Studies on Quinoline Derivatives and Related Compounds. IV. Synthesis of 4-Substituted 1-Alkyl-1,4-dihydro-3-quinolinecarboxylic Acid (1)

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By the displacement reactions of 1-ethyl-4-chloro-3-carboethoxy-6,7-methylenedioxyquinolinium iodide (**3a**), several 4-substituted derivatives including the 4-thioxo (**1c**) and 4-amino derivatives (**6**) of oxolinic acid were prepared. The acid **1c** and its N_1-substituted derivatives (**18a-h**) were prepared alternatively by alkylation of ethyl 4-ethylmercapto-6,7-methylenedioxy-3-quinolinecarboxylate (**15**) followed by treatment with sodium hydrosulfide and hydrolysis.

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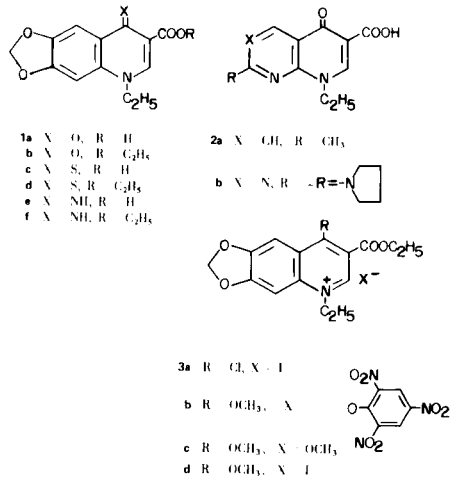
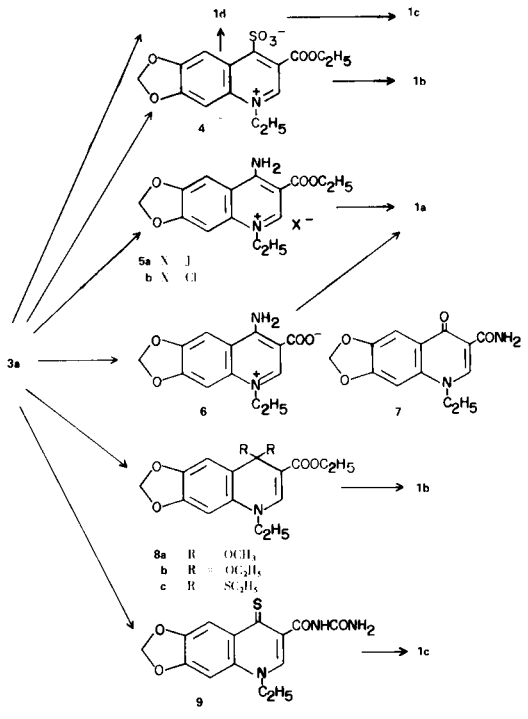
Substitutions at the *N* atom (2), of the carboxyl group (3) or in the benzene ring (4) of 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids have been carried out in a great number because some congeners of this type of acid, notably oxolinic (**1a**) (2), nalidixic (**2a**) (5) and piromidic acids (**2b**) (6) exhibit significant antibacterial activity. In the course of a study on 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids, we became interested in the preparation of oxolinic acid analogs with modification of the keto carbonyl group at C_4 atom to examine whether the presence of the 4-oxo group in this type of acid is essential for the antibacterial activity.

In a previous paper (7), we reported a new improved synthesis of oxolinic acid *via* 4-chloro-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium iodide (**3a**), which was expected to be highly reactive towards nucleophilic reagents.

The reactions of 2- or 4-halogenoquinolinium salts with nucleophilic reagents, such as sodium hydrosulfide (8), sodium bisulfite (9) and alkyl or aralkyl amine (10), have been reported. Hence the reactions of the 4-chloroquinolinium iodide **3a** with these nucleophilic reagents



Scheme 1



were carried out by the application of the reported methods. When the 4-chloroquinolinium iodide **3a** was treated with aqueous sodium hydrosulfide, ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**1d**) was formed in 63% yield. The same product was also obtained by heating ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**1b**) with phosphorus pentasulfide in pyridine in 58% yield. Alkaline hydrolysis of **1d** gave 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic acid (**1c**). Treatment of **3a** with sodium bisulfite gave 3-carboethoxy-1-ethyl-6,7-methylenedioxy-4-sulfoquinolinium betaine (**4**) in satisfactory yield, which led to the esters **1b** and **1d**, respectively, by heating with water or by treating with aqueous sodium hydrosulfide. Yields were quantitative. The structure of **4** was determined on the basis of elementary analysis, nmr and ir spectra. In the nmr spectrum the signal due to the C-5 proton is shifted

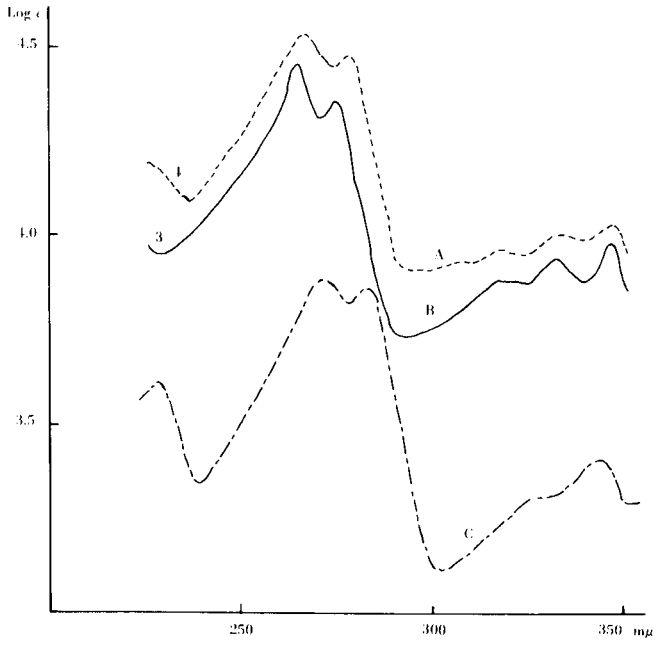


Figure 1. Uv spectra in ethanol of compounds (5a) (A); (6) (B); (1f) (C).

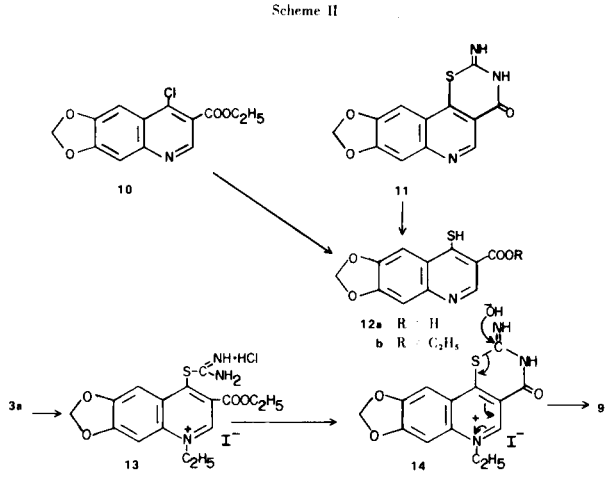
downfield by the anisotropy effect of the SO_3 group at C_4. The ir spectrum shows the absorption bands of the SO_3 group at 1180 and 1057 cm^{-1}.

