The Synthesis of some 2,4-Disubstituted Derivatives of Quinolone-3-carboxylic Acids and Carbonitriles

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In order to prepare the 2-chloro derivative of oxolinic acid, ethyl 1-ethyl-1,4-dihydro-2-hydroxy-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate was treated with phosphorus oxychloride. The compound obtained was the 4-chloro-2-oxo-quinoline. The structure was confirmed by ^{13}C nmr and mass spectral techniques. The 2-halocarbonitrile was obtained by a Sandmeyer reaction but could not be hydrolysed into the acid.

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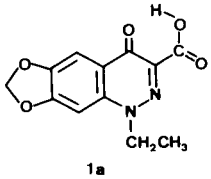
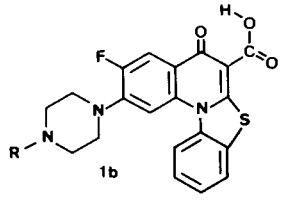
Introduction.

Quinolone derivatives are an important class of compounds that has attracted increasing attention as a source of new antibacterial agents.

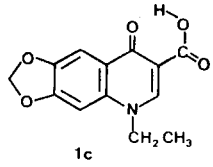
Modification at the 2-position of the quinolone moiety has an important effect upon the biological activity. Introduction of a 2-methyl or 2-hydroxyl function results in complete inactive compounds [1] [2]. However this is not the case for cinoxacin (**1a**) [3] and the recently developed thiosubstituted derivatives **1b** [4].



1a

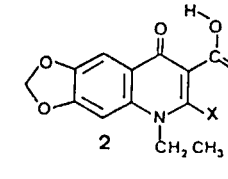


1b



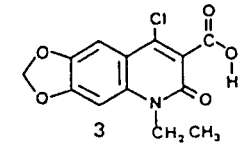
1c

In view of the aforesaid a synthetic programme aiming at new quinolone chemotherapeutics was started. We used oxolinic acid (**1c**) as a model compound. In this paper we wish to comment upon the results obtained during an investigation aiming at the synthesis of 2-chloro and 2-bromo derivatives of 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids **2**. Substitution of a 2-hydroxy group using phosphorus oxychloride, the Sandmeyer reaction on 2-amino derivatives and halogenation of the pyridine *N*-oxide compound after lithiation [5] [6] were investigated. This paper describes the methods used and gives the compound identification by nmr and mass spectrometry. We did not succeed in the preparation of the desired compound. Only 4-chloro-2-oxo-3-quinolinecarboxylic acid (**3**) and a 2-bromo-4-oxo-3-quinolinecarbonitrile (**4**) were obtained.



2

a. X = Cl
b. X = Br



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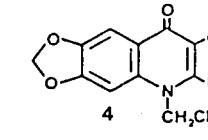

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Chemistry.

The reaction of isatoic anhydrides, with active methylene compounds produces a wide variety of substituted quinolones, depending on the nature of the active methylene compound employed [7].

