1-Ethyl-1,4-dihydro-4-oxo-7-(pyridinyl)-3-quinolinecarboxylic Acids. II. Synthesis

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The preparation of a variety of 1-ethyl-1,4-dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic acids with a range of substituents on the pyridine ring is described. Starting with the appropriately substituted aniline and using the first two steps of the Gould-Jacobs quinoline synthesis the 7-pyridinyl-3-quinolinecarboxylates can be obtained. Ethylation at the 1-position and hydrolysis of the ester group gives the desired acid products. These compounds have significant antibacterial activity: 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid is now in clinical study and 7-(2,6-dimethyl-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid is under advanced evaluation.

J. Heterocyclic Chem., **21**, 1857 (1984).

The finding of exceptional antibacterial activity in 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid **6a** and 7-(2,6-dimethyl-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid **6g** encouraged us to explore related compounds, especially examining the effect of substituents on the pryidine ring on antibacterial activity. The preparation of the required intermediate anilinopyridines is described in the preceding paper [1]. Their use to prepare the desired 1-alkyl-1,4-dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic acids **6** along with further manipulation of the attached pyridine ring are described in this paper. The biological activity of some of these compounds has been described [2].

SCHEME 1

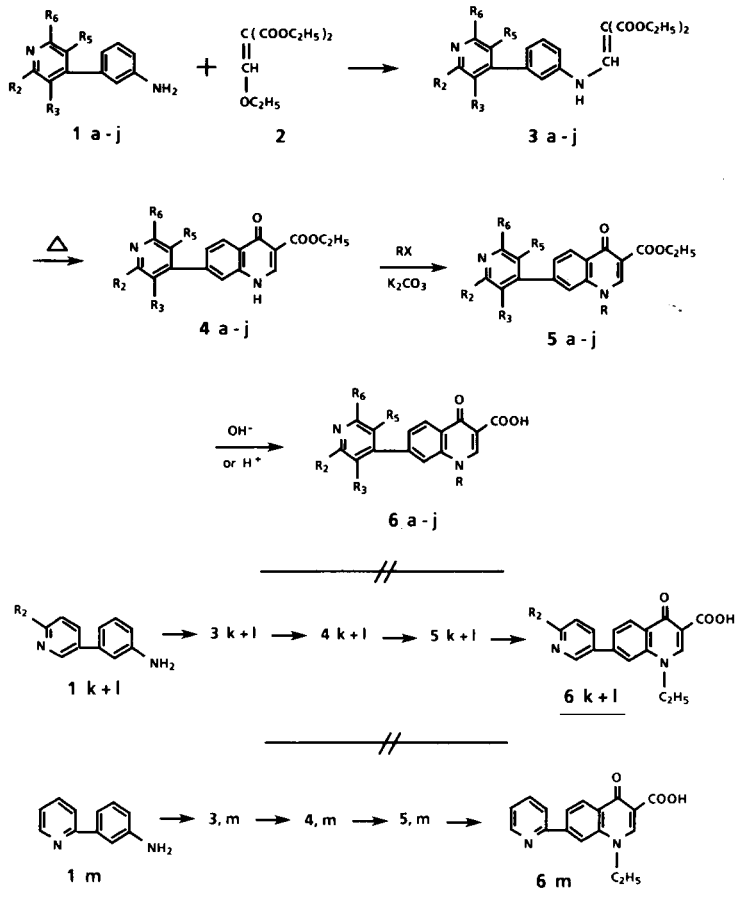
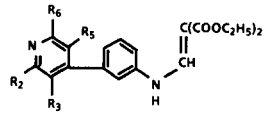


Table 1

Diethyl [[[3-(4-Pyridinyl)phenyl]amino]methylene]propanedioates **3**



Compound No.	R_2	R_3	R_5	R_6	Mp (°C)	Yield (%) [a]
3a	H	H	H	H	89-91	91
3b	CH_3	H	H	H	[b]	[c]
3c	C_2H_5	H	H	H	69-71 [b]	87
3d	H	CH_3	H	H	88-91	76
3e	CH_3	CH_3	H	H	74-76	88
3f	CH_3	H	CH_3	H	86-87	91
3g	CH_3	H	H	CH_3	78-80	78
3h	CH_3	H	H	OCH_3	[b]	[c]
3i	C_2H_5	H	H	C_2H_5	65-67	79
3j	CH_3	CH_3	CH_3	H	112-114 [b]	86
		Py				
3k		3-pyridinyl			84-86	95
3ℓ		2-CH_3-5-pyridinyl			[b]	[c]
3m		2-pyridinyl			[b]	[c]

[a] All prepared by Procedure A. [b] Not analyzed. [c] Used in the next step without purification.

