SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 3-HYDROXYQUINOLONES

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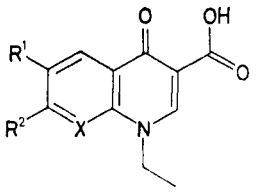
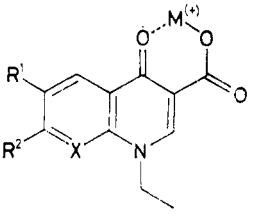
A reductive decarboxylation of 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (*Id*) with sodium borohydride provided the respective 1,2,3,4-tetrahydro derivative *Va*, which was treated with selenium dioxide to give product of dehydrogenation *VIa*. 3-Acetyl-1--ethyl-1,4-dihydroquinolin-4-ones *VIb* and *VIc* were oxidized with 3-chloroperoxybezoic acid to the respective 3-hydroxyderivatives *IIIa* and *IIIb*. Compound *IIIb* was benzylated on a hydroxy group at position 3 to corresponding 3-benzyloxy derivative *VIf* which after prolonged heating with N-methylpiperazine in a sealed tube provided directly 3-hydroxy-7-(4-methyl-1-piperazinyl) derivative *IIIc*.

Structure–activity relationships in antibacterial quinolones of general formula *I* – (e.g. oxolinic acid *Ia*, pefloxacin *Ib*, nalidixic acid *Ic*) suggested that presence of a carboxy group at position 3 and a carbonyl group at position 4 is necessary for potent antibacterial activity[1,2]. This fact is explained by an important, but still unknown, biointeraction of this beta-keto structure. Ability of this structure to form chelates *II* with divalent transition metal ions has been known; it was observed for nalidixic acid[3] (*Ic*) and later for some other quinolones. We have found that all attempts of structural modifications of quinolones at positions 3 and 4 led to compound which could not form such chelates or could form chelates with substantially lower stability constants[4].

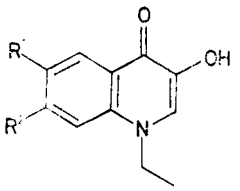




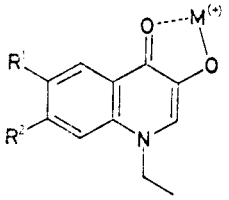
Ia oxolinic acid ; X = CH ; $R^1 + R^2$ = O—CH_2—O
Ib, pefloxacin ; X = CH ; R^1 = F ; R^2 = 4-methyl-1-piperazinyl
Ic, nalidixic acid ; X = N ; R^1 = H ; R^2 = CH_3
Id, X = CH ; R^1 = F ; R^2 = Cl

II

Therefore we decided to prepare 3-hydroxyquinolones of a general formula *III* which could form with divalent transition metal chelates *IV*. It is well known that similar chelates having a five membered ring have generally comparable stability constants as respective six-membered chelates[4,5]. Our present work describes synthesis and antibacterial activity of 3-hydroxyquinolones *IIIa–IIIc*. Compounds *IIIa* and *IIIc* were of a special interest as analogs of clinically useful drugs oxolinic acid (*Ia*) and pefloxacin (*Ib*).

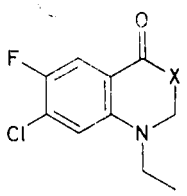


IIIa, $R^1 + R^2 = O-CH_2-O$
IIIb, $R^1 = F$; $R^2 = Cl$
IIIc, $R^1 = F$; $R^2 = 4$-methyl-piperazinyl

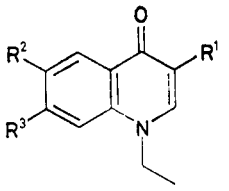


IV

A decarboxylative reduction of *Id* with sodium borohydride yielded corresponding 1,2,3,4-tetrahydro derivative *Va*. Since similar cyclic ketones could be oxidized with selenium oxide to corresponding alpha diketones[6,7], we tried similar oxidation of *Va* which could provide *Vb*. This structure represents an oxo form of the required structure *IIIb*. But product of dehydrogenation *VIa* was the only product of this oxidation. Similar oxidation of *Va* with isoamylnitrite provided a complex mixture but according to the TLC (Silufol UV 254, toluene–ethanol 9 : 1) the main component was again *VIa*.