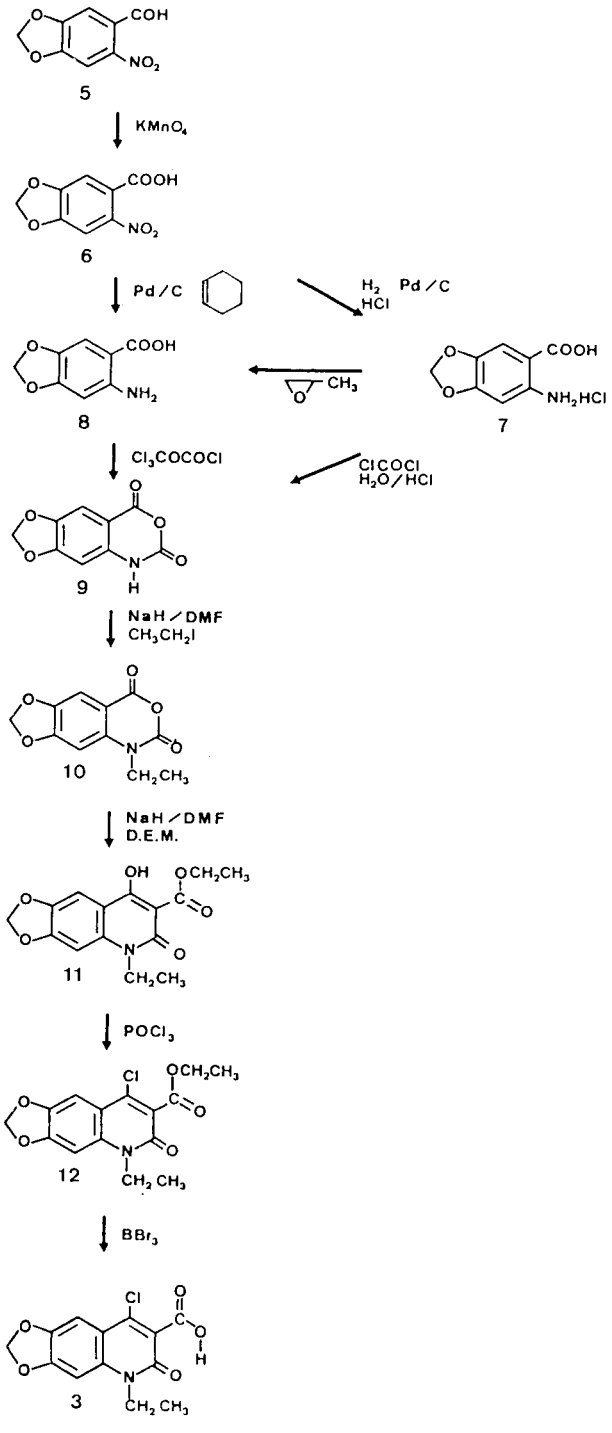
Therefore we synthesized 5,6-methylenedioxyisatoic anhydride **9** as an intermediate for our synthesis. This was done by a modified method, previously described by Mitscher *et al.* [1].

As the starting material, 6-nitropiperonal (**5**) was oxidized with potassium permanganate to 6-nitropiperonylic acid (**6**). This compound was converted into the 4,5-methylenedioxyanthranilic acid hydrochloride (**7**) by catalytic hydrogenation in acidic medium. Catalytic reduction with

Pd/C-cyclohexene afforded 4,5-methylenedioxyanthranilic acid (**8**) in moderate yield. Compound **8** was also obtained by converting the hydrochloride **7** into the free amine **8** with propylene oxide in quantitative yield.

According to the general procedure of Wagner and Fegley [8], the isatoic anhydride analogue **9** was prepared by treatment of **8** with phosgene (60% yield). As phosgene presents a severe hazard in laboratory use, mainly because of its high volatility, we tried the usefulness of trichloromethyl chloroformate as a potential substitute [9]. It has physical properties which make it considerably safer and more convenient to handle than phosgene. Moreover it seems to have advantages over phosgene: quantitative conversion of **8** into **9**.

Scheme I

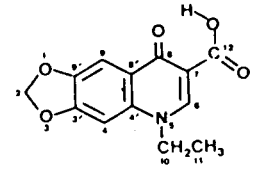


Subsequently *N*-alkylation was performed by sodium hydride/ethyl iodide in *N,N*-dimethylformamide. Reaction of **10** with malonate yielded the 2-hydroxyquinolone derivative **11**, which was converted into the chloro compound **12** by means of phosphorus oxychloride. Hydrolysis of this ester in alkaline or acidic medium resulted in decarboxylation. Hydrolysis however with boron tribromide at −78° produced the carboxylic acid **3** (Scheme 1).

To prove the site of the chlorine atom, compound **3** was compared with oxolinic acid.

The ^{13}C-nmr data (see Table I) show a remarkable up-field shift (51 ppm to 40 ppm) of the N-CH_2-CH_3 signal. This can only be explained in terms of conversion of the quinolone nitrogen of oxolinic acid into an amide. Moreover there is a clear up-field shift (175 ppm to 165 ppm) of the quinolone carbonyl group signal. The proposed formula **3** agrees well with the ^{13}C-nmr data given in the literature [10] [11].