Table 1a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
3a	$C_{19}H_{20}N_2O_4$	67.05	66.90	5.92	5.97	8.23	8.21
3d	$C_{20}H_{22}N_2O_4$	67.78	67.72	6.26	6.31	7.91	7.91
3e	$C_{21}H_{24}N_2O_4$	68.46	68.28	6.57	6.54	7.60	7.80
3f	$C_{21}H_{24}N_2O_4$	68.46	68.33	6.57	6.52	7.60	7.54
3g	$C_{21}H_{24}N_2O_4$	68.46	68.50	6.57	6.59	7.60	7.60
3i	$C_{23}H_{28}N_2O_4$	69.68	69.43	7.12	7.14	7.07	6.91
3k	$C_{19}H_{20}N_2O_4$	67.05	67.06	5.92	5.88	8.23	8.23

Scheme 1 outlines the synthetic path used to convert these anilines **1a-m** to the desired quinolonecarboxylic acids **6a-m**. The first two steps of the Gould-Jacobs reaction sequence [3] were used to react with the anilines **1** to give the acrylates **3** in good yields (Table 1). These were then cyclized in refluxing Dowtherm A® to the quinolone esters **4** in generally good yields (Tables 2 and 5). Although not looked for carefully, none of the possible isomeric quinolones was detected in these cyclizations. The quinolone esters **4a-m** were alkylated with dialkyl sulfates, alkyl iodides or alkyl tosylates in dimethylformamide with potassium carbonate to give **5a-m** (Tables 3 and 5). Hydrolysis of **5a-m** gave the desired 1-ethyl-1,4-dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic acids **6a-m** (Tables 4 and 5).

Ethyl has generally been found to be the optimum substituent at the 1-position for maximum antibacterial activity [4]. This was also found to be true in this series but other lower alkyl groups were also prepared and are listed at the end of Tables 3 and 4. The preparation of the 1-(2-

SCHEME 2

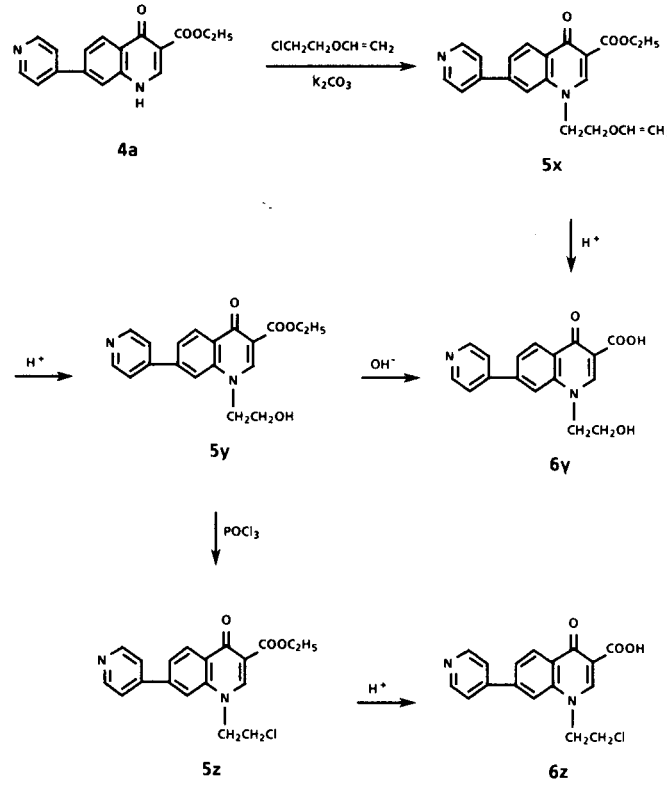
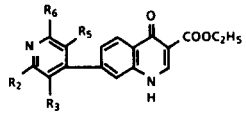


Table 2

Ethyl 1,4-Dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylates **4**



Compound No.	R_2	R_3	R_5	R_6	Mp (°C)	Yield (%) [a]
4a	H	H	H	H	292-294	75
4b	CH_3	H	H	H	185-188 [b]	26
4c	C_2H_5	H	H	H	245 dec	59 [c]
4d	H	CH_3	H	H	[b]	[d]
4e	CH_3	CH_3	H	H	269-271 [d]	91
4f	CH_3	H	CH_3	H	[b]	87
4g	CH_3	H	H	CH_3	>320 dec	85
4h	CH_3	H	H	OCH_3	[b]	[d]
4i	C_2H_5	H	H	C_2H_5	>300 [b]	90
4j	CH_3	CH_3	CH_3	H	281-282	45

[a] All prepared by Procedure B. [b] Not analyzed. [c] Hydrochloride salt. [d] Used in the next step without purification.

