SYNTHESIS OF SOME 1-ARYL-1,4-DIHYDRO-4-OXOQUINOLINE--3-CARBOXYLIC ACIDS AND THEIR ANTIBACTERIAL ACTIVITY

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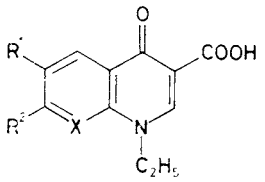
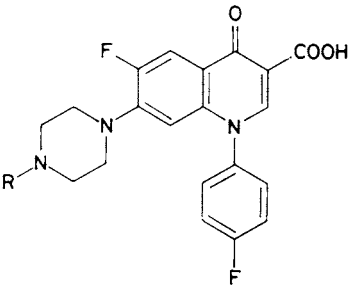
1,4-Dihydro-4-oxoquinoline-3-carboxylic acids *VIIIc* and *VIIId* were prepared via their ethyl esters *VIIIa* and *VIIIb*, which were obtained by a direct arylation of ethyl 7-chloro-6-fluoro-1,4--dihydro-4-oxoquinoline-3-carboxylate (*VIa*). When treated with piperazine or N-methylpiperazine compound *VIIId* yields *VIIIe* or *VIIIf*, respectively. Reduction of *VIIId*, *VIIIe*, and *VIIIf* with ferrous sulfate yields *VIIIg*, *VIIIh*, and *VIIIi*, respectively. Diazotization and introduction of fluorine into *VIIIg* using hydrogen fluoride–pyridine yields *VIIIj*. The compounds prepared were tested for their antimicrobial activity in vitro.

Many compounds with a 4-pyridone-3-carboxylic acid fragment have been studied as potential antibacterial agents. Antibacterial quinolones have attracted increasing attention during the last several years[1,2]. Nalidixic acid (*Ia*), the first agent of this type, lacked substantial Gram-positive activity and its blood levels were below the minimum inhibitory concentrations. After the discovery of norfloxacin (*Ib*) and pefloxacin (*Ic*), which were the first drugs of the type with a broad spectrum of antibacterial activity, many useful agents have been prepared. The recent discovery[3,4] of active 1-aryl derivatives A-56 620 (*IIa*) and difloxacin (*IIb*) has stimulated considerable interest in the synthesis of new compounds having 1-aryl substituents.

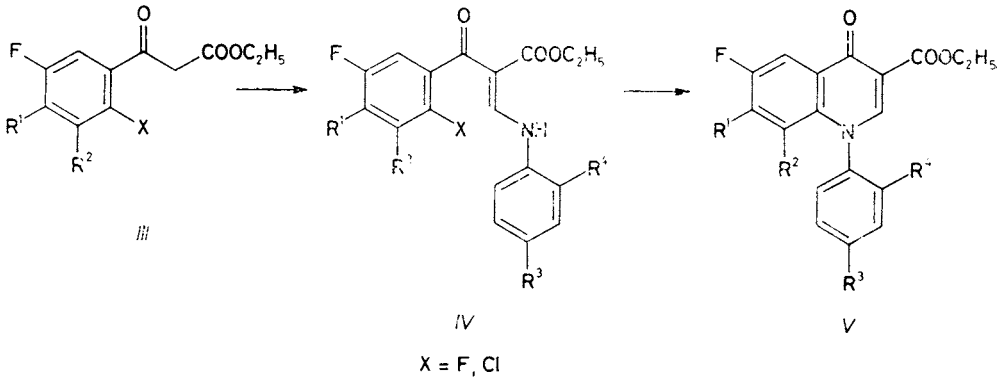




Ia, X = N ; R^1 = H ; R^2 = CH_3
Ib, X = CH ; R^1 = F ; R^2 = piperazinyl
Ic, X = CH ; R^1 = F ; R^2 = 4-methylpiperazinyl

IIa, R = H
IIb, R = CH_3

Common synthetic pathway (Scheme 1) starts from the respective benzoylacetate *III* having a leaving group at the position 2. Treatment of the compounds with ethyl orthoformate and appropriate aryl amine yields compounds of a general formula *IV*, and their intramolecular nucleophilic displacement reaction yields the desired compounds *V* (refs[3-7]).