Table I



	Oxolinic Acid **1c**	Compound **3**
C_2	104 (t)	105 (t)
$C_{3'}$	154	152
C_4	97 (d)	95 (d)
$C_{4'}$	138	135
C_{10}	51 (t)	40 (t)
C_{11}	15 (q)	12 (q)
C_6	147 (d)	165
C_7	119	113
C_{12}	173	173
C_8	175	130
$C_{8'}$	124	127
C_9	104 (d)	102 (d)
$C_{9'}$	145	144

The ei-mass spectrum of compound **12** is depicted in Figure I. The base peak is formed by the molecular ion M^+ at m/z = 323 (^{35}Cl). The fragment ion at m/z = 295 (^{35}Cl)

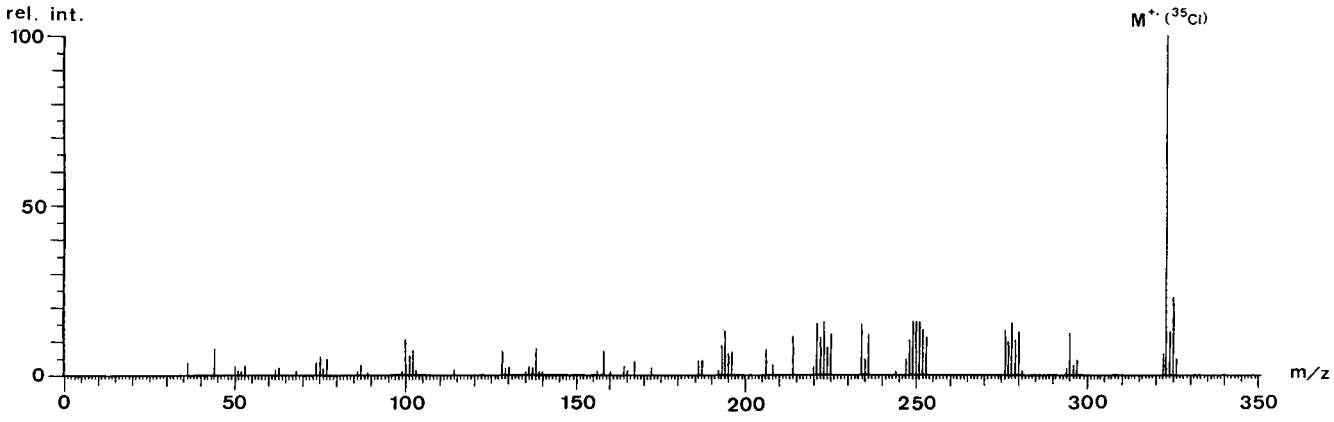


Figure I

can be explained by either a McLafferty rearrangement involving the *N*-ethyl group and the adjacent carbonyl function in **12** or by elimination of ethylene out of the ethoxycarbonyl function in both **12** and the 2-chloro isomer **2a**. Therefore the occurance of m/z = 295 alone does not enable us to distinguish between the two possible structures. However, since **12** can eliminate ethylene using both pathways, two structurally different ions at m/z = 295 can be formed (Scheme II). Further fragmentation of these ions can explain the set fragment ions at m/z = 249 (^{35}Cl), m/z = 221 (^{35}Cl) and 193 (^{35}Cl) and the set detected at m/z = 278 (^{35}Cl) and m/z = 250 (^{35}Cl) (Scheme II).

The former series can be considered as indicative for structure **12**. Furthermore, since the 2-chloro isomer is not able to use the *N*-ethyl function in a rearrangement process we would at least expect some fragment ions at m/z = 308 (^{35}Cl) and m/z = 294 (^{35}Cl) due to *beta* or *alpha* cleavage with respect to the nitrogen atom. These ions were not detected.

Based upon this data structure **12** was assigned to the compound.

It should be clear, from the arguments cited above, that the 4-chloroquinolone **3** was formed instead of the desired 2-chloro analogue **2a**. Therefore an alternative way was attempted.

Once more we used the versatility of isatoic anhydride analogues. We prepared the 2-amino-3-cyano-4-hydroxyquinolone **13** by reaction of **9** with sodium malononitrile. Diazotation in pyridine with sodium nitrite in diluted sulfuric acid, followed by displacement by a halogen, yielded the 2-halogenated compound **14**. However all our attempts to hydrolyse the carbonitrile group failed. The same was true for the hydrolysis of the *N*-ethyl compound **4** (recovery of the starting material or degradation by decarboxylation of the intermediary carboxylic acid formed).