Table 2a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
4a	$C_{17}H_{14}N_2O_3$	69.38	69.17	4.79	4.82	9.52	9.45
4c	$C_{19}H_{18}N_2O_3$·HCl	63.60	63.30	5.34	5.44	7.81	7.78
4g	$C_{19}H_{18}N_2O_3$	70.79	70.50	5.63	5.59	8.69	8.66
4j	$C_{20}H_{20}N_2O_3$	71.41	71.22	5.99	5.85	8.33	8.10

hydroxyethyl) derivative **5y** by direct alkylation of **4a** with 2-chloroethanol or ethylene epoxide was unsatisfactory, so we resorted to alkylation with 2-chloroethyl vinyl ether (Scheme 2) giving **5x** followed by hydrolytic removal of the vinyl group to give **5y**. Hydrolysis of **5y** gave the desired **6y**. Chlorination of **5y** followed by hydrolysis of the ester gave the 1-(2-chloroethyl) acid **6z**.

The preparation of the *N*(py)-oxide of **5a** gave the very useful **5n** (Scheme 3). It was hydrolysed to the corresponding acid **6n**. The *N*(py)-oxide **5n** was rearranged in acetic anhydride to give after hydrolysis the 2-pyridone acid **6o**. *O*-Methylation of **5o** with methyl iodide and silver oxide gave **5p** which was hydrolysed to the corresponding acid **6p**. The chlorination of the *N*(py)-oxide **5n** with phosphorus oxychloride gave the 2-chloropyridine **5q** in respectable yield [5]. This was fortunate because attempts to prepare **5q** in chlorination of the 2-pyridone **5o** were unsuccessful because here chlorination also took place at the 4-position of the quinoline ring with loss of the *N*-ethyl group, as well as the production of tars. Acid hydrolysis of **5q** gave the corresponding acid **6q**.

The 2-dimethylaminopyridine derivatives **5r** and **6r** were also obtained from **5q**. Teatment of **5n** with dimethyl

SCHEME 3

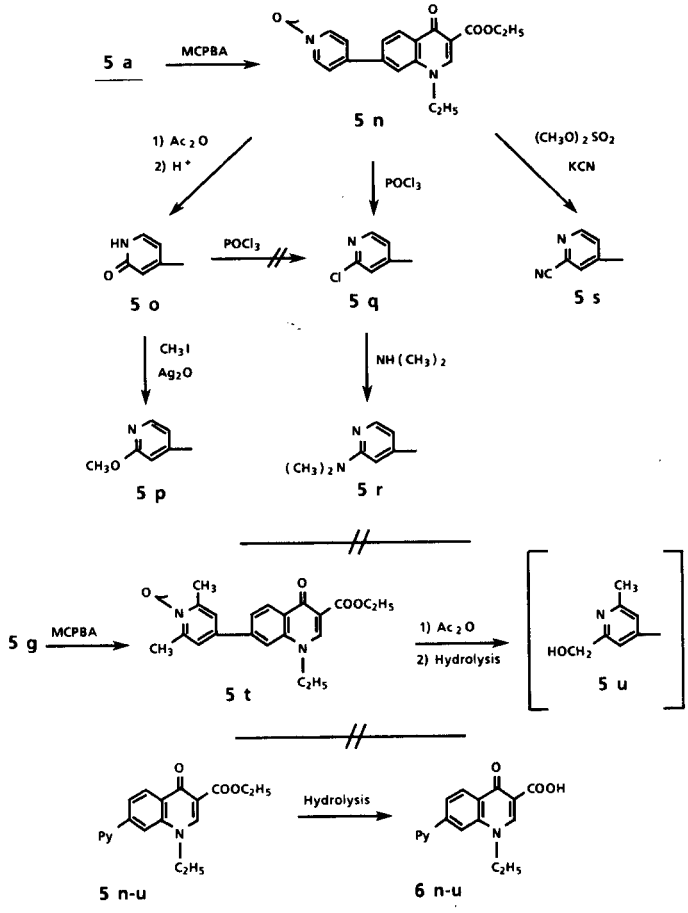
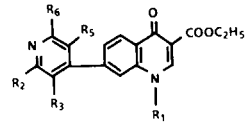