In the reaction of **3a** with 28% aqueous ammonia, there was obtained a mixture of ethyl 4-amino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium iodide (**5a**) and chloride (**5b**) in 67 and 10% yields, respectively, separated by fractional recrystallization from methanol. The chloride **5b** was identical with a sample prepared by treating **1b** with phosphorous oxychloride (7), followed by aqueous ammonia at room temperature.

The conversion of **5a** to **1f** was attempted under various reaction conditions but failed. When an ethanolic solution of **5a** was treated with aqueous ammonia at 55-65° for 10 minutes, the unchanged starting material was recovered. Heating **5a** in aqueous potassium hydroxide under reflux for 22 hours gave **1a**, while treatment of **5a** with aqueous potassium hydroxide at 80-90° for 15 minutes or with aqueous ammonia at 80° for 1 hour yielded a white solid having m.p. 325-328° dec., in quantitative yields. This product also yielded oxolinic acid (**1a**) on heating with potassium hydroxide, and was assigned 4-amino-3-carboxy-1-ethyl-6,7-methylenedioxyquinolinium betaine (**6**). The isomeric 1-ethyl-1,4-dihydro-4-oxo-6,7-methylenedioxy-3-quinolinecarboxamide (**7**) (11), prepared by the reaction of **1b** with aqueous ammonia in ethanol, was not identical with the compound mentioned above. The betaine structure **6** was favored rather than the tautomeric isomer **1e** because the uv spectrum of **6** resembles that of **5a** and distinctly differs from that of ethyl 1-ethyl-1,4-dihydro-4-imino-6,7-methylenedioxy-3-quinolinecarboxylate (**1f**) (12), as shown in Figure 1. The chemical shifts of the three aromatic ring protons of **6** are also similar to those of **5a**.

The quinolinium iodide **3a** further was allowed to react with sodium alkoxide, sodium alkylmercaptide and thiourea. When **3a** was treated with one molar equivalent of sodium methoxide, there was obtained a mixture of ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**1b**) and 3-carboethoxy-1-ethyl-4-methoxy-6,7-methylenedioxyquinolinium salt, isolated as a picrate (**3b**), in 90 and 3% yields, respectively. The use of two molar equivalents of sodium methoxide gave ethyl 1-ethyl-1,4-dihydro-4,4-dimethoxy-6,7-methylene-

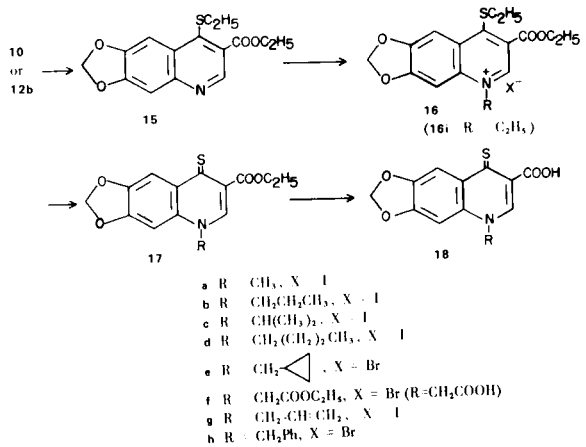
Scheme II



dioxy-3-quinolinecarboxylate (**8a**). The formation of **8a** may occur through the intermediate **3d**. The identity of **8a** as δ complex at C_4 like a Meisenheimer complex (13) rather than ion complex **3c** rests on the nmr spectrum showing two equivalent methoxy signals as a singlet and three ring protons further upfield than those of **3a** in deuteriodimethyl sulfoxide. Compound **8a** was readily hydrolyzed by heating with water to give **1b** in quantitative yield.

The 4-chloroquinolinium iodide **3a** likewise reacts with sodium ethoxide to give the corresponding ethyl 4,4-diethoxy-1-ethyl-1,4-dihydro-6,7-methylenedioxy-3-quinolinecarboxylate (**8b**) in 15% yield, together with **1a** and **1b** in 15 and 53% yields, respectively, and with sodium ethylmercaptide to give ethyl 1-ethyl-4,4-diethylmercapto-1,4-dihydro-6,7-methylenedioxy-3-quinolinecarboxylate (**8c**) in 16% yeild.

Scheme III



In the reaction of **3a** with thiourea, there was obtained 1-ethyl-1,4-dihydro-4-thioxo-6,7-methylenedioxy-3-quinolinecarbonylurea (**9**) in quantitative yield. The structure of **9** was confirmed on the basis of elementary analysis, spectral evidence and the conversion to the corresponding carboxylic acid **1c** by alkaline hydrolysis.

In order to find a clue on the reaction mechanism the reaction of ethyl 4-chloro-6,7-methylenedioxy-3-quinolinecarboxylate (**10**) with thiourea was carried out, and the cyclized product **11** was obtained in quantitative yield. Alkaline hydrolysis of **11** afforded 4-mercapto-6,7-methylenedioxy-3-quinolinecarboxylic acid (**12a**), which was identical with **12a** prepared by treating **10** with sodium hydrosulfide followed by hydrolysis.

The structure assignment for **11** is based upon elementary analysis and the ir spectrum which shows the absorption band due to the amide group at 1650 cm^{-1}. The nmr spectrum also supports the assigned structure. The formation of **11** from **10** is consistent with the fact that the reaction of methyl 2-chloro-3,5-dinitrobenzoate with thiourea gives 2,3-dihydro-2-imino-6,8-dinitro-4*H*-1,3-benzothiazin-4-one (14). The 4*H*-[1,3]thiazino[5,6-c]-quinoline ring system obtained in the present study has not been reported in the literature. The reaction mechanism for the formation of **9** from **3a**, therefore, is rationally explained by the pathway as given in Scheme II. The isothiouronium chloride **13** would initially be formed and cyclized to the intermediate **14** with elimination of ethanol. In the key intermediate **14**, the formal positive charge on the nitrogen atom would cause electron shift to facilitate the fission of C-S bond and attack of hydroxide anion, giving the product **9**.

Table I

1-Substituted 1,4-Dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylates

Compound No.	Appearance	Recrystallization Solvent	M.P., °C	Empirical Formula		Analysis, % C	H	N	S
17a	yellow needles	Methanol	222-224	$C_{14}H_{13}NO_4S$	Calcd.	57.73	4.46	4.81	11.00
					Found	57.65	4.31	4.53	11.08
1d	yellow needles	Ethanol	162-163	$C_{15}H_{15}NO_4S$	Calcd.	59.07	4.96	4.59	10.51
					Found	58.94	4.76	4.58	10.46
17b	orange scales	Ethanol	119-120	$C_{16}H_{17}NO_4S$	Calcd.	60.18	5.05	4.39	10.04
					Found	60.32	5.35	4.37	10.05
17c	yellow prisms	Ethanol	194-196	$C_{16}H_{17}NO_4S$	Calcd.	60.18	5.05	4.39	10.04
					Found	60.21	5.31	4.25	9.78
17d	orange scales	Ethanol	103-104	$C_{17}H_{19}NO_4S$	Calcd.	61.23	5.74	4.20	9.62
					Found	61.02	5.55	4.38	9.37
17e	yellow needles	Ethanol	180-181	$C_{17}H_{17}NO_4S$	Calcd.	61.68	5.51	4.23	9.67
					Found	61.96	5.31	4.34	9.35
17f	red plates	Ethanol	174-176	$C_{17}H_{17}NO_6S$	Calcd.	56.20	4.68	3.86	8.82
					Found	56.05	4.74	3.77	8.73

The in vitro antibacterial activities of 4-substituted quinoline derivatives **1c**, **4**, **6**, **8a-c** and **9** obtained in this study were tested by a 2-fold serial dilution method used by Turner, *et al.*, (15). Among these compounds, only the compound **1c** showed activity comparable to piromidic acid (**2b**) (6) against gram negative pathogens.

