SOME