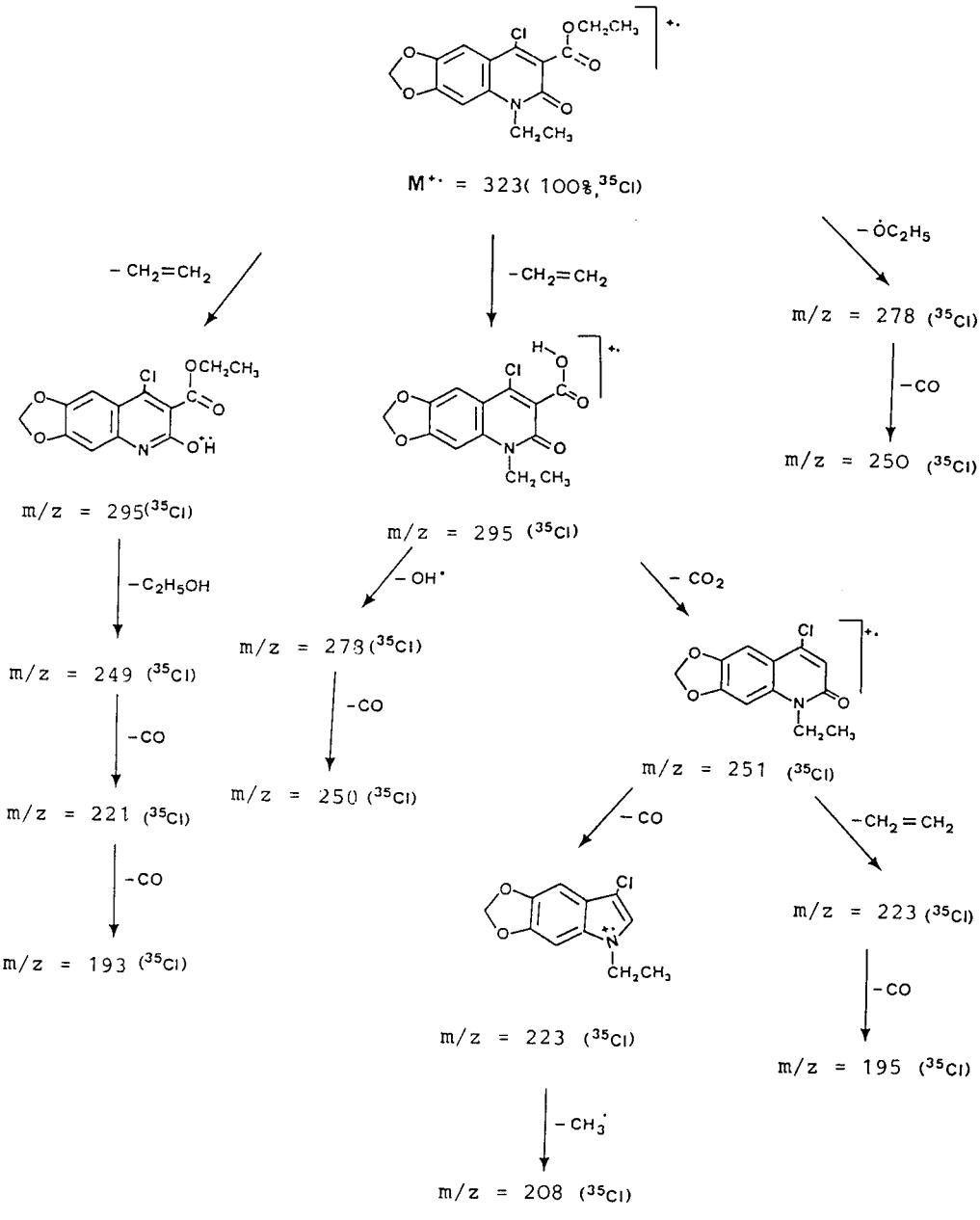
Table II

Compound No.	Formula				
6	$C_8H_5NO_6$	211.3	C	45.51	45.60
			H	2.38	2.39
			N	6.63	6.61
7	$C_8H_8ClNO_4$	217.61	C	44.15	43.99
			H	3.70	3.71
			N	6.43	6.44
			Cl	16.29	16.36
8	$C_8H_7NO_4$	181.15	C	53.04	52.84
			H	3.89	3.90
			N	7.73	7.75
9	$C_9H_5NO_5$	207.14	C	52.18	52.20
			H	2.43	2.44
			N	6.76	6.72
10	$C_4H_9NO_6$	235.20	C	56.17	56.03
			H	3.85	3.84
			N	5.95	5.95
11	$C_{15}H_{15}NO_6$	305.29	C	59.01	58.92
			H	4.95	4.93
			N	4.58	4.59
12	$C_{15}H_{14}ClNO_5$	323.74	C	55.65	55.64
			H	4.35	4.33
			N	4.32	4.33
			Cl	10.95	10.92
3	$C_{13}H_{10}ClNO_5$	295.68	C	52.80	53.00
			H	3.40	3.41
			N	4.73	4.74
			Cl	11.99	12.01
13	$C_{11}H_7N_3O_3$	229.20	C	57.64	57.88
			H	3.07	3.06
			N	18.33	18.40
14	$C_{11}H_5BrN_2O_3$	293.0	B	45.78	44.76
			N	9.55	9.57
			Br	27.56	27.15

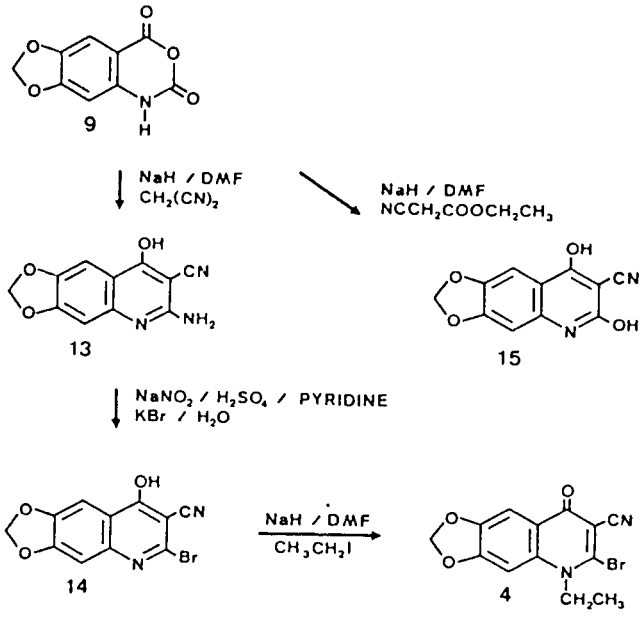
Table II (continued)

Compound No.	Formula				
15	$C_{11}H_6N_2O_4$	230.18	C	57.39	57.21
			H	2.62	2.60
			N	12.17	12.20
4	$C_{13}H_9BrNO_3$	321.13	C	48.62	48.45
			H	2.82	2.83
			N	8.72	8.68
			Br	24.88	24.95

Although we prepared 2-halogenated analogues by this reaction sequence, no desired oxolinic acid derivative was obtained. In order to obtain a compound which could be hydrolysed with greater ease, we tried the reaction of **9** with sodium ethyl cyanoacetate. Instead of the desired ethyl 2-amino-3-carboxylate, the 2-hydroxy-3-carbonitrile **15** was obtained in 45% yield. These results are in good agreement with those found by Coppola *et al.* [12] [13] (Scheme III).