Table 3

Ethyl 1-Alkyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylates **5**



Compound No.	R_2	R_3	R_5	R_6		Mp (°C)	Yield (%)	Procedure
5a	C_2H_5	H	H	H		169-170.5	45	C
5b	C_2H_5	CH_3	H	H	H	[a]	[b]	C
5c	C_2H_5	C_2H_5	H	H	H	143-144 [a]	73	C
5d	C_2H_5	H	CH_3	H	H	162-163	16	C
5e	C_2H_5	CH_3	CH_3	H	H	101-103	23	C
5f	C_2H_5	CH_3	H	CH_3	H	157-158 [a]	46	C
5g	C_2H_5	CH_3	H	H	CH_3	168-170	65	C
5h	C_2H_5	CH_3	H	H	OCH_3	171-173	29	C
5i	C_2H_5	C_2H_5	H	H	C_2H_5	135-137 [a]	77	C
5j	C_2H_5	CH_3	CH_3	CH_3	H	226-228 [a]	91	C
5o	C_2H_5	OH	H	H	H	263-266 [a]	53	—
5p	C_2H_5	OCH_3	H	H	H	196-197	65	—
5q	C_2H_5	Cl	H	H	H	164-166 [a]	70	—
5r	C_2H_5	$N(CH_3)_2$	H	H	H	[a]	[b]	—
5s	C_2H_5	CN	H	H	H	258-261	62	—
5v	CH_3	H	H	H	H	[a]	[b]	C
5w	C_3H_7	H	H	H	H	[a]	[b]	C
5x	$CH_2CH_2OCH=CH_2$	H	H	H	H	191-193 [a]	61	C
5y	CH_2CH_2OH	H	H	H	H	154-156 [a]	74	—
5z	CH_2CH_2Cl	H	H	H	H	205 dec [a]	72	—
5aa	CH_3	CH_3	H	H	CH_3	215-217 [a]	82	C
5ab	C_3H_7	CH_3	H	H	CH_3	135-136 [a]	76	C

[a] Not analyzed. [b] Used in the next step without purification.

Table 3a

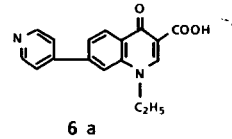
Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
5a	$C_{19}H_{18}N_2O_3$	70.79	70.76	5.63	5.71	8.69	8.46
5d	$C_{20}H_{20}N_2O_3$	71.41	71.19	5.99	5.92	8.33	8.68
5e	$C_{21}H_{22}N_2O_3$	71.98	71.69	6.33	6.29	7.99	7.89
5g	$C_{21}H_{22}N_2O_3$	71.98	71.99	6.33	6.37	7.99	7.99
5h	$C_{21}H_{22}N_2O_4$	68.84	68.46	6.05	6.02	7.65	7.66
5p	$C_{20}H_{20}N_2O_4$	68.17	68.01	5.72	5.66	7.95	7.97
5s	$C_{20}H_{17}N_3O_3$	69.15	69.04	4.93	4.96	12.10	12.29

sulfate and then potassium cyanide (Scheme 3) gave the 2-cyanopyridine **5s** [6]. This was converted to the diacid **6s** by basic hydrolysis.

Scheme 3 also outlines the conversion of the 2,6-dimethylpyridine **5g** to its *N*(py)-oxide **5t** which was hydrolysed to the acid **6t**, as well as rearranged in acetic anhydride followed by hydrolysis, to the 2-hydroxymethyl-6-methylpyridine derivative **6u**.

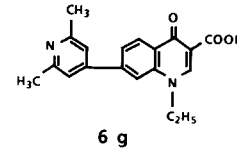
After further biological evaluation **6a** was chosen for clinical studies as an agent for gonorrheal infections and urinary tract infections, as well as for systemic gram-negative infections [2]. Its generic name is rosoxacin [7].

The 2,6-dimethylpyridinyl derivative **6g** was found to have surprisingly potent antistaphylococcal activity and is being developed for this indication.



6 a

rosoxacin



6 g

EXPERIMENTAL

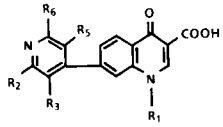
Melting points are uncorrected. All new compounds have compatible ir, ms and/or nmr spectra.

Procedure A. Diethyl [[[3-(4-Pyridinyl)phenyl]amino]methylene]propanedioate (**3a**).

A mixture of 4-(3-aminophenyl)pyridine (**1a**) (112 g, 0.66 mole) and diethyl ethoxymethylenemalonate (**2**) (148 g, 0.68 mole) was heated at 130° for eight minutes and then allowed to cool to 100°. The resulting oil was taken up in 100 ml of 2-propanol and cyclohexane was added to incipient cloudiness. This was treated with charcoal, filtered and cooled to yield 205 g (91%) of adduct **3a**, mp 86-88°. An analytical sample was obtained by recrystallization from ethanol, mp 89-91°.