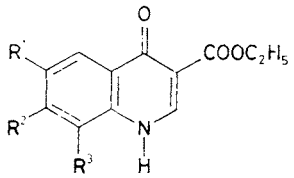


SCHEME 1

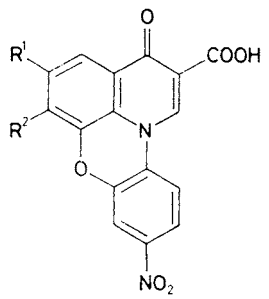
N-Alkylation of 1,4-dihydro-4-oxoquinoline-3-carboxylates is a well established method which has been used for many years[8]. However, no direct N-arylation of these compounds has been reported. Therefore it was decided to explore the possibility of a direct N-arylation of ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3--carboxylate (*VIa*). Earlier we managed to N-arylate ethyl 1,4-dihydro-8-methoxy-4--oxoquinoline-3-carboxylate (*VIb*) by 2,4-dinitrochlorobenzene after its treatment with sodium hydride in N,N-dimethylformamide[9]. Similar arylation of 8-hydroxy derivatives *VIc*–*VIe* is supposed to be the first step in the synthesis of pyrido-[3,2,1-*kl*]phenoxazines *VIIa*–*VIIc* by an intramolecular aromatic denitrocyclization reaction[9].

Treatment of *VIa* with potassium carbonate and 2,4-dinitrochlorobenzene in N,N-dimethylformamide yielded *VIIIa*. When 1-chloro-4-nitrobenzene was used instead of 2,4-dinitrochlorobenzene, no reaction was observed even at the reflux temperature of both N,N-dimethylformamide and dimethyl sulfoxide. Nevertheless, more reactive 1-fluoro-4-nitrobenezene yielded *VIIIb* in good yields.

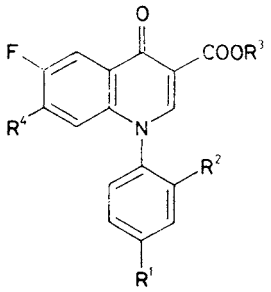
About 10 years ago Khan and Rocha described conditions where indoles can be N-arylated with either bromobenzene or a halonitrobenzene in the presence of potassium carbonate and cupric oxide in N,N-dimethylformamide[10]. Recently similar N-arylation of isatins has been reported[11]. Our attempts for applying this method to the reaction of *VIa* with either 4-bromofluorobenzene or 1-chloro-4-nitrobenzene failed. No reaction was observed even after 24 h.



VI a, $R^1 = F$; $R^2 = Cl$; $R^3 = H$
VI b, $R^1 = R^2 = H$; $R^3 = OCH_3$
VI c, $R^1 = R^2 = H$; $R^3 = OH$
VI d, $R^1 = H$; $R^2 = Cl$; $R^3 = OH$
VI e, $R^1 = R^2 = F$; $R^3 = OH$



VII a, $R^1 = R^2 = H$
VII b, $R^1 = H$; $R^2 = Cl$
VII c, $R^1 = R^2 = F$



VIII a, $R^1 = R^2 = NO_2$; $R^3 = C_2H_5$; $R^4 = Cl$
VIII b, $R^1 = NO_2$; $R^2 = H$; $R^3 = C_2H_5$; $R^4 = Cl$
VIII c, $R^1 = R^2 = NO_2$; $R^3 = H$; $R^4 = Cl$
VIII d, $R^1 = NO_2$; $R^2 = H$; $R^3 = H$; $R^4 = Cl$
VIII e, $R^1 = NO_2$; $R^2 = R^3 = H$; R^4 = piperazinyl
VIII f, $R^1 = NO_2$; $R^2 = R^3 = H$; R^4 = 4-methylpiperazinyl
VIII g, $R^1 = NH_2$; $R^2 = R^3 = H$; $R^4 = Cl$
VIII h, $R^1 = NH_2$; $R^2 = R^3 = H$; R^4 = piperazinyl
VIII i, $R^1 = NH_2$; $R^2 = R^3 = H$; R^4 = 4-methylpiperazinyl
VIII j, $R^1 = F$; $R^2 = R^3 = H$; $R^4 = Cl$