Va, X = CH_2
Vb, X = C=O



VIa, $R^1 = H$; $R^2 = F$; $R^3 = Cl$
VIb, $R^1 = COCH_3$; $R^2 + R^3 = O-CH_2-O$
VIc, $R^1 = COCH_3$; $R^2 = F$; $R^3 = Cl$
VId, $R^1 = OCOCH_3$; $R^2 + R^3 = O-CH_2-O$
VIe, $R^1 = OCOCH_3$; $R^2 = F$; $R^3 = Cl$
VIf, $R^1 = OCH_2Ph$; $R^2 = F$; $R^3 = Cl$
VIg, $R^1 = OCH_2Ph$; $R^2 = F$; $R^3 = 4$-methyl-1-piperazinyl

3-Acetyl derivative *VIb* had been previously used as an intermediate in a synthesis of oxolinic acid[8]. In the same way starting 3-chloro-4-fluoroaniline and ethyl 2-ethoxymethyleneacetoacetate were condensed and then cyclized to 3-acetyl-7-chloro-6-fluoro-1,4-dihydroquinolin-4-one which was N-ethylated with iodoethane providing *VIc*. Baeyer–Villiger oxidation of *VIb* and *VIc* with 3-chloroperbenzoic acid provided exclusively intermediates *VId* and *VIe* respectively, which were without isolation transferred into the required compounds *IIIa* and *IIIb*. Compound *IIIb* did not react with N-methylpiperazine at 110°C in various solvents (excess of N-methylpiperazine, pyridine, N,N-dimethylformamide, dimethyl sulfoxide). Prolonged heating of *IIIb* with an excess of N-methylpiperazine in a sealed tube at 150°C provided a complex mixture in which *IIIb* still prevailed. In order to circumvent possible reactions of the 3-hydroxy group we prepared *VIf* by a benzylation of *IIIb* with benzyl chloride. This compound again did not react with N-methylpiperazine under usual conditions. Its prolonged heating in a sealed tube (about 180°C, 50 h) did not provide the supposed derivative *VIg* but led directly to *IIIc*. It is evident that nucleophilic displacement reaction of a chlorine at position 7 was accompanied by a O-debenzylation which is unusual under the conditions used.

All the prepared compounds were tested for their antimicrobial activity in vitro 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 at the Department of Microbiology of the Institute (Dr V. Holá, Head). The organisms are from the State Collection of Strains, Prague. The minimum inhibitory concentrations in mg/l are given unless they exceed 128 mg/l: *S. aureus*, *IIIa* 128, *IIIb* 64, *IIIc* 64; *S. pyogenes*, *IIIa* 64, *IIIb* 16; *S. faecalis*, *IIIb* 64; *E. coli*, *IIIa* 128, *IIIb* 64; *P. vulgaris*, *IIIa* 64.

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, unless otherwise stated; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam PU 8 800 spectrophotometer in ethanol, molar absorption coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. Mass spectra were measured on MCH 1 320 and MAT 44 S spectrometers. ^1H NMR spectra (100 MHz) and ^{13}C NMR spectra (25·14 MHz) were measured on an apparatus BS-487 (Tesla Brno) 100 MHz in hexadeuterated dimethylsulfoxide (^{13}C NMR at 100°C). The standard for ^1H NMR spectra was 3-trimethylsilylpropanoic acid, unless otherwise stated, the ^{13}C NMR spectra were calculated on tetramethylsilane. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz.

7-Chloro-1-ethyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-one (*Va*)

A freshly prepared solution of sodium borohydride (7·5 g, 0·2 mol) in methanol (100 ml) was

added during 10 min to a stirred suspension of *Id* (13·5 g, 0·05 mol) in methanol (500 ml) and the formed solution was stirred at room temperature for 1 h and then refluxed for further 1 h. The solution was evaporated to dryness, the residue was dissolved in trichloromethane (250 ml) and the solution was washed with water, dried with magnesium sulfate and evaporated. The residue (9·5 g) was crystallized from hexane to yield 8·3 g (73%) of yellow crystals, m.p. 83–84°C. For $C_{11}H_{11}ClFNO$ (227·7). calculated: 58·03% C, 4·87% H, 15·57% Cl, 8·34% F, 6·15% N; found: 57·77% C, 4·86% H, 15·41% Cl, 8·36% F, 6·10% N. ^{1}H NMR spectrum ($CDCl_3$): 1·20 t, 3 H (CH_3, $J = 7$); 2·69 t, 2 H (H-3, $J = 6$); 3·42 g, 2 H (CH_2, $J = 7$); 3·50 t, 2 H (H-2, $J = 6$); 6·78 d, 1 H (H-8, $J_{H,F} = 6$); 7·66 d, 1 H (H-5, $J_{H,F} = 9·5$). Mass spectrum: $m/z = 227$ (M^+).