Scheme II



Scheme III

The third method, halogenation of the pyridine *N*-oxide after lithiation with butyllithium was unsuccessful with the *N*-oxide of oxolinic acid.

Conclusion.

We did not succeed in the preparation of the desired compounds. The phosphorus oxychloride method afforded the 4-chloro-1-ethyl-1,2-dihydro-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylic acid (**3**). With the Sandmeyer technique the 2-halocarbonitrile **4** was obtained but could not be hydrolyzed to the free carboxylic acid. The compounds showed no antibacterial activity.

EXPERIMENTAL

All compounds were checked for their structure with ir spectrophotometry, ^{1}H-nmr, ^{13}C-nmr, mass spectrometry and elemental analysis. The ir spectra were obtained with a Beckmann Acculab-4 spectrophotometer. The ν max are given in cm^{-1}. All compounds were examined as potassium bromide pellets. The ^{1}H-nmr spectra were recorded on a Varian EM 360 A spectrometer. The ^{13}C-nmr spectra were obtained on a Jeol FX-100 spectrometer operating at 25 MHz for carbon. Chemical shifts are given in ppm (δ) relative to tetramethylsilane. Low resolution ei-mass spectra were recorded on a JEOL JMS-01SG-II double focusing mass spectrometer connected to a JEC-6-computer system. The ionisation energy was 70 eV and the emission current was 200 μA. The product was introduced by a direct insertion probe. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Elemental analysis (Table II) were within acceptable limits.