Esters *VIIIa* and *VIIIb* obtained by the N-arylation served as starting materials for synthesis of new 1-aryl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids for antibacterial screening. The esters were hydrolyzed to the appropriate acids *VIIIc* and *VIIId* by refluxing with a mixture of hydrochloric and acetic acids. Compound *VIIId* was also prepared by an alkaline saponification of *VIIIb*. Upon a treatment of *VIIId* with piperazine or N-methylpiperazine in pyridine a displacement reaction proceeded at C-7 to give *VIIIe* and *VIIIf* respectively. Similar treatment of *VIIIc*

gave complex mixtures. Compound *VIIId* was reduced by ferrous sulfate under alkaline conditions. The method starting from ester *VIIIb* which was refluxed with an aqueous sodium hydroxide solution and then directly reduced by ferrous sulfate proved to be more advantageous especially for the preparation of larger amounts of *VIIIg*. Similar reduction of *VIIIe* and *VIIIf* yielded *VIIIh* and *VIIIi* respectively. We failed to prepare *VIIIi* from *VIIIg* and N-methylpiperazine.

Of primary interest was the possibility to prepare 1-(4-fluorophenyl) derivative *VIIIj* from 1-(4-aminophenyl) derivative *VIIIg*. This methodology could represent an alternate and relatively simple four-step sequence for the synthesis of *VIIIj*, which is the key intermediate in the synthesis of antibacterial drugs under development A-56 620 (*IIa*) and difloxacin (*IIb*), from readily available[12] compound *VIa*. Since compound *VIIIg* is very poorly soluble both in most organic solvents and in acidic aqueous solutions, our attempts to prepare respective diazonium halides failed. Therefore Baltz–Schiemann method, which is a well known procedure for synthesis of fluoroaromates from aryl amines, could not be applied. Application of an improved procedure[13,14] using hydrogen fluoride–pyridine agent proved to be fruitful for the preparation of *VIIIj*. Authetic sample of *VIIIj* was prepared by the earlier described method[5] starting from ethyl 2,4-dichloro-5-fluorobenzoylacetete. The idenitty was confirmed by satisfactory elemental analyses, and IR and UV spectra.

UV and IR spectra of all compounds prepared were measured and were in accordance with the proposed structures. NMR spectra of the compounds could not be measured due to their low solubility.

Compounds *VIIIa–VIIIi* were tested for their antimicrobial activity in vitro at the Department of Microbiology of the Institute (Dr V. Holá, Head). Difloxacin base monohydrate was used for comparison. The drug was prepared by a described way[5] from *VIIIj* obtained by the method starting from ethyl 2,4-dichloro-5-fluorobenzoylacetate. The minimum inhibitory concentrations in mg/l are given in Table I.

Table I summarises the in vitro antibacterial activity of compounds *VIIIa–VIIIi* against Gram-positive bacteria (*Staphylococcus aureus* 1/45, *Streptococcus pyogenes* 4/49, *Streptococcus faecalis* D 16/66) and Gram-negative organisms (*Escherichia coli* 326/61, *Proteus vulgaris* 2/35, *Pseudomonas aeruginosa* 26/56). The organisms are from the State Collection of Strains, Prague. The data for difloxacin base monohydrate are included for comparison. It is evident that esters *VIIIa* and *VIIIb* lack activity in vitro. Acid *VIIIc* has an interesting activity against *S. aureus*, *E. coli* and *P. vulgaris*. On the other hand acids *VIIId* and *VIIIg* have no substantial activity. Introduction of a piperazine group to the position 7 of these compounds substantially increases their antibacterial activity. Compound *VIIIe* has excellent activity against Gram-negative organisms while its activity against Gram-positive bacteria is mild. Similar derivative *VIIIf*, having 4-methylpiperazinyl group, is substantially less active against both Gram-positive and Gram-negative organisms.