Table 4

1-Alkyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic Acids **6**



Compound No.	R_2	R_3	R_5	R_6		Mp (°C)	Yield (%) [a]
6a	C_2H_5	H	H	H	H	284-286	89
6b	C_2H_5	CH_3	H	H	H	302-303 dec	76 [b]
6c	C_2H_5	C_2H_5	H	H	H	>300	87 [b]
6d	C_2H_5	H	CH_3	H	H	284-287 dec	62 [b]
6e	C_2H_5	CH_3	CH_3	H	H	326-328 dec	64
6f	C_2H_5	CH_3	H	CH_3	H	>300	87 [b]
6g	C_2H_5	CH_3	H	H	CH_3	282-284 dec	24
6h	C_2H_5	CH_3	H	H	OCH_3	277-278	81
6i	C_2H_5	C_2H_5	H	H	C_2H_5	210-212	89
6j	C_2H_5	CH_3	CH_3	CH_3	H	277-279 dec	72
6o	C_2H_5	OH	H	H	H	352-354	69
6p	C_2H_5	OCH_3	H	H	H	238-240	75
6q	C_2H_5	Cl	H	H	H	264-265 dec	66
6r	C_2H_5	$N(CH_3)_2$	H	H	H	225-245 dec	19 [b]
6s	C_2H_5	COOH	H	H	H	246-247	59
6u	C_2H_5	CH_3	H	H	CH_2OH	250-251	64
6v	CH_3	H	H	H	H	329-330 dec	38
6w	C_3H_7	H	H	H	H	295-297 dec	42
6y	CH_2CH_2OH	H	H	H	H	285-287	68
6z	CH_2CH_2Cl	H	H	H	H	>300	69 [b]
6aa	CH_3	CH_3	H	H	H	>335	85 [b]
6ab	C_3H_7	CH_3	H	H	CH_3	233-235	77

[a] Prepared by Procedure D. [b] Hydrochloride salt.

Table 4a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
6a	$C_{17}H_{14}N_2O_3$	69.38	69.33	4.79	4.80	9.52	9.59
6b	$C_{18}H_{16}N_2O_3 \cdot HCl$	62.70	62.50	4.97	4.97	8.12	8.09
6c	$C_{19}H_{18}N_2O_3 \cdot HCl$	63.60	63.48	5.34	5.33	7.81	7.71
6d	$C_{18}H_{16}N_2O_3 \cdot HCl$	62.70	63.03	4.97	4.91	8.12	8.24
6e	$C_{19}H_{18}N_2O_3$	70.79	70.63	5.63	5.59	8.69	8.71
6f	$C_{19}H_{18}N_2O_3 \cdot HCl$	63.60	63.55	5.34	5.23	7.81	7.66
6g	$C_{19}H_{18}N_2O_3$	70.79	70.70	5.63	5.53	8.69	8.88
6h	$C_{19}H_{18}N_2O_4$	67.45	67.23	5.36	5.35	8.28	8.61
6i	$C_{21}H_{22}N_2O_3$	71.98	71.80	6.33	6.24	7.99	7.86
6j	$C_{20}H_{20}N_2O_3$	71.41	71.21	5.99	5.93	8.33	8.16
6o	$C_{17}H_{14}N_2O_4$	65.80	65.76	4.55	4.50	9.03	9.12
6p	$C_{18}H_{16}N_2O_4$	66.66	66.72	4.97	5.31	8.64	8.64
6q	$C_{17}H_{13}ClN_2O_3$	62.11	61.97	3.99	3.99	8.52	8.91
6r	$C_{19}H_{19}N_3O_3 \cdot HCl$	61.04	60.82	5.39	5.29	11.24	11.06
6s	$C_{18}H_{14}N_2O_5$	63.90	63.70	4.17	4.26	8.20	8.21
6u	$C_{19}H_{18}N_2O_4$	67.45	67.66	5.36	5.31	8.28	8.28
6v	$C_{16}H_{12}N_2O_3$	68.57	68.44	4.32	4.35	9.99	9.96
6w	$C_{18}H_{16}N_2O_3$	70.12	70.06	5.23	5.22	9.09	9.09
6y	$C_{17}H_{14}N_2O_4$	65.80	65.75	4.55	4.54	9.03	9.22
6z	$C_{17}H_{13}ClN_2O_3 \cdot HCl$	55.90	55.96	3.86	3.86	7.67	7.71
6aa	$C_{18}H_{16}N_2O_3 \cdot HCl$	62.07	62.47	4.97	4.86	8.12	8.09
6ab	$C_{20}H_{20}N_2O_3$	71.41	71.05	5.99	5.92	8.33	8.27

Procedure B. Ethyl 1,4-Dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**4a**).