2-Nitro-4,5-methylenedioxybenzoic Acid **6**.

Compound **6** was prepared according to the method of Mitscher *et al.* [1], yield 85%, mp 167° dec; ir (potassium bromide): ν max 1720 (C=O), 1525, 1340 (NO_2); ^{1}H-nmr (deuteriochloroform): δ 6.35 (s, 2H, O-CH_2-O), 6.85 and 7.45 (each s, 1H, arom-H).

4,5-Methylenedioxyanthranilic Acid Hydrochloride **7**.

Compound **7** was prepared according to the method of Mitscher *et al.* [1], yield 95%, mp >300°; ir (potassium bromide): ν max 1680 (C=O), 2500, 1510 (NH_3^+); ^{1}H-nmr (DMSO-d_6): δ 6.2 (s, 2H, O-CH_2-O), 6.9 and 7.4 (each s, 1H, arom-H), 10.3 (s, 3H, NH_3^+).

4,5-Methylenedioxyanthranilic Acid **8**.

To a mechanically stirred solution of 21.1 g (0.1 mole) of **6** and 41.0 g (0.5 mole) of cyclohexene in 200 ml of ethanol, 5 g of 10% Pd/C was added. The solution was heated under reflux for 3 hours. The resulting solution was filtered hot to remove the Pd/C. Diethyl ether was added (100 ml) and the mixture cooled. The precipitated acid was filtered off and washed with a minimal amount of cold ethanol and diethyl ether, yielding 12.7 g (70%) of **7** as white crystals, mp 178° dec; ir (potassium bromide): ν max 3460, 3360, 1600, 1240 (arom-NH_2), 1665 (C=O); ^{1}H-nmr (DMSO-d_6): δ 6.1 (s, 2H, O-CH_2-O), 6.5 and 7.35 (each s, 1H, arom-H), 8.3 (br, 2H, arom-NH_2).

To a mechanically stirred solution of 21.8 g (0.1 mole) of **7** in 200 ml of dry ethanol, 58.1 g (1.0 mole) of propylene oxide was added. The reaction mixture was heated under reflux for 2 hours. The solvent was removed *in vacuo* and the residue recrystallized from tetrahydrofuran, yielding 18.0 g (quantitative) of **8** as white crystals.

2*H*-6,7-Methylenedioxy-3,1-benzoxazine-2,4(1*H*)-dione **9**.

Method a.

Compound **9** was prepared according to the general procedure of Wagner and Fegley [6], utilizing 10.9 g (0.05 mole) of **7** and phosgene, yielding 6.2 g (60%) of **9** in four successive crops. Recrystallization from *N*,*N*-dimethylformamide/ethanol (1/1) yielded the isatoic anhydride analogue as colourless needles, mp 258°; ir (potassium bromide): ν max 1890, 1720 (C=O), 1320, 1270 (C-O); ^{1}H-nmr (deuteriochloroform): δ 6.3 (s, 2H, O-CH_2-O), 6.8 and 7.4 (each s, 1H, arom-H), 11.8 (br, 1H, -NH).

Method b.

To a mechanically stirred solution of 1.81 g (0.01 mole) of **8** in 10 ml of dry dioxane, 3.96 g (0.02 mole) of trichlormethyl chloroformate was added. The reaction mixture was heated under reflux for 6 hours. Hexane (10 ml) was added and the mixture cooled. The precipitate was collected and washed with hexane, yield 2 g (quantitative).

2*H*-6,7-Methylenedioxy-3,1-benzoxazine-2,4-(1-ethyl)-dione **10**.

To a stirred suspension of 0.490 g (0.0102 mole) of benzene washed 50% sodium hydride in 50 ml of dry *N*,*N*-dimethylformamide, was added portionwise 2.07 g (0.01 mole) of **9**. The mixture was heated at 80° for 30 minutes and 3.9 g (0.025 mole) of ethyl iodide added. The brown-red solution was kept at 80° for another 2 hours. After evaporation of the solvent *in vacuo*, the residue was taken up in chloroform, washed with water dried over sodium sulphate and the chloroform distilled off *in vacuo*. The resulting solid was recrystallized from ethanol, yielding 2.1 g (89%) of **10** as colourless crystals, mp 207°; ir (potassium bromide): ν max 1780, 1730 (C=O), 1310, 1250 (C-O); ^{1}H-nmr (deuteriochloroform): δ 1.3 (t, 3H, J = 7 Hz, N-CH_2-CH_3), 4.15 (q, 2H, J = 7 Hz, N-CH_2-CH_3), 6.40 (s, 2H, O-CH_2-O), 7.30 and 7.55 (each s, 1H, arom-H).