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TABLE I

In vitro antibacterial activity of compounds *VIIIa*–*VIIIi* (MIC given in mg/l)

Organisms	*VIIIa*	*VIIIb*	*VIIIc*	*VIIId*	*VIIIe*	*VIIIf*	*VIIIg*	*VIIIh*	*VIIIi*	*IIb*[a]
Staphyloccocus aureus	>128	>128	2	128	16	64	128	4	2	≤1
Streptococcus pyogenes	16	>128	64	>128	8	128	128	≤1	16	8
Streptococcus faecalis	>128	128	128	>128	64	>128	128	16	16	8
Escherichia coli	>128	>128	8	64	≤1	8	128	≤1	≤1	≤1
Proteus vulgaris	>128	>128	≤1	32	≤1	32	64	≤1	≤1	≤1
Pseudomonas aeruginosa	>128	>128	64	>128	≤1	128	>128	8	32	8

[a] Difloxacin base, monohydrate.

Reduction of the 4-nitrophenyl group to the 4-aminophenyl one leads to compounds *VIIIh* and *VIIIi*, the activity of which is comparable with those of difloxacin.

The effect of substitutions on the 1-phenyl ring of the 1,4-dihydro-6-fluoro-4-oxo--1-phenyl-7-piperazinylquinoline-3-carboxylic acids on the in vitro antibacterial activity has been studied. Structure–activity relationship studies[5] revealed that the most active compounds had either 4-fluorophenyl or 4-hydroxyphenyl substituents at the position 1 and either piperazinyl or 4-methylpiperazinyl substituents at the position 6. It is evident from our results that the 4-aminophenyl substituent at the position 1 is also compatible with the high level of antibacterial activity.

EXPERIMENTAL

The melting points were determined on a Mettler FP 5 apparatus, those exceeding 300°C were determined on a Kofler block, and were not corrected. IR spectra were taken on a Unicam SP-2 006 spectrometer in KBr pellets; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam PU 8800 spectrophotometer in ethanol, molar absorbtion coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. Mass spectra were measured on MCH 1320 and MAT 44 S spectrometers. The spectral data and elemental analyses were consistent with the assigned structures.

Ethyl 7-Chloro-1-(2,4-dinitrophenyl)-6-fluoro-1,4-dihydro-4--oxoquinoline-3-carboxylate (*VIIIa*)

A mixture of *VIa* (2·7 g, 10 mmol), potassium carbonate (1·4 g, 10 mmol) and N,N-dimethylformamide (25 ml) was stirred at 100°C for 1 h, a solution of 2,4-dinitrochlorobenzene (2·2 g, 11 mmol) in N,N-dimethylformamide (10 ml) was added and the mixture was stirred at 100°C for 15 h. Then the mixture was evaporated to dryness in reduced pressure, the residue was treated with water (25 ml) and acidified with acetic acid. The insoluble portion was separated by filtration and crystallized from N,N-dimethylformamide; yield 1·4 g (32%), m.p. 263–268 (decomp.). For $C_{18}H_{11}ClFN_3O_7$ (435·75) calculated: 49·61% C, 2·54% H, 8·14% Cl, 4·36% F, 9·64% N; found: 50·11% C, 2·95% H, 8·40% Cl, 4·10% F, 9·11% N. IR spectrum: 1 720 (COO); 1 610 (CO); 1 550 (NO_2). UV spectrum, λ_{max} (log ε): 207 (3·62), 320 (3·12), 332 (3·13), λ_{infl} 236 (3·57), 248 (3·53), 257 (3·45). Mass spectrum (*m/z*): 435 (M^+).