These biological results prompted us to synthesize 1-substituted-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic acids (**18a-h**). Ethyl 4-ethylmercapto-6,7-methylenedioxy-3-quinolinecarboxylate (**15**) was chosen as a starting material and prepared by treating **10** with sodium ethyl mercaptide or by alkylation of **12b** with ethyl iodide. The alkylation of **15** was accomplished by heating with an alkyl halide to yield the corresponding 1-alkyl-3-carboethoxy-4-ethylmercapto-6,7-methylenedioxyquinolinium halides (**16**). With the exception of the methyl (**16a**) and the ethyl derivatives (**16i**) the alkylquinolinium halides **16** could not be isolated as a pure crystalline form, and the crude **16** was used for the next step without purification.

Heating **15** with isopropyl iodide under reflux gave a 30% yield of hydroiodide of **15**, isolatable by fractional recrystallization from a mixture of ethanol and ether, and a residual oily fraction containing the isopropylquinolinium iodide **16c**. The hydroiodide of **15** may be formed by *beta* elimination from **16c**. Similar findings have been observed in the reaction of quinoline with *sec*- or *t*-butyl iodide, in which only quinoline hydroiodide was obtained (16).

The quinolinium iodides **16a** and **16i** react with sodium hydrosulfide at room temperature giving the corresponding 4-thioxoquinolines **17a** and **1d** in 99 and 74% yields, respectively. When the quinolinium halides **16c**, **16e** and **16f** was similarly treated with sodium hydrosulfide, ethyl 4-thioxo-3-quinolinecarboxylates **17c**, **17e** and **17f** were obtained. On the other hand, the reaction of the *n*-propyl and butylquinolinium iodides, **16b** and **16d**, with aqueous sodium hydrosulfide was accompanied by hydrolysis, giving the corresponding esters, **17b** and **17d**, and the carboxylic acids, **18b** and **18d**. Acidic hydrolysis of the esters **17a-f** afforded the corresponding acids **18a-f** in satisfactory yields.

1-Allyl- (**18g**) and 1-benzyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic acids (**18h**) were further prepared by the same series of reactions from **15**. Compound **15** was allowed to react with allyl bromide or benzyl bromide, and the crude reaction product treated with sodium hydrosulfide followed by dilute hydrochloric acid. The intermediate quaternary salts and the 4-thioxoquinoline-3-carboxylic esters were not isolated. The overall yields from **15** were 17% for **18g**, and 8% for **18h**.

The acids **18a-h** thus obtained were tested for anti-

Table II

1-Substituted 1,4-Dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic Acids

Compound No.	Appearance	Recrystallization Solvent	M.p., °C	Empirical Formula		Analysis, % C	H	N	S
18a	yellow prisms	DMF (a)	335 dec.	$C_{12}H_9NO_4S$	Calcd.	54.80	3.45	5.33	12.19
					Found	54.92	3.42	5.22	11.98
1c	yellow prisms	DMF	301 dec.	$C_{13}H_{11}NO_4S$	Calcd.	56.36	4.00	5.06	11.58
					Found	56.58	4.00	5.06	11.58
18b	yellow needles	DMF	249-250	$C_{14}H_{13}NO_4S$	Calcd.	57.71	4.50	4.82	11.01
					Found	57.95	4.53	4.92	10.98
18c	yellow prisms	DMF-H_2O	282-283 dec.	$C_{14}H_{13}NO_4S$	Calcd.	57.71	4.50	4.82	11.01
					Found	57.83	4.28	4.75	10.94
18d	yellow needles	DMF	217-219	$C_{15}H_{15}NO_4S$	Calcd.	59.00	4.95	4.59	10.50
					Found	59.01	4.91	4.59	10.28
18e	yellow needles	DMF	279-280 dec.	$C_{15}H_{13}NO_4S$	Calcd.	59.46	4.32	4.62	10.58
					Found	59.76	4.40	4.75	10.52
18f	yellow needles	DMF	233-235	$C_{15}H_{13}NO_6S$	Calcd.	53.78	3.91	4.18	9.57
					Found	53.52	3.89	3.77	9.64
18g	yellow prisms	DMF-H_2O	250-253 dec.	$C_{14}H_{11}NO_4S$	Calcd.	58.18	3.84	4.85	11.10
					Found	57.88	3.76	4.90	10.88
18h	yellow prisms	DMF-H_2O	292 dec.	$C_{18}H_{13}NO_4S \cdot 1/3H_2O$	Calcd.	62.66	4.09	4.06	9.29
					Found	62.78	4.01	4.40	9.25

(a) DMF = dimethylformamide.

microbial activities. No significant activities, however, were observed.

EXPERIMENTAL (17)

Ethyl 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**1d**).

Method A.

A mixture containing 5 g. of 4-chloro-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinum iodide (**3a**), 3 g. of 70% sodium hydrosulfide and 40 ml. of water was stirred at room temperature for 3 hours. The resulting solid was filtered, washed with water and dried. Recrystallization from ethanol gave 2.21 g. (63%) of **1d** as yellow needles. M.p.s, analytical and nmr data are

Table III

Nmr Data for Ethyl 1-Alkyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate

Compound No.	CH_3CH_2	CH_3CH_2	CH_2	H_2	H_5	H_8	Alkyl Group at N Atom
17a (a)	1.48 (t) J = 7	4.6 (q) J = 7	6.4	9.18	7.9	7.47	CH_3, 4.43.
1d	1.18 (t) J = 7 1.24 (t) J = 7	4.1 (q) J = 7 4.18 (q) J = 7	6.08	8.08	7.63	6.75	
17b	1.37 (t) J = 7	4.4 (q) J = 7	6.11	8.37	7.7	7.47	CH_3, 0.97 (dt), J = 7, J = 2; CH_2, 1.53-2.1 (m); CH_2, 4.22 (bq), J = 7.
17c	1.4 (t) J = 7	4.39 (q) J = 7	6.13	8.53	7.97	7.01	CH_3, 1.6 (d), J = 7; CH, 4.9 (q), J = 7.
17d	(b)	4.27 (bq) J = 7	6.13	8.33	7.7	6.8	$CH_3CH_2CH_2$, 0.33-2.07 (m); CH_2, 4.27 (bq), J = 7.
17e	1.38 (t) J = 7	4.38 (q) J = 7	6.12	8.35	7.81	6.9	Cyclopropyl Protons, 0.32-0.92 (m); CH_2, 4.03 (d), J = 7.
17f	1.38 (t) J = 7 1.4 (t) J = 7	4.28 (q) J = 7 4.4 (q) J = 7	6.13	8.2	7.63	6.6	CH_2, 4.98.