Ethyl 1-Ethyl-1,2-dihydro-2-hydroxy-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylate **11**.

In 20 ml of dry *N*,*N*-dimethylformamide 1.280 g (8 mmoles) of diethyl malonate was combined with 0.384 g (8 mmoles) of benzene washed 50% sodium hydride. The reaction mixture was stirred at 110° for 30 minutes and 0.940 g (4 mmoles) of **10** was added portionwise. The resulting solution was heated under reflux for another 2 hours (carbon dioxide evolution occurs). The reaction mixture was evaporated to dryness *in vacuo*, followed by benzene azeotrope to remove residual *N*,*N*-dimethylformamide. The residue was then taken up in water and washed with chloroform. The water layer was separated and acidified with concentrated hydrochloric acid. The precipitated ester was collected, washed with water and recrystallized from isopropyl ether, yielding 2.07 g (85%) of **11** as colourless crystals, mp 176°; ir (potassium bromide): ν max 1650, 1620 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.3 and 1.45 (each t, 3H, J

= 7 Hz, N-CH_2-CH_3 and O-CH_2-CH_3), 4.4 and 4.55 (each q, 2H, J = 7 Hz, N-CH_2-CH_3 and O-CH_2-CH_3), 6.32 (s, 2H, O-CH_2-O), 7.20 and 7.60 (each s, 1H, arom-H), 14.3 (br, s, -OH); ms: (m/e) 305 M^+.

Ethyl 4-Chloro-1-ethyl-1,2-dihydro-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylate **12**.

A solution of 0.915 g (3 mmoles) of **7** in 20 ml of freshly distilled phosphorus oxychloride was refluxed for 3 hours. The reaction mixture was evaporated to dryness *in vacuo* and ice added. After neutralization with 1*N* sodium hydroxide, the solution was extracted several times with chloroform. The organic layers were collected, washed with water, dried over sodium sulphate and evaporated under reduced pressure. The residue was triturated with hexane and cooled. The precipitate was collected and recrystallized from ethyl acetate/hexane (1/1), yielding 0.68 g (70%) of **8** as yellow crystals, mp 149°; ir (potassium bromide): ν max 1725 (C=O), 1650 (amide), 1615 (C=C); ^{1}H-nmr (deuteriochloroform + 50% DMSO-d_6): δ 1.32 and 1.42 (each t, 3H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 4.37 and 4.50 (each q, 2H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 6.28 (s, 2H, O-CH_2-O), 7.18 and 7.50 (each s, 1H, arom-H); ms (m/e) 323/325 M^+ (100%), 295/297 M-CH_2=CH_2, 278/280 M-OCH_2CH_3, 250/252 M-$COOCH_2CH_3$.

4-Chloro-1-ethyl-1,2-dihydro-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylic Acid **3**.

In an inert atmosphere, 0.324 g (1 mmole) of **12** was dissolved in 10 ml of dry dichloromethane and cooled to −78°. To this stirred solution, 5 ml of a 1 *M* solution (5 mmoles) of boron tribromide in dichloromethane was added dropwise. Stirring at −78° was continued for 1 hour. After 2 hours, ice was added to the reaction mixture which was allowed to come to room temperature. The organic layer was collected, washed with water, dried over sodium sulphate and concentrated to dryness *in vacuo*. The residue was taken up in 0.1 *N* sodiumhydroxide at 0° and slowly acidified with cooled 0.1 *N* hydrochloric acid, yielding 0.280 g (94%) of **3** as colourless crystals, mp 212° dec; ir (potassium bromide): ν max 1730 (C=O), 1630 (C=C), 1590 (amide); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.70 (t, 3H, J = 7 Hz, N-CH_2-CH_3), 4.96 (q, 2H, J = 7 Hz, N-CH_2-CH_3), 6.52 (s, 2H, O-CH_2-O), 7.64 and 8.32 (each s, 1H, arom-H); ms: (m/e) 295/297 M^+, 267/269 M-CH_2=CH_2, 260 M-Cl, 259 M-HCl, 251/253 M-CO_2.