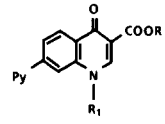
Dowtherm A® (500 ml) was heated to boiling with stirring. Diethyl [[[3-(4-pyridinyl)phenyl]amino]methylene]propanedioate (**3a**) (50 g, 0.15 mole) was added all at once and the solution was boiled vigorously with stirring for 12 minutes. After the solution had cooled to room temperature, it was diluted with one volume of *n*-hexane and the resulting tan solid was collected and washed well with ether. The product (32.7 g, 75%) melted at 242-245°. This material was satisfactory for further use. An analytical sample was obtained by recrystallization from dimethylformamide, collecting the crystals at 60-70° to avoid gel formation which occurs on further cooling. The product **4a** was washed with ethanol and dried, mp 292-294°.

Procedure C. Ethyl 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**5a**).

A mixture of dimethylformamide (1 *l*), potassium carbonate (milled, 165 g, 1.2 mole) and ethyl 1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**4a**) (100 g, 0.34 mole) was stirred at 60° for 15 minutes. Diethyl sulfate (52.5 g, 0.34 mole) was added and the mixture stirred for one hour. The dimethylformamide was evaporated and the resulting residue was partitioned between water and chloroform (emulsion, broken by filtration). The chloroform was evaporated and the dark residual oil was taken up in 2-propanol (1 *l*), treated with charcoal and cooled. An orange solid (49.0 g, 45%) was collected. An analytical sample of **5a** was obtained by recrystallization from 2-propanol, mp 169-170.5°.

Table 5

1,4-Dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylates



Compound No.	Py	R_1	R	Mp (°C)	Yield (%)	Procedure
4k	3-pyridinyl	H	C_2H_5	253-256 [a]	85	B
5k	3-pyridinyl	C_2H_5	C_2H_5	[a]	[b]	C
6k	3-pyridinyl	C_2H_5	H	268-269	39	D
4ℓ	2-CH_3-5-pyridinyl	H	C_2H_5	[a]	[b]	B
5ℓ	2-CH_3-5-pyridinyl	C_2H_5	C_2H_5	[a]	[b]	C
6ℓ	2-CH_3-5-pyridinyl	C_2H_5	H	277-280 dec	26 [c] [d]	D
4m	2-pyridinyl	H	C_2H_5	[a]	[b]	B
5m	2-pyridinyl	C_2H_5	C_2H_5	[a]	[b]	C
6m	2-pyridinyl	C_2H_5	H	219-220	35	D
5n	4-pyridinyl *N*-oxide	C_2H_5	C_2H_5	222-224	61	C
6n	4-pyridinyl *N*-oxide	C_2H_5	H	307-309 dec	80	D
5t	2,6-$(CH_3)_2$-4-pyridinyl *N*-oxide	C_2H_5	C_2H_5	238-241	68	C
6t	2,6-$(CH_3)_2$-4-pyridinyl *N*-oxide	C_2H_5	H	295-296 dec	64	D

[a] Not analyzed. [b] Used in next step without purification. [c] Hydrochloride salt. [d] Yield is for alkylation and hydrolysis steps.

Table 5a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
6k	$C_{17}H_{14}N_2O_3$	69.38	69.07	4.79	4.74	9.52	9.72
6ℓ	$C_{18}H_{16}N_2O_3 \cdot HCl$	62.70	62.42	4.97	5.07	8.12	8.11
6m	$C_{17}H_{14}N_2O_3$	69.38	69.53	4.79	4.78	9.52	9.35
5n	$C_{19}H_{18}N_2O_4$	67.45	67.29	5.36	5.35	8.28	8.18
6n	$C_{17}H_{14}N_2O_4$	65.80	65.72	4.55	4.48	9.03	9.00
5t	$C_{21}H_{22}N_2O_4$	68.84	68.73	6.05	6.09	7.65	7.84
6t	$C_{19}H_{18}N_2O_4$	67.45	67.19	5.36	5.41	8.28	8.33

Procedure D. 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic Acid (**6a**).

A mixture of ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**5a**) (41.0 g, 0.13 mole) and 400 ml of 10% potassium hydroxide solution was stirred and heated on a steam bath for one hour. The resulting solution was treated with charcoal, filtered and the filtrate acidified to *p*H 6 with acetic acid. The suspension was cooled and the product **6a** (33.0 g, 89%) was collected. An analytical sample was obtained by crystallization from dimethylformamide, mp 284-286°.