Chemical shift in δ units (ppm) in deuteriochloroform with TMS as internal standard. (a) Taken in trifluoroacetic acid. (b) The methyl protons coalesces with propyl protons.

Table IV

Nmr Data for 1-Substituted 1,4-Dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic Acid

Compound No.	CH_2	H_2	H_5	H_8	Alkyl or Benzyl Group at N atom
18a	6.43	9.37	7.92	7.53	CH_3, 4.5.
1c	6.4	9.4	7.87	7.5	CH_3, 1.78 (t), J = 7; CH_2, 4.87 (q), J = 7.
18b (a)	6.52	9.42	8.2	7.78	CH_3, 0.95 (t), J = 7; CH_2, 1.88 (s), J = 7; CH_2, 4.68 (q), J = 7.
18c	6.43	9.43	7.97	7.7	CH_3, 1.88 (d), J = 7; CH, 4.9 (q), J = 6.
18d	6.43	9.32	7.93	7.57	CH_3, 1.1 (t), J = 6; $(CH_2)_2$, 1.3-2.37 (m); CH_2, 4.83 (t), J = 6.
18e	6.38	9.6	7.92	7.6	Cyclopropyl Protons, 0.6-1.3 (m); CH_2, 4.6 (d), J = 7.
18f	6.43	9.45	7.95	7.4	CH_2, 5.75.
18g	6.43	9.4	7.97	7.6	Allyl protons, 5.15-6 (m).
18h	6.38	9.37	7.93	(b)	Phenyl protons, 7.1-7.73 (m); CH_2, 5.97.

Chemical shift in δ units (ppm) in trifluoroacetic acid with TMS as internal standard. (a) Taken in deuteriodimethylsulfoxide. (b) This proton coalesces with phenyl protons. In Tables III and IV, coupling constant J in cps. Signals are designated as follows: d, doublet; t, triplet; q, quartet; s, sixtet; m, multiplet; dt, doublet of triplets; bq broad quartet.

summarized in Tables I and III.

Method B.

To a boiling solution containing 1.45 g. of ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**1b**) and 20 ml. of anhydrous pyridine was added dropwise 2 g. of phosphorus pentasulfide over a period of 0.5 hour. The solution was kept at the same temperature for an additional 1 hour. After cooling, a yellow solid that deposited was collected by filtration and recrystallized from ethanol, yielding 0.8 g. (58%) of **1d**, undepressed on admixture with a sample prepared in Method A.

3-Carboethoxy-1-ethyl-6,7-methylenedioxy-4-sulfoquinolinium Betaine (**4**).

A mixture containing 0.87 g. of **3a**, 0.458 g. of sodium bisulfite and 10 ml. of water was stirred at room temperature for 4 hours. The resulting yellow solid was collected by filtration, washed with water and dried, yielding 0.62 g. (87%) of **4**, m.p. 298° dec.; ir: cm^{-1}, 1740 (C=O), 1180 (SO_3), 1057 (SO_3); nmr (trifluoroacetic acid): 1.48 δ (CH_3, t), 1.83 δ (CH_3, t), 4.6 δ (CH_2, q), 5.02 δ (CH_2, q), 6.43 δ (CH_2, s), 7.67 δ (C-8 proton, s), 8.67 δ (C-5 proton, s), 8.97 δ (C-2 proton, s).

Anal. Calcd. for $C_{15}H_{15}NO_7S$: C, 51.03; H, 4.28; N, 3.97; S, 9.08. Found: C, 51.21; H, 4.19; N, 3.85; S, 9.12.

Hydrolysis of **4**.

A mixture of 0.35 g. of **4** and 10 ml. of water was heated under reflux for 1 hour. After cooling, a white solid that separated was extracted with chloroform. The chloroform extract was washed with water and dried over sodium sulfate. Evaporation of the extract and recrystallization of the residue from aqueous ethanol gave 0.25 g. (85%) of **1b** as colorless needles, m.p. 177-178°, undepressed on admisture with a sample prepared by the reported method (7).

Reaction of **4** with Sodium Hydrosulfide.

A mixture of 0.35 g. of **4**, 0.12 g. of 70% sodium hydrosulfide, and 10 ml. of water was stirred at room temperature for 2 hours. The resulting solid was collected by filtration, washed with water and dried. Recrystallization from ethanol afforded 0.27 g. (90%) of **1d**, m.p. 162-163°, undepressed on admixture with a sample prepared by method A. The ir spectra of the two samples were identical.

4-Amino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium Iodide (**5a**) and Chloride (**5b**) from **3a**.

A mixture containing 20 g. of **3a**, 300 ml. of chloroform, and 40 ml. of 28% aqueous ammonia was stirred at room temperature for 3 hours. The resulting solid was filtered, washed with water and dried. Recrystallization from methanol afforded 12.79 g. (67%) of **5a** as orange prisms, m.p. 246-247° dec.; nmr (trifluoroacetic acid): 1.52 δ (CH_3, t), 1.68 δ (CH_3, t), 4.58 δ (CH_2, q), 4.65 δ (CH_2, q), 6.33 δ (CH_2, s), 7.37 δ (C-5 proton, s), 7.7 δ (C-8 proton, s), 9.0 δ (C-2 proton, s).

Anal. Calcd. for $C_{15}H_{17}IN_2O_4$: C, 43.28; H, 4.09; N, 6.74; I, 30.55. Found: C, 43.33; H, 4.91; N, 6.80; I, 30.51.

The methanolic filtrate was condensed to a small volume and cooled, whereupon **5b** separated out as colorless needles which were collected by filtration and dried, weighting 1.5 g. (9.6%). Recrystallization from methanol gave 0.65 g. (4.2%) of pure **5b**, m.p. 244° dec.; nmr (trifluoroacetic acid): 1.5 δ (CH_3, t), 1.68 δ (CH_3, t), 4.57 δ (CH_2, q), 4.6 δ (CH_2, q), 6.3 δ (CH_2, s), 7.33 δ (C-5 proton, s), 7.6 δ (C-8 proton, s), 8.97 δ (C-2 proton, s).

Anal. Calcd. for $C_{15}H_{17}ClN_2O_4$: C, 55.46; H, 5.27; N, 8.62; C, 10.91. Found: C, 55.33; H, 5.29; N, 8.46; Cl, 10.76.

Condensation of the mother liquor gave 0.3 g. (1.9%) of a second crop, m.p. 240-242° dec.; shown to be pure **5b** by spectral examination.

4-Amino-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium Chloride (**5b**).

A mixture containing 10 g. of ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate (**1b**) and 100 ml. of phosphorus oxychloride was stirred at 100-105° for 2 hours. After the reaction had been completed, the excess phosphorus oxychloride was removed *in vacuo*. The residue was poured into *ca.* 70 ml. of ice water. To the resulting solution was added dropwise 80 ml. of 28% aqueous ammonia with stirring under ice water cooling. The precipitate was collected by filtration, washed with water and dried. Recrystallization from methanol yielded 7.88 g. (81%) of **5b** as colorless needles, m.p. 240-243° dec.; the nmr and ir spectra of which were identical with those of a sample described above.