7-Chloro-1-ethyl-6-fluoro-1,4-dihydroquinolin-4-one (*VIa*)

Selenium dioxide (0·3 g, 2·75 mmol) was dissolved in a mixture of ethanol (5 ml) and water (0·1 ml) at 50°C and *Va* (0·56 g, 2·5 mmol) was added to this solution. The mixture was refluxed for 6 h and then the hot mixture was filtered, the insoluble selenium containing portion was washed with boiling ethanol (5 ml) and the filtrate was cooled down. The formed crystals were filtered off and recrystallized from ethanol; yield 0·30 g (53%), m.p. 211–212°C. For $C_{11}H_9ClFNO$ (225·65) calculated: 58·55% C, 4·02% H, 15·71% Cl, 8·42% F, 6·21% N; found: 58·36% C, 3·92% H, 15·42% Cl, 8·47% F, 6·10% N. ^{1}H NMR spectrum ($CDCl_3$): 1·50 t, 3 H (CH_3, $J = 7$); 4·15 q, 2 H (CH_2, $J = 7$); 6·24 d, 1 H (H-3, $J = 8$); 7·52 d, 1 H (H-8, $J_{H,F} = 5$); 7·54 d, 1 H (H-2, $J = 8$); 8·18, 1 H (H-5, $J_{H,F} = 9·5$). Mass spectrum: $m/z = 225$.

3-Acetyl-7-chloro-6-fluoro-1,4-dihydroquinolin-4-one

A mixture of 3-chloro-4-fluoroaniline (14·6 g, 100 mmol) and ethyl ethoxymethyleneacetoacetate (19·5 g, 105 mmol) was stirred at 130°C until some liquid distilled off and then the residue was added to diphenyl ether (200 g) at 200°C. The mixture was refluxed for 30 min and then cooled down. Formed precipitate portion was filtered off, washed with hexane and dried yielding 14·6 g (61%) of light brown powder not melting up to 300°C which was used for forther step without any purification. An analytical sample was crystallized from N,N-dimethylformamide. For $C_{11}H_7ClFNO_2$ (239·6) caulculated: 55·13% C, 2·94% H, 14·79% Cl, 7·93% F, 5·85% N; found: 54·84% C, 3·09% H, 14·66% Cl, 8·14% F, 5·93% N.

3-Acetyl-7-chloro-1-ethyl-6-fluoro-1,4-dihydroquinolin-4-one (*VIc*)

A mixture of 3-acetyl-7-chloro-6-fluoro-1,4-dihydroquinolin-4-one (12 g, 50 mmol), N,N-dimethylformamide (100 ml), and potassium carbonate (17·5 g, 127 mmol) was stirred at 90°C for 30 min and then iodoethane (15·6 g, 0·1 mol) was added and the mixture was stirred for 8 h at this temperature. The same amount of ethyl iodide was added and the mixture was stirred at the same temperature for additional 8 h. Then the mixture was evaporated to dryness under reduced pressure, the residue was triturated with water (200 ml) and the mixture was extracted with dichloromethane, the extract was washed with water and dried with magnesium sulfate. The filtrate was evaporated and crystallized from ethanol; yield 10·5 g (78%), m.p. 215–216°C. For $C_{13}H_{11}ClFNO_2$ (267·7) calculated: 58·33% C, 4·14% H, 13·24% Cl, 7·10% F, 5·23% N; found: 58·34% C, 4·13% H, 13·21% Cl, 7·24% F, 5·15% N. IR spectrum: 1 660, 1 600 (C=O), 1 635, 1 550, 1 490 (heteroaromat. system). UV spectrum, λ_{max} (log ε): 325 (3·17), 267 (3·35), 258 (3·24), 217 (3·40); $\lambda_{infl} = 228$ (3·31).

1-Ethyl-1,4-dihydro-3-hydroxy-6,7-methylenedioxyquinolin-4-one (*IIIa*)

A mixture of 3-acetyl derivative *VIb* (0·52 g, 2 mmol), 3-chloroperoxybenzoic acid (61%, 0·87 g, 3 mmol) and trichloromethane (20 ml) was stirred at room temperature for 2 days. Insoluble portion was filtered off, washed with water and dried. Filtrate was washed with saturated aqueous solution of sodium hydrogen carbonate, then with water and the trichloromethane layer was dried with magnesium sulfate and evaporated. The residue was combined with the insoluble portion obtained directly from reaction mixture and the collected material was refluxed with ethanol (50 ml) for 4 h. The mixture was evaporated and crystallized from ethanol: yield 0·2 g (43%), m.p. 224–229°C. For $C_{12}H_{11}NO_4$ (233·2) calculated: 61·80% C, 4·75% H, 6·01% N; found: 61·67% C, 4·08% H, 5·61% N. IR spectrum: 3 100 (OH), 1 670 (C=O), 1 130, 1 050 (cycl. ether), 1 630, 1 590, 1 550, 1 495 (heteroaromat. system), UV spectrum, λ_{max} (log ε): 356 (2·94), 342 (2·93), 314 '(2·76), 258 (3·45), 229 (3·11).