Ethyl 7-Chloro-6-fluoro-1,4-dihydro-1-(4-nitrophenyl)-4-oxoquinoline-3-carboxylate (*VIIIb*)

A mixture of *VIa* (13·5 g, 50 mmol), 1-fluoro-4-nitrobenzene (7·5 g, 53 mmol), potassium carbonate (17·5 g, 138 mmol), and N,N-dimethylformamide (125 ml) was stirred at 100°C for 15 h. Then the mixture was poured into water (500 ml), the separated solid was filtered off and crystallized from ethanol; yield 11·9 g (61%), m.p. 263–265°C. For $C_{18}H_{12}ClFN_2O_5$ (390·75) calculated: 55·33% C, 3·10% H, 9·07% Cl, 4·86% F, 7·17% N; found: 55·13% C, 3·12% H, 8·90% Cl, 5·06% F, 7·31% N. IR spectrum: 1 720 (COO); 1 610 (CO); 1 540 (NO_2). UV spectrum, λ_{max} (log ε): 212 (3·53), 251 (3·46), 260 (3·42), 323 (3·19), 335 (3·21), λ_{infl} 310 (3·01).

7-Chloro-1-(2,4-dinitrophenyl)-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (*VIIIc*)

A) A mixture of *VIIIa* (0·44 g, 1 mmol), acetic acid (4 ml) and concentrated hydrochloric acid (4 ml) was refluxed for 8 h, cooled down, the separated solid was filtered off and washed

with water. Crystallization from N,N-dimethylformamide yielded 0·23 g (56%) of *VIIIc*, m.p. 290–298°C (decomp.). For $C_{16}H_7ClFN_3O_7$ (407·70) calculated: 47·14% C, 1·73% H, 8·70% Cl, 4·66% F, 10·31% N; found: 47·34% C, 1·98% H, 8·72% Cl, 4·53% F, 10·15% N. IR spectrum: 3 340 (OH); 1 740 (COOH); 1 620 (CO); 1 550, 1 360 (NO_2). UV spectrum, λ_{max} (log ε): 215 (3·55), 250 (3·52), 337 (3·09), λ_{infl} 327 (3·05).

B) Sodium hydride (55% dispersion in mineral oil, 0·5 g, 11 mmol) was added to a stirred suspension of *VIa* (2·7 g, 10 mmol) in N,N-dimethylformamide (25 ml) and the mixture was stirred at room temperature for 2 h. Then a solution of 2,4-dinitrochlorobenzene (2·2 g, 11 mmol) in N,N-dimethylformamide (10 ml) was added and the mixture was stirred at 110°C under nitrogen for 15 h. The mixture was evaporated to dryness under reduced pressure, the residue was refluxed with a mixture of acetic acid (50 ml) and concentrated hydrochloric acid (50 ml) for 8 h. The cold reaction mixture was diluted with water (100 ml) and the insoluble portion was filtered off, crystallized from N,N-dimethylformamide; yield 2·1 g (51%), m.p. 290–297°C (decomp.).

7-Chloro-6-fluoro-1,4-dihydro-1-(4-nitrophenyl)-4-oxoquinoline-3-carboxylic Acid (*VIIId*)

A) A suspension of *VIIIb* (0·5 g, 1·3 mmol) in a solution of sodium hydroxide (0·3 g) in water (4 ml) was refluxed for 4 h, cooled down and acidified with acetic acid. The separated solid was filtered off, washed with water and crystallized from N,N-dimethylformamide; yield 0·2 g (43%), m.p. 305–309°C (decomp.). For $C_{16}H_8ClFN_2O_5$ (362·70) calculated: 52·98% C, 2·22% H, 9·77% Cl, 5·24% F, 7·72% N; found: 52·99% C, 2·30% H, 10·06% Cl, 5·19% F, 7·62% N. IR spectrum: 3 300 (OH); 1 720 (COOH); 1 610 (CO); 1 530 (NO_2). UV spectrum, λ_{max} (log ε): 212 (3·46), 251 (3·51), 259 (3·50), 322 (3·13), 334 (3·15).