Hydrolysis of **5a**.

A mixture containing 1 g. of **5a** and 10 ml. of 5% aqueous potassium hydroxide was stirred and heated at 80-90° for 22 hours. After the reaction was completed, the solution was acidified by the addition of 6*N* hydrochloric acid. There was obtained 0.56 g. (90%) of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**1a**), m.p. 317° dec. The ir and nmr spectra were identical with those of a sample prepared according to the procedure of Kaminsky and Meltzer (2).

4-Amino-3-carboxy-1-ethyl-6,7-methylenedioxyquinolinium Betaine (**6**).

Method A.

A mixture containing 1 g. of **5a** and 10 ml. of 5% aqueous potassium hydroxide was stirred at 80-90° for 15 minutes. After cooling, a white solid that precipitated was collected by filtration, washed with water and dried. Recrystallization from acetic acid gave 0.5 g. (89%) of **6** as white prisms, m.p. 324° dec.; nmr (trifluoroacetic acid): 1.73 δ (CH_3, t), 4.67 δ (CH_2, q), 6.37 δ (CH_2, s), 7.43 δ (C-5 proton, s), 7.68 δ (C-8 proton, s), 9.05 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.92; H, 4.69; N, 10.68.

Method B.

A mixture containing 20 g. of **3a** and 200 ml. of 28% aqueous ammonia was stirred at 80° for 1 hour. After cooling, the resulting solid was collected by filtration, washed with water and dried. Recrystallization from acetic acid gave 11.36 g. (91%) of **6** as white powder, m.p. 327° dec., the nmr and ir spectra of which were identical with those of the sample prepared in Method A.

1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxamide (**7**).

A mixture containing 2 g. of **1b**, 25 ml. of ethanol and 40 ml. of 28% aqueous ammonia was heated at 90-95° for 63 hours. The carboxamide **7** that deposited as a white solid was filtered, washed with water and dried, weighing 0.15 g. (8.3%), m.p. 336° dec., [lit. (11) m.p. > 315°]; nmr (trifluoroacetic acid): 1.73 δ (CH_3, t), 4.47 δ (CH_2, q), 6.4 δ (CH_2, s), 7.48 δ (C-8 proton, s), 7.92 δ (C-5 proton, s), 9.18 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.95; H, 4.75; N, 10.54.

Hydrolysis of **6**.

A mixture containing 1.5 g. of **6** and 20 ml. of 10% aqueous sodium hydroxide was refluxed for 3 hours. After cooling, the solution was acidified by the addition of 6*N* hydrochloric acid while hot. The white solid that precipitated was filtered, washed with water and dried, yielding 1.38 g. (92%) of **1a**, m.p. 315° dec. The infrared and nmr spectra were identical with those of a sample described above.

Reaction of 4-Chloro-3-carboethoxy-1-ethyl-6,7-methylenedioxyquinolinium Iodide (**3a**) with One Equivalent of Sodium Methoxide.

A mixture containing 4.36 g. of **3a**, 0.56 g. of sodium methoxide and 20 ml. of methanol was stirred at room temperature for 5 hours. After the reaction was completed, the methanol was evaporated *in vacuo* below 30°. The resulting residue was mixed with ice water and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated *in vacuo*, yielding 2.6 g. (90%) of a white solid, m.p. 178-180°. Recrystallization from acetone gave 2.1 g. (73%) of **1b** as colorless needles, m.p. 178.5-180°, undepressed on admixture with a sample described above. The infrared and nmr spectra of the two samples were identical. To the aqueous mother liquor after extraction with chloroform was added *ca.* 10 ml. of ethanol saturated with picric acid. The yellow needles that precipitated were collected by filtration, and washed consecutivly with water and aqueous ethanol, giving 0.17 g. (3%) of 3-carboethoxy-1-ethyl-4-methoxy-6,7-methylenedioxyquinolinium picrate (**3b**), m.p. 113-115°, nmr (deuterioacetone): 1.43 δ (CH_3, t), 1.75 δ (CH_3, t), 4.5 δ (CH_3, s), 4.62 δ (CH_2, q), 5.23 δ (CH_2, q), 6.67 δ (CH_2, s), 7.98, 8.12, 9.56 δ (quinolyl ring protons, s), 8.65 δ (phenyl ring protons, s).

Anal. Calcd. for $C_{22}H_{20}N_4O_{12}$: C, 49.63; H, 3.79; N, 10.52. Found: C, 49.59; H, 3.66; N, 10.76.

Ethyl 1-Ethyl-1,4-dihydro-4,4-dimethoxy-6,7-methylenedioxy-3-quinolinecarboxylate (**8a**).

A mixture containing 4.36 g. of **3a**, 1.2 g. of sodium methoxide and 20 ml. of methanol was stirred at 0-5° for 0.5 hour. After the reaction was completed, the methanol was evaporated *in vacuo* below 40° and the residue extracted with chloroform. The chloroform extracts were washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from a mixture of ether-petroleum benzine to give 2.65 g. (85%) of **8a** as colorless needles, m.p. 130-131°; nmr (deuteriochloroform): 1.32 δ (CH_3, t), 1.38 δ (CH_3, t), 2.88 δ (CH_3, t), 3.88 δ (CH_2, q), 4.3 δ (CH_2, q), 6.02 δ (CH_2, q), 6.58 δ (C-8 proton, s), 7.25 δ (C-5 proton, s), 7.97 δ (C-2 proton, s).

Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.67; H, 6.03; N, 4.31.

Ethyl 4,4-Diethoxy-1-ethyl-1,4-dihydro-6,7-methylenedioxy-3-quinolinecarboxylate (**8b**).

To a solution of sodium methoxide prepared from 3.45 g. of sodium and 150 ml. of anhydrous ethanol was added 21.8 g. of **3a** with external cooling with ice water. Stirring was continued for 40 minutes with ice water cooling, and then for 6 hours at room temperature. The sodium chloride that precipitated was removed by filtration and the filtrate evaporated *in vacuo* without heating. The resulting solid was mixed with ice water, filtered and washed with water. The collected solid was extracted exhaustively with ether. The material insoluble in ether melted at 177-178° and ir spectrum of which was identical with that of a sample of **1b** described above. Yield 7.7 g. (53%). The ethereal extract was evaporated, leaving 2.68 g. (15%) of **8b**. The analytical sample was recrystallized from ether, giving colorless rhombs, m.p. 110-112°; nmr (deuteriochloroform): 1.1 δ (CH_3, t), 1.33 δ (CH_3, t), 1.37 δ (CH_3, t), 2.5-3.37 δ (CH_2, m), 3.85 δ (CH_2, q), 4.3 δ (CH_2, q), 6.0 δ (CH_2, s), 6.55 δ (C-8 proton, s), 7.33 δ (C-5 proton, s), 7.88 δ (C-2 proton, s).

Anal. Calcd. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.87; H, 7.02; N, 3.84.

