H, m), 6.13 δ ($O\text{-}CH_2\text{-}O$, s), 5.62 δ ($N\text{-}CH_2$, s), 4.23 δ (CO_2CH_2, q) 1.23 δ (CH_3, t).

Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.60; H, 4.62; N, 3.97.

1-Benzyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic Acid (**19**).

A mixture containing 0.7 g. of **18** and 20 ml. of aqueous 2 *N* sodium hydroxide was heated at 90-95° for half an hour, acidified with hydrochloric acid to *p*H 3 and filtered. The crude product was purified by recrystallization from dimethylformamide, m.p. 312-313°, yield 0.43 g. (67%). No depression of the m.p. was observed when admixed with the sample of 1-benzyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid prepared by the known method (3).

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