Ethyl 1-[2-(Ethenyloxy)ethyl]-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**5x**).

Ethyl 1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**4a**) (37 g, 0.13 mole) was stirred together with potassium carbonate (milled, 28 g, 0.2 mole) in dimethylformamide (250 ml) on a steam bath for one hour. 2-Chloroethyl vinyl ether (13.8 g, 0.13 mole) was then added and heating was continued for 3.5 hours. The hot mixture was filtered, the filtrate chilled, and the resulting solid was collected, washed with ethanol and dried (10.5 g). The filtrate was heated on a steam bath for an additional 15 hours and again chilled to obtain a second crop of product (5.5 g). The two crops were combined and recrystallized from dimethylformamide to give 26.2 g (61%) of product **5x**, mp 191-193°.

Ethyl 1,4-Dihydro-1-(2-hydroxyethyl)-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**5y**).

The vinyl ether **5x** (26.2 g, 0.07 mole) was dissolved in acetic acid (50 ml) with warming. Water (5 ml) was added and the solution heated on a steam bath for one hour. The solution was concentrated and the residual solid was triturated with water, washed with ethanol, dried and recrystallized from dimethylformamide to give 18.0 g (74%) of product **5y**, mp 154-156°.

1,4-Dihydro-1-(2-hydroxyethyl)-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic Acid (**6y**).

The ester **5y** (4.2 g, 0.012 mole) was heated on a steam bath with 5% potassium hydroxide (30 ml) for two hours with stirring. The solution was neutralized (*p*H ~ 6) with dilute hydrochloric acid. The resulting precipitate was collected, recrystallized twice from dimethylformamide and dried giving 2.6 g (68%) of product **5y**, mp 285-287°.

1-(2-Chloroethyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic Acid Monohydrochloride (**6z**).

The ester **5y** (15.0 g, 0.044 mole) was suspended in 800 ml of dry chloroform and thionyl chloride (17 ml) was added with stirring, a tar formed. The mixture was heated on a steam bath with stirring for five hours and the tar solidified. This solid was collected, dried and suspended in water (250 ml). The mixture was slowly neutralized (*p*H ~ 7.5) with 10% potassium hydroxide, and resulting solid was collected and recrystallized twice from ethanol to give 11.4 g (72%) of a tan solid of im-

precise melting point (*ca* 205°). Its nmr spectrum confirmed that this was reasonably pure ethyl 1-(2-chloroethyl)-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate. This ester was heated with stirring on a steam bath with 300 ml of 2*N* hydrochloric acid for 1.5 hours. The mixture was filtered and the filter cake was triturated with water, washed with ethanol and dried to give 11.1 g (96%; yield from both steps, 69%) of the product **6z**, mp >300°.

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate *N*(py)-Oxide (**5n**).

To a stirred solution of ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate (**5a**) (18.0 g, 0.056 mole) in 250 ml of methylene dichloride was added 85% *m*-chloroperoxybenzoic acid (12.2 g, 0.06 mole). A white solid crystallized after one hour. Stirring was continued for one more hour. The *m*-chlorobenzoic acid salt of the *N*-oxide product was collected and then boiled five minutes in a mixture of 25 ml of dimethylformamide and 100 ml of ethanol. This suspension was cooled, the solid collected and stirred for ten minutes with a warm sodium bicarbonate solution. The white solid was collected, washed with water, dried and recrystallized from ethanol. The product **5n** (11.5 g, 61%) melted at 222-224°.

Ethyl 1-Ethyl-1,4-dihydro-7-(1,2-dihydro-2-oxo-4-pyridinyl)-4-oxo-3-quinolinecarboxylate (**5o**).

A mixture of the *N*(py)-oxide **5n** (46.0 g, 0.136 mole) and acetic anhydride (460 ml) was refluxed for eight hours. The green solution was evaporated to a green gum. The gum was stirred with ethanol and the gray-green solid collected. The solid was recrystallized from ethanol and then from dimethylformamide. This was then washed with acetonitrile and recrystallized again from ethanol. The product **5o** (24.3 g, 53%) melted at 263-266°.

Ethyl 1-Ethyl-1,4-dihydro-7-(2-methoxy-4-pyridinyl)-4-oxo-3-quinolinecarboxylate (**5p**).