B) A mixture of *VIIIb* (9·7 g, 25 mmol), acetic acid (75 ml), and concentrated hydrochloric acid (75 ml) was refluxed for 4 h, the mixture was cooled down and the solid was filtered off and washed with water. Crystallization from pyridine afforded 7·1 g (78%), m.p. 306–309°C (decomp.).

6-Fluoro-1,4-dihydro-1-(4-nitrophenyl)-4-oxo-7-piperazinyl-quinoline-3-carboxylic Acid (*VIIIe*)

A mixture of *VIIId* (5·4 g, 14 mmol), anhydrous piperazine (2·15 g, 25 mmol), and pyridine (100 ml) was stirred at 100°C under nitrogen for 67 h, the mixture was evaporated to dryness under reduced pressure and boiled with ethanol (50 ml). The solid was filtered off, dissolved in 5% solution of sodium hydrogen carbonate (75 ml), the solution was boiled with charcoal and after filtering the filtrate was acidified with acetic acid. The precipitated solid was filtered off, washed with water and then with ethanol; yield 4·3 g (74%), m.p. 292–295°C (decomp.). For $C_{20}H_{17}FN_4O_5$ (412·38) calculated: 58·25% C, 4·16% H, 4·61% F, 13·59% N; found: 57·90% C, 4·14% H, 4·07% F, 13·50% N. IR spectrum: 3 320 (OH, NH); 1 725 (COOH); 1 625 (CO); 1 525, 1 350 (NO_2). UV spectrum, λ_{max} (log ε): 205 (3·45), 231 (3·23), 280 (3·52), 330 (3·20).

6-Fluoro-1,4-dihydro-7-(4-methylpiperazinyl)-1-(4-nitrophenyl)--4-oxoquinoline-3-carboxylic Acid (*VIIIf*)

A mixture of *VIIId* (3·5 g, 10 mmol), N-methylpiperazine (2·5 g, 25 mmol) and pyridine (50 ml) was stirred under nitrogen at 100°C for 30 h, the mixture was evaporated to dryness and boiled with ethanol (100 ml). The insoluble portion was filtered off, washed with ethanol, water, and ethanol; yield 2·5 g (59%), not melted up to 340°C. For $C_{21}H_{19}FN_4O_5$ (426·40) calculated: 59·15% C

4·49% H, 4·46% F, 13·14% N; found: 59·04% C, 4·49% H, 4·56% F, 12·86% N. IR spectrum: 1 720 (COOH); 1 625 (CO); 1 530 (NO_2). UV spectrum, λ_{max} (log ε): 204 (3·30), 279 (3·38), 329 (3·03).

1-(4-Aminophenyl)-7-chloro-6-fluoro-4-oxoquinoline-3-carboxylic Acid (*VIIIg*)

A) To a stirred, boiling suspension of *VIIId* (7 g, 20 mmol) in a solution of sodium hydroxide (40 g) in water (1·2 l), a solution of ferrous sulfate heptahydrate (75 g, 270 mmol) in water (500 ml) was added and the mixture was refluxed for 30 min. The hot mixture was filtered, the solid was washed with hot water (200 ml) and the filtrate was cooled down and acidified with acetic acid. The precipitate was filtered off and washed with cold water. Crystallization from ethanol yielded 5·75 g (86%) of yellow crystals, m.p. 296–298°C. For $C_{16}H_{10}ClFN_2O_3$ (332·72) calculated: 57·76% C, 3·03% H, 10·66% Cl, 5·71% F, 8·42% N; found: 57·90% C, 3·18% H, 10·59% Cl, 5·80% F, 8·22% N. IR spectrum: 3 340, 3 250 (NH_2); 1 720 (COOH); 1 610 (CO). UV spectrum, λ_{max} (log ε): 205 (3·52), 214 (3·52), 238 (3·55), 319 (3·08), λ_{infl} 330 (3·04).

B) A suspension of *VIIIb* (7 g, 18 mmol) in a solution of sodium hydroxide (40 g) in water (1 l) was stirred under reflux for 4 h, then the mixture was treated according to the procedure *A*). Yield 4·7 g of *VIIIg* (79%), m.p. 296–298°C.