Acidification of the aqueous filtrate afforded 1.92 g. (15%) of **1a**.

Ethyl 1-Ethyl-4,4-diethylmercapto-1,4-dihydro-6,7-methylenedioxy-3-quinolinecarboxylate (**8c**).

A mixture containing 2.2 g. of sodium, 25 g. of ethyl mercaptane and 30 ml. of petroleum benzine was stirred under ice water cooling for 3 hours, until all of the metallic sodium disappeared. To the resulting mixture was added a mixture of 1.5 g. of **3a** and 50 ml. of chloroform. Then the mixture was kept at the same temperature with stirring for 24 hours. Water (*ca.* 50 ml.) was added, the chloroform layer separated and the aqueous layer was extracted with chloroform. The combined chloroform solution was washed with water, dried over sodium sulfate, decolorized with charcoal and evaporated *in vacuo* to dryness, yielding 5.13 g. of a fawn solid, which was washed with aqueous ethanol to give 3.33 g. of a pale yellow solid. Recrystallization from ether gave 2.15 g. (16%) of **8c** as pale yellow prisms, m.p. 132-133° dec.; nmr (deuteriochloroform): 1.1 δ (CH_3, t), 1.17 δ (CH_3, t), 2.08-2.77 δ (CH_2, m), 3.83 δ (CH_2, q), 4.43 δ (CH_2, q), 6.2 δ (CH_2, s), 6.57 δ (C-8 proton, s), 7.87 δ (C-5 proton, s), 8.0 δ (C-2 proton, s).

Anal. Calcd. for $C_{19}H_{25}NO_4S_2$: C, 57.77; H, 6.38; N, 3.55; S, 16.24. Found: C, 58.00; H, 6.23; N, 3.58; S, 16.10.

1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarbonylurea (**9**).

A mixture containing 5 g. of **3a**, 3 g. of thiourea and 50 ml. of water was stirred and heated at 90-95° for 2 hours. After cooling, the resulting solid was filtered, washed with water and dried, yielding 3.46 g. (98%) of **9** as a yellow solid, m.p. 288° dec., nmr (trifluoroacetic acid): 1.82 δ (CH_3, t), 4.87 δ (CH_2, q), 6.43 δ (CH_2, s), 7.57 δ (C-5 proton, s), 7.93 δ (C-8 proton, s), 9.07 δ (C-2 proton, s).

Anal. Calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.71; H, 4.11; N, 13.17, S, 10.05. Found: C, 52.63; H, 4.11; N, 12.94; S, 9.81.

Hydrolysis of **9**.

A mixture containing 1 g. of **9** and 30 ml. of 10% aqueous sodium hydroxide was stirred and heated at 90-95° for 3 hours. After the reaction was completed, the resulting solution was acidified by the addition of 6*N* hydrochloric acid while hot. The deposited solid was filtered, washed with water and dried. Recrystallization from dimethylformamide gave 0.5 g. (57%) of 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic acid (**1c**). M.p.s., analytical and nmr data are summarized in Tables II and IV.

2,3-Dihydro-2-imino-8,9-methylenedioxy-4-oxo-4*H*-[1,3]thiazino-[5,6-*c*]quinoline (**11**).

A solution containing 2.8 g. of ethyl 4-chloro-6,7-methylenedioxy-3-quinolinecarboxylate (**10**) (7), 0.86 g. of thiourea, 0.64 g. of potassium carbonate and 60 ml. of ethanol was refluxed for 1 hour. The white powder that deposited was filtered, washed with ethanol and dried, yielding 2.45 g. (90%) of **11**, m.p. over 300°,

nmr (trifluoroacetic acid): 6.35 δ (CH_2, s), 7.57, 7.75, 9.85 δ (ring proton, s).

Anal. Calcd. for $C_{12}H_7N_3O_3S$: C, 52.79; H, 2.59; N, 15.39; S, 11.75. Found: C, 52.78; H, 2.49; N, 15.01; S, 11.81.

Ethyl 4-Mercapto-6,7-methylenedioxy-3-quinolinecarboxylate (**12b**).

To a refluxing solution containing 1 g. of 70% sodium hydrosulfide and 30 ml. of ethanol was added dropwise a solution of 2 g. of the 4-chloroquinoline **10** and 30 ml. of ethanol over 0.5 hour. The solution was heated under reflux for an additional 2 hours. After the reaction was completed, the resulting solution was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in *ca.* 50 ml. of water and the resulting solution acidified by the addition of 6*N* hydrochloric acid. The yellow solid that precipitated was collected by filtration, washed with water, and dried. Recrystallization from aqueous dimethylformamide gave 1.08 g. (55%) of **12b** as yellow needles, m.p. 241-242° dec.; nmr (deuteriodimethylsulfoxide): 1.3 δ (CH_3, t), 4.25 δ (CH_2, q), 6.23 δ (CH_2, s), 7.1, 8.1, 8.15 δ (ring protons, s).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.36; H, 4.00; N, 5.06. Found: C, 56.53; H, 4.00; N, 5.03.

4-Mercapto-6,7-methylenedioxy-3-quinolinecarboxylic Acid (**12a**).

Method A.

A mixture containing 2 g. of **11** and 30 ml. of 10% aqueous sodium hydroxide was heated under reflux for 15 hours. The resulting solution was acidified by the addition of 6*N* hydrochloric acid while hot and the yellow precipitate collected by filtration, yielding 1 g. (55%) of **12a**. Recrystallization from dimethylformamide afforded 0.67 g. (37%) of yellow prisms, m.p. 296° dec., nmr (trifluoroacetic acid): 6.45 δ (CH_2, s), 7.47 δ (C-8 proton, s), 7.87 δ (C-5 proton, s), 9.33 δ (C-2 proton, s).

Anal. Calcd. for $C_{11}H_7NO_4S$: C, 53.06; H, 2.83; N, 5.63; S, 12.88. Found: C, 53.31; H, 2.76; N, 5.89; S, 12.66.

Method B.

A mixture containing 0.1 g. of the ester **12b** and 30 ml. of 5% aqueous potassium hydroxide was heated with stirring at 90-95° for 12 hours. The resulting solution was acidified by the addition of 6*N* hydrochloric acid while hot and a yellow solid that precipitated was collected by filtration, washed with water and dried. Recrystallizaiton from dimethylformamide gave 0.05 g. (56%) of yellow prisms, m.p. 296° dec. The ir and nmr spectra were identical with those of a sample prepared in Method A.

Ethyl 4-Ethylmercapto-6,7-methylenedioxy-3-quinolinecarboxylate (**15**).

Method A.

A mixture containing 1.23 g. of ethylmercaptane, 0.412 g. of sodium and 25 ml. of dry benzene was refluxed for 2.5 hours until all of the metallic sodium disappeared. To the resulting mixture was added 5 g. of **10**. The reaction mixture was refluxed for an additional 2 hours, and the solvent was evaporated *in vacuo*. The residue was mixed with water and extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. Evaporation of the solvent left 4.9 g. (90%) of a yellow solid which was recrystallized from petroleum benzine to give 3.97 g. (73%) of **15** as yellow prisms, m.p. 66-66.5°; nmr (deuteriochloroform): 1.18 δ (CH_3, t), 2.93 δ (CH_2, q), 4.47 δ (CH_2, q), 6.17 δ (CH_2, s), 7.33, 7.85, 8.83 δ (ring proton, s).