A mixture of ethyl 1-ethyl-1,4-dihydro-7-(1,2-dihydro-2-oxo-4-pyridinyl)-4-oxo-3-quinolinecarboxylate (**5o**) (19.0 g, 0.056 mole), silver carbonate (31.0 g, 0.112 mole) and 500 ml tetrahydrofuran was heated to reflux with stirring. Methyl iodide (16.1 g, 0.113 mole) was added during five minutes. After three hours of reflux, another 10 ml of methyl iodide was added and refluxing was continued 15 hours longer. After the mixture was cooled the solid was collected and the filtrate evaporated to a yellow solid. This solid was taken up in chloroform, this was filtered through a short column of Florisil and the filtrate evaporated. The resulting solid was recrystallized twice from acetonitrile and then from dioxane to give 12.8 g (65%) of product **5p**, mp 196-197°.

Ethyl 7-(2-chloro-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**5q**).

A mixture of ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate *N*(py)-oxide (**5n**) (15.0 g, 0.044 mole) and phosphorus oxychloride (200 ml) was heated eight hours on the steam bath. The excess phosphorus oxychloride was evaporated and the residue partitioned between saturated sodium bicarbonate solution and chloroform. The organic phase was separated and evaporated to give 13.5 g of a red gum which was crystallized from 100 ml of ethanol to give 11.0 g (70%) of a pale pink solid **5q**, mp 164-166°.

7-[2-(Dimethylamino)-4-pyridinyl]-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid Monohydrochloride (**6r**).

A solution of ethyl 7-(2-chloro-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**5q**) (5.0 g, 0.014 mole) in 100 ml of ethanol and 50 ml of dimethylamine was heated to 150° for eight hours in a rocking autoclave. The solution was evaporated to a dark oil which solidified. This solid was combined with 50 ml of methanol, 35 ml of 35% sodium hydroxide and 100 ml of water and then heated on a steam bath for two hours. The solution was evaporated and the residue was taken up in a little water and neutralized with dilute hydrochloric acid. The solid was collected, dissolved in methanol and treated with 5 ml of concentrated hydrochloric acid. The cream solid which formed was collected and recrystallized from boiling 6*N* hydrochloric acid. The product **6r** (1.0 g, 19%) melted at 225-245° dec.

Ethyl 7-(2-Cyano-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**5s**).

A mixture of ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylate *N*(py)-oxide (**5n**) (27.0 g, 0.08 mole), dimethyl sulfate (20.2 g, 0.16 mole) and 75 ml of acetonitrile was refluxed with stirring for 30 minutes, giving a clear solution. The solution was cooled to 25° and 30 g of potassium cyanide in 100 ml of water was added rapidly with vigorous stirring. A thick white paste formed. After ten minutes the mixture was diluted with one volume of water, stirred a few minutes and the solid collected and washed with water. The dried solid was recrystallized twice by dissolving in hot dimethylformamide, filtering, adding acetonitrile till cloudy and cooling. The product **5s** (17.2 g, 62%) melted at 258-261°.

7-(2-Carboxy-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid (**6s**).

A mixture of ethyl 7-(2-cyano-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (**5s**) (7.0 g, 0.02 mole), 30 ml of water and 20 ml of 10% sodium hydroxide solution was refluxed for three hours. The solution was acidified with dilute hydrochloric acid, the resulting white solid was collected and washed with water. The dried solid was recrystallized from dimethylformamide-ethanol. The resulting solid was dissolved in dilute ammonium hydroxide, the solution was filtered and then acidified with dilute hydrochloridc acid. The white solid was washed with water and dried. The product **6s** (4.0 g, 59%) melted at 246-247°.

Ethyl 7-(2,6-Dimethyl-4-pyridinyl)-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate *N*(py)-Oxide (**5t**).

This compound was prepared from **5g** in the same manner as **5n** in 68% yield, mp 238-241°.

1-Ethyl-1,4-dihydro-7-[2-(hydroxymethyl)-6-methyl-4-pyridinyl]-4-oxo-3-quinolinecarboxylic Acid (**6u**).

Acetic anhydride (30 ml) was heated to boiling, the heat was removed and the *N*(py)-oxide **5t** (10.0 g, 0.027 mole) was added in portions with stirring during five minutes. The dark solution was refluxed for one-half hour, concentrated to a gum which was then refluxed one hour in 50 ml of 6*N* hydrochloric acid. The solution was concentrated, resulting in a gum which when triturated with ethanol gave a red solid. The solid was taken up in water, treated with charcoal and the resulting filtrate treated with a saturated sodium acetate solution. The yellow solid that formed was collected, air dried and recrystallized successively from acetonitrile, methanol and acetonitrile. The product **6u** (5.9 g, 64%) melted at 250-251°.

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[7] Erdacil™ is the Sterling Drug brand of rosoxacin.