1-(4-Aminophenyl)-6-fluoro-4-oxo-7-piperazinylquinoline-3-carboxylic Acid (*VIIIh*)

To a stirred, boiling solution of *VIIIe* (0·82 g, 2 mmol) in a solution of sodium hydroxide (2 g) in water (50 ml), a solution of ferrous sulfate heptahydrate (5·5 g, 20 mmol) in water (20 ml) was added and the mixture was refluxed for 30 min. The hot mixture was filtered, the cold filtrate was acidified with acetic acid and cooled down. The precipitate was filtered off and crystallized twice from 50% aqueous methanol; yield 0·42 g (55%), m.p. 256–259°C. For $C_{20}H_{19}FN_4O_3$ (382·39) calculated: 62·82% C, 5·01% H, 4·97% F, 14·65% N; found: 62·39% C, 4·77% H, 4·71% F, 14·32% N. IR spectrum: 3 330, 3 280, 3 140 (NH, NH_2, OH); 1 720 (COOH); 1 630 (CO); 1 610 (Ar–NH_2). UV spectrum, λ_{max} (log ε): 205 (3·49), 281 (3·50), λ_{infl} 332 (3·09).

1-(4-Aminophenyl)-6-fluoro-7-(4-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acid (*VIIIi*)

To a stirred, boiling solution of *VIIIf* (0·43 g, 1 mmol) in a solution of sodium hydroxide (1 g) in water (25 ml), a solution of ferrous sulfate heptahydrate (2·8 g, 10 mmol) in water (10 ml) was added and the mixture was refluxed for 30 min. The hot mixture was filtered, the cold filtrate was acidified with acetic acid and cooled down. The precipitate was filtered off, dissolved in 10% aqueous solution of ammonia, the insoluble portion was filtered off and the filtrate was acidified with acetic acid. The precipitated solid was filtered off, washed with water and dried; yield 0·27 g (68%), m.p. 248–252°C (decomp.). For $C_{21}H_{21}FN_4O_3$ (396·42) calculated: 63·63% C, 5·34% H, 4·79% F, 14·13% N; found: 63·73% C, 5·28% H, 4·42% F, 13·76% N. IR spectrum: 3 340, 3 260 (NH_2); 2 800 (NCH_3); 1 720 (COOH); 1 620 (CO). UV spectrum, λ_{max} (log ε): 204 (3·53), 279 (3·55), λ_{infl} 315 (3·15), 330 (3·14).

7-Chloro-6-fluoro-1-(4-fluorophenyl)-4-oxoquinoline-3-carboxylic Acid (*VIIIj*)

To a solution of hydrogen fluoride in pyridine (25 g, 70% HF) in a polyethylene bottle was added *VIIIg* (1·66 g, 5 mmol) at 0°C and the mixture was stirred at room temperature for 30 min (until *VIIIg* has completely dissolved). After cooling down to 0°C, sodium nitrite was added

(0·42 g, 6 mmol). The solution was maintained at this temperature for 30 min and then at 30°C for additional 30 min. The reaction mixture was then stirred and the temperature was gradually raised during 2 h to 70°C (at about 50°C an evolution of nitrogen was observed) and the stirring at this temperature continued for an additional 1 h. Then the mixture was poured onto ice (50 g) and the mixture was left overnight at room temperature. The precipitate was filtered off and washed with water; yield 0·9 g (54%), m.p. 260–264°C. For $C_{16}H_8ClF_2NO_3$ (335·69) calculated: 57·24% C, 2·40% H, 10·56% Cl, 11·32% F, 4·17% N; found: 56·96% C, 2·46% H, 10·11% Cl, 11·70% F, 4·04% N. IR spectrum: 3 300 (OH); 1 725 (COOH); 1 610 (CO). UV spectrum, λ_{max} (log ε): 212 (3·43), 246 (3·20), 321 (3·06), 334 (3·04).

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