S, 10.51. Found: C, 59.20; H, 5.11; N, 4.67; S, 10.25.

Method B.

A solution containing 27.05 g. of **12b**, 4 g. of sodium hydroxide and 200 ml. of ethanol was stirred at 70-75° for 0.5 hour. A solution containing 4.22 g. of ethyl iodide and 30 ml. of ethanol was added dropwise over 1 hour and the resulting solution was stirred at the same temperature for an additional 5 hours. The ethanol was evaporated *in vacuo*, the residue diluted with water and extracted with ether. The ethereal solution was washed with water and evaporated to dryness, yielding 27.12 g. (91%) of a yellow oil, which was crystallized from petroleum benzine to give 25.32 g. (85%) of **15** as yellow needles, undepressed on admixture with a sample prepared in Method A.

3-Carboethoxy-4-ethylmercapto-1-methyl-6,7-methylenedioxyquinolinium Iodide (**16a**).

A mixture containing 5 g. of **15**, 20 ml. of methyl iodide, and 20 ml. of ethanol was heated under reflux for 24 hours. After the reaction was over, the volatile material was removed *in vacuo*, yielding 8.36 g. of a dark syrup, which was washed with ether and crystallized from a mixture of ethanol-ether. Recrystallization from a mixture of ethanol-ether gave 6.35 g. (87%) of yellow needles, m.p. 180-182° dec.

Anal. Calcd. for $C_{16}H_{18}INO_4S$: C, 42.95; H, 4.03; N, 3.13; S, 7.17; I, 28.39. Found: C, 42.76; H, 3.98; S, 7.19; I, 28.56.

3-Carboethoxy-1-ethyl-4-ethylmercapto-6,7-methylenedioxyquinolinium Iodide (**16i**).

A mixture containing 1.92 g. of **15** and 30 ml. of ethyl iodide was heated under reflux for 13 hours and worked up in the same manner as described above for the preparation of **16a**. There was obtained 2.87 g. (99%) of a yellow solid. Recrystallization from a mixture of ethanol-ether gave 2.24 g. (77%) of **16i** as yellow needles, m.p. 133-134°; nmr (deuteriochloroform): 1.33, 1.52, 1.73 δ (CH_3, t), 3.22, 4.57, 5.37 δ (CH_2, q), 6.53 δ (CH_2, s), 8.00, 8.03, 9.9 δ (ring protons, s).

Anal. Calcd. for $C_{17}H_{20}INO_4S$: C, 44.25; H, 4.34; N, 3.04; S, 6.96; I, 27.53. Found: C, 44.13; H, 4.25; N, 2.87; S, 7.15; I, 27.32.

Reaction of a 4-Ethylmercaptoquinolinium Iodide **16** with Sodium Hydrosulfide.

Ethyl 1,4-Dihydro-1-methyl-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**17a**).

A mixture containing 5.26 g. of **16a**, 1.63 g. of 70% sodium hydrosulfide and 50 ml. of water was stirred at room temperature for 5 hours. A yellow solid which had formed was collected by filtration, washed with water and dried. Recrystallization from ethanol gave 3.4 g. (99%) of **17a**.

Ethyl 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**1d**).

Prepared in the same procedure as described above. There was obtained 0.31 g. (74%) of **1d**.

Ethyl 1,4-Dihydro-6,7-methylenedioxy-1-*n*-propyl-4-thioxo-3-quinolinecarboxylate (**17b**) and 1,4-Dihydro-6,7-methylenedioxy-1-*n*-propyl-4-thioxo-3-quinolinecarboxylic Acid (**18b**).

A mixture containing 5 g. of **15** and 25 g. of *n*-propyl iodide was heated under reflux for 26 hours. After evaporation of the excess *n*-propyl iodide the residue was dissolved in acetone and added to a solution containing 2.62 g. of 70% sodium hydrosulfide

temperature for 26 hours and the acetone concentrated *in vacuo* without heating. The residual solid was extracted with chloroform, the chloroform layer separated, washed with water and dried over sodium sulfate. Evaporation of the solvent left a yellow solid, which was dissolved in chloroform and poured on a silica gel column for chromatography. The fraction eluted with chloroform gave 3.58 g. (69%) of **17b**. Acidification of the separated aqueous solution by the addition of 6*N* hydrochloric acid gave 1.2 g. (25%) of the corresponding acid **18b**.

Ethyl 1,4-Dihydro-6,7-methylenedioxy-1-*i*-propyl-4-thioxo-3-quinolinecarboxylate (**17c**).

A mixture containing 4 g. of **15** and 25 g. of *i*-propyl iodide was refluxed for 27 hours. After evaporation of the excess reagent *in vacuo*, the resulting yellow solid was washed with ether and recrystallized from a mixture of ethanol-ether, yielding 2 g. (35%) of hydroiodide of **15** as yellow needles, m.p. 190-193° dec.; nmr (deuteriochloroform): 1.33, 1.47 δ (CH_3, t), 3.17, 4.53 δ (CH_2, q), 6.43 δ (CH_2, s), 8.00, 8.22, 8.87 δ (ring protons, s).

Anal. Calcd. for $C_{15}H_{16}INO_4S$: C, 41.57; H, 3.70; N, 3.23; S, 7.41; I, 29.31. Found: C, 41.36; H, 3.65; N, 3.11; S, 7.42; I, 29.61.

The filtrate was evaporated *in vacuo*, yielding 4 g. of crude **16c** as a black syrup, which was dissolved in 100 ml. of chloroform. The chloroform solution was added to a solution of 0.5 g. of 70% sodium hydrosulfide dissolved in 50 ml. of water. The mixture was vigorously stirred at room temperature for 2 hours and the chloroform layer separated, washed with water, dried over sodium sulfate and evaporated *in vacuo*. The resulting syrup was three times washed with ether, forming 1 g. (22%) of a brown solid. Recrystallization from ethanol gave 0.55 g. (12%) of **17c**. The ethereal washings were evaporated *in vacuo* to give 1.25 g. (31%) of **15** as yellow prisms, the ir and nmr spectra of which were identical with the sample described above.

Ethyl 1-*n*-Butyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**17b**) and 1-*n*-Butyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic Acid (**18d**).

A stirred mixture containing 5 g. of **15** and 25 g. of *n*-butyl iodide was heated at 120-125° for 24 hours. After evaporation of the excess reagent, the resulting syrupy material was treated in the same manner as described for the reaction of **15** with *n*-propyl iodide. There were obtained 0.43 g. (8%) of the ester **17d** and 2.8 g. (56%) of the acid **18d**.

Ethyl 1-Cyclopropylmethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**17e**).

A stirred mixture containing 3 g. of **15** and 6 ml. of cyclopropylmethyl bromide was heated at 80-85° for 15 hours. After evaporation of the excess reagent, the resulting syrup was washed with ether, forming 3.82 g. (83%) of a yellow solid. Recrystallization from a mixture of ethanol-ether gave 2.35 g. (53%) of the quinolinium bromide **16e** as yellow needles, m.p. 115-116°. Being hygroscopic, this material failed to give correct analytical values. Treatment of **16e** with 70% sodium hydrosulfide in the same manner as described in the preparation of **17a** gave the corresponding ester **17e** in 90% yield.

Ethyl 1-Ethoxycarbonylmethyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylate (**17f**).

A stirred mixture containing 10 g. of **15** and 25 g. of ethyl bromoacetate was heated at 80° for 12 hours. After evaporation of the excess reagent *in vacuo*, the resulting syrup was dissolved in 300 ml. of ethanol and 70% sodium hydrosulfide (7 g.) was added. The mixture was stirred at room temperature for 4 hours. After evaporation of the solvent *in vacuo*, the resulting syrupy material was extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated *in vacuo* to give a dark brown solid. Purification by silica gel chromatography using chloroform as solvent afforded 7.89 g. (66%) of a brown solid which was recrystallized from ethanol to give 4.65 g. (39%) of **17f** as orange needles.

1-Allyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic Acid (**18g**).

A stirred mixture containing 4 g. of **15**, 25 g. of allyl iodide was heated at 95-100° for 15 hours. After evaporation of the excess reagent, the resulting syrup was dissolved in a solution containing 50 ml. of ethanol and 4 g. of 70% sodium hydrosulfide. The mixture was stirred and heated at 60-70° for 3 hours. The ethanol was removed *in vacuo* and the resulting syrup extracted with chloroform. The chloroform solution was washed with water, treated with charcoal, dried over sodium sulfate and evaporated *in vacuo* to give the syrupy material, which was extracted with 80 ml. of 20% hydrochloric acid to remove tarry material. The hydrochloric acid solution was heated with stirring at 80-90° for 1 hour. After cooling, a yellow solid that precipitated was collected by filtration, washed with water, and dried, yielding 1.06 g. (23%) of **18g**. Recrystallization from dimethylformamide gave 0.64 g. (17%) of yellow prisms.

1-Benzyl-1,4-dihydro-6,7-methylenedioxy-4-thioxo-3-quinolinecarboxylic Acid (**18h**).

A stirred mixture containing 5 g. of **15** and 50 g. of benzylbromide was heated at 100° for 40 hours. After cooling, ether (100 ml.) was added. The precipitate was collected by filtration, washed with ethanol and dried, yielding 1.2 g. (23%) of a yellow solid. Recrystallization from dimethylformamide gave 0.53 g. (10%) of 1-benzyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid, m.p. 312-313°, undepressed on admixture with a sample prepared by the known method (7). The ethanolic filtrate was evaporated *in vacuo*, yielding 6.69 g. (88%) of crude **16h**, as a brown solid which was used for the next procedure without further purification. Thus, a mixture containing 6.69 g. of **16h**, 3 g. of 70% sodium hydrosulfide and 50 ml. of ethanol was stirred at room temperature for 12 hours. The ethanol was removed by distillation, the residue extracted with chloroform and the chloroform extract washed with water, dried over sodium sulfate and evaporated *in vacuo* to give 2.02 g. of a syrup, which was extracted with 10% aqueous hydrochloric acid to remove the tarry material. The aqueous extract was stirred at 70-80° for 1 hour. After cooling, a yellow solid that deposited was collected by filtration, washed with water, and dried. Recrystallization from dimethylformamide gave 0.35 g. of (8%) of **18h**.

Physical properties, analytical and nmr data of **17** and **18** are listed in Tables I-IV.

General Preparation of **18** by Hydrolysis.

A mixture containing an ester **17a-f** and a 10 fold volume of 6*N* hydrochloric acid solution was stirred under reflux for 3-5 hours. After cooling, a yellow solid that deposited was collected by filtration, washed with water and dried. Recrystallization from the solvent shown in Table II yielded the corresponding **18a-f** in moderate yield. Physical properties, analytical and nmr data of **18a-f** are listed in Tables II and IV.

REFERENCES AND NOTES

(1) H. Agui, H. Tobiki, and T. Nakagome, *J. Heterocyclic Chem.*, **12**, 1245 (1975).

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

(3a) M. Pesson, P. de Lajudie, and M. Antoine, *C. R. Acad. Sci.*, serie C, **273**, 907 (1971); (b) R. Albrecht, *Chim. Ther.*, **8**, 45 (1973).

(4a) N. Barton, A. F. Crowther, W. Hepworth, D. N. Richardson, and G. W. Driver, British Patent 830,832 (1960): *Chem. Abstr.*, **55**, 7442e (1961); (b) R. Albrecht and H. J. Kessler, *Chim. Ther.*, **7** (4), 345 (1973); (c) H. Agui, T. Komatsu, and T. Nakagome, *J. Heterocyclic Chem.*, **12**, 557 (1975).

(5) G. Y. Lesher, E. J. Foelich, M. D. Gruett, J. H. Bailey, and R. P. Brundage, *J. Med. Chem.*, **5**, 1063 (1962).

(6a) M, Shimizu, S. Nakamura, and Y. Takase, "*Antimicrobial Agents and Chemotherapy*" 1970, p. 117; (b) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, **19**, 1426 (1971).

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

(8) N. N. Sveshnikov and N. A. Damir, *Dokl. Akad. Nauk. SSSR*, **164**, 1077 (1965); through *Chem. Abstr.*, **64**, 3470a (1966).

(9a) N. N. Sveshnikov, N. A. Damir, and N. S. Stokovskaya, U. S. S. R. Patent, 159,532 (1963); through *Chem. Abstr.*, **60**, 15845c (1964); (b) H. Larive and R. Baralle, French Patent, 408,737 (1965); through *Chem. Abstr.*, **64**, 853e (1966).

(10) R. U. Schock, *J. Am. Chem. Soc.*, **79**, 1670 (1957).

(11) K. Okumura, *et al.*, prepared the same compound by hydrolyzing 1,4-dihydro-1-ethyl-4-ethylimino-6,7-methylenedioxy-3-quinolinecarbonitrile with aqueous sodium hydroxide. Japanese Patent, 8315 (1972); *Chem. Abstr.*, 77, 5441u (1972).

(12) K. Okumura, T. Adachi, M. Tomie, K. Kondo, and I. Inoue, *J. Chem. Soc., Perkin Trans. I*, 173 (1972).

(13a) J. Meisenheimer, *Ann. Chem.*, **323**, 205 (1902); (b) S. Sekiguchi, T. Itagaki, T. Hirose, K. Matsui, and K. Sekine, *Tetrahedron*, **29**, 3527 (1973).

(14) D. S. Deorha and S. P. Sareen, *J. Indian Chem. Soc.*, **42**, 97 (1965).

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

(16) W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 2770 (1954).

(17) All Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. The ir spectra were determined for Nujol mulls on a JASCO IRA-1 spectrophotometer. The uv spectra were taken in ethanol with a Hitachi 323 spectrophotometer, nmr spectra with a Varian T 60 spectrometer and compared with TMS as an internal standard. In thin layer chromatography silica gel on plastic sheet (Spotfilm fluorescent, Tokyo Kasei Kogyo Co. Ltd.) was used throughout this work unless otherwise stated.