2-Amino-4-hydroxy-6,7-methylenedioxy-3-quinolinecarbonitrile **13**.

In 20 ml of dry *N,N*-dimethylformamide, 1.320 g (0.020 mole) of malononitrile was combined with 0.960 g (0.020 mole) of benzene washed with 50% sodium hydride. The reaction mixture was stirred at 110° for 1 hour and 2.070 g (0.010 mole) of **9** was added portionwise. The resulting solution was heated under reflux for another 10 hours (carbon dioxide evolution occurs). Workup was done as described for the preparation of **7**. Recrystallization from *N,N*-dimethylformamide/ethanol (1/1) yielded 1.48 g (65%) of **13** as colourless crystals, mp >300°; ir (potassium bromide): ν max 3400, 3330, 1635 (ar-NH_2), 2220 (C≡N), 1610 (C=C), 1240 (OH); ^{1}H-nmr (deuteriochloroform + 50% DMSO-d_6): δ 6.36 (s, 1H, O-CH_2-O), 7.20 and 7.63 (each s, 1H, arom-H), 9.1 (br, 2H, NH_2), 11 (br, 1H, OH).

2-Bromo-4-hydroxy-6,7-methylenedioxy-3-quinolinecarbonitrile **14**.

A solution of 3.45 g (0.05 mole) of sodium nitrite in 10 ml of water was added dropwise to 25 ml of sulphuric acid at −10°. This solution was dropped into a stirred solution of 3.29 g (0.01 mole) of **13** in a minimal amount of pyridine at −10°. The reaction mixture was stirred at 0° for 1 hour, after which a concentrated solution (25 ml) of potassium bromide in water was added. After 16 hours at room temperature, ice was added. The precipitate was collected and washed with water. Recrystallization from *N,N*-dimethylformamide/ethanol yielded 2.16 g (55%) of **14** as a cream-coloured amorphous powder, mp >300°; ir (potassium bromide): ν max 2250 (C≡N), 1660 (C=C), 1230 (OH); ^{1}H-nmr (deuteriochloroform + 50% DMSO-d_6): δ 6.4 (s, 2H, O-CH_2-O), 7.3 and 7.91 (each s, 1H, arom-H), 12.5 (br, 1H, OH).

2,4-Dihydroxy-6,7-methylenedioxy-3-quinolinecarbonitrile **15**.

In 10 ml of dry *N,N*-dimethylformamide, 2.262 g (0.020 mole) of ethyl cyanoacetate was combined with 0.960 g (0.020 mole) of benzene washed 50% sodium hydride. The reaction mixture was stirred at 110° for 1 hour and 2.070 g (0.010 mole) of **9** was added portionwise. The reaction was carried out as described for **13**, yielding 1.04 g (45%) of **15** as colourless crystals, mp >300°; ir (potassium bromide): ν max 2235 (C≡N), 1610 (C=C), 1230 (OH); ^{1}H-nmr (deuteriochloroform): δ 6.38 (s, 2H, O-CH_2-O), 7.24 and 7.66 (each s, 1H, arom-H), 11 (br, 2H, 2x-OH).

2-Bromo-1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarbonitrile **4**.

To a stirred suspension of 0.490 g (0.0102 mole) of benzene washed 50% sodium hydride in 50 ml of dry *N,N*-dimethylformamide, was added portionwise 2.93 g (0.01 g mole) of **14**. The mixture was heated at 80° for 1 hour and 3.90 g (0.025 mole) of ethyl iodide added. After another 4 hours at 80°, the solvent was evaporated *in vacuo*. The residue was taken up in chloroform, washed with water, dried over sodium sulphate and the chloroform distilled off *in vacuo*. The resulting solid was recrystallized from *N,N*-dimethylformamide/ethanol (1/1), yielding 2.9 g (90%) of **4** as colourless needles, mp >300°; ir (potassium bromide): ν max 2240 (C≡N), 1630 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7 Hz, O-CH_2-CH_3), 4.45 (q, 2H, J = 7 Hz, O-CH_2-CH_3), 6.35 (s, 2H, O-CH_2-O), 7.25 and 7.65 (each s, 1H, arom-H); ms: (m/z), 321 M^+.

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