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-3-hydroxyquinolin-4-one (*IIIb*)

A solution of 3-acetyl derivative *VIc* (1·35 g, 5 mmol), 3-chloroperoxybenzoic acid (61%, 2·1 g, 7 mmol) in trichloromethane (20 ml) was stirred at room temperature for 5 days. The solution was washed with saturated aqueous solution of sodium hydrogen carbonate and then with water. The filtrate was evaporated, the residue was refluxed with ethanol (100 ml) for 14 h. The mixture was evaporated and crystallized from ethanol; yield 0·6 g (55%), m.p. 209–211°C. For $C_{11}H_9ClFNO_2$ (241·6) calculated: 54·67% C, 3·75% H, 14·67% Cl, 7·86% F, 5·80% N; found: 54·33% C, 3·91% H, 14·36% Cl, 8·01% F, 5·66% N. IR spectrum: 3 150 (OH), 1 630 (C=O), 1 580, 1 535 (heteroaromat. system). UV spectrum, λ_{max} (log ε): 366 (2·96), 293 (2·26), 260 (3·57), 216 (3·30). ^{1}H NMR spectrum: 1·34 t, 3 H (CH_3, $J = 7$); 4·32 q, 2 H (CH_2, $J = 7$); 7·94 s, 1 H (H-2); 8·02 d, 1 H (H-5, $J_{H,F} = 10$); 8·10 d, 1 H (H-8, $J_{H,F} = 6$).

3-Benzyloxy-7-chloro-1-ethyl-6-fluoro-1,4-dihydroquinolin-4-one (*VIf*)

Benzyl chloride (6·3 g, 50 mmol) was added to a stirred mixture of *IIIb* (2·4 g, 10 mmol) and potassium carbonate (4·6 g, 33 mmol) in N,N-dimethylformamide (50 ml) and the mixture was stirred at 100°C for 2 h. The mixture was evaporated in vacuo to dryness, the residue was triturated with water (20 ml) and extracted with trichloromethane and the extract was washed with water and dried with magnesium sulfate. The filtrate was evaporated to dryness and the residue was crystallized from ethanol; yield 2·3 g (70%), m.p. 138–140°C. For $C_{18}H_{15}ClFNO_2$ (331·8) calculated: 65·16% C, 4·56% H, 10·69% Cl, 5·73% F, 4·22% N; found: 65·10% C, 4·58% H, 10·67% Cl, 5·96% F, 4·08% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 4·30 q, 2 H (N—CH_2, $J = 7$); 5·10 s, 2 H (O—CH_2); 7·40 m, 5 H (H of phenyl); 8·04 d, 1 H (H-5, $J_{H,F} = 9$); 8·10 s, 1 H (H-2); 8·12 d, 1 H (H-8, $J_{H,F} = 6$).

1-Ethyl-6-fluoro-1,4-dihydro-3-hydroxy-7-(4-methyl-1-piperazinyl)quinolin-4-one (*IIIc*)

A mixture of *VIf* (0·5 g, 2 mmol) and N-methylpiperazine (20 ml) was heated to 170–190°C in a sealed tube for 50 h, then it was evaporated to dryness in reduced pressure, triturated with water (20 ml) and insoluble portion was filtered off, washed with cold water and crystallized from ethanol, m.p. 235–245°C (decomp.). For $C_{16}H_{20}FN_3O_2$ (305·3) calculated: 62·94% C, 6·60% H, 6·22% F, 13·76% N; found: 62·70% C, 6·71% H, 6·20% F, 14·61% N. IR spectrum: 3 210 (OH), 1 635, 1 620 (C=O), 1 578, 1 565, 1 530, 1 447 (aromat. system), 1 466, 1 458, 1 405 (CH_2, CH_3), 885, 860 (1 H). UV spectrum, λ_{max} (log ε): 332 (3·04), 271 (3·52), 236 (3·25); $\lambda_{infl} = 364$, 344.

^{1}H NMR spectrum: 1·34 t, 3 H (CH_3 of ethyl, $J = 7$); 2·27 s, 3 H (CH_3); 2·53 t, 4 H (H-3′, H-5′ of piperazine); 3·22 t, 4 H (H-2′, H-6′ of piperazine); 4·28 q, 2 H (CH_2 of ethyl, $J = 7$); 6·94 d, 1 H (H-7, $J_{H,F} = 7$); 7·78 d, 1 H (H-5, $J_{H,F} = 12$); 7·80 s, 1 H (H-2). Mass spectrum: $m/z = 305$ (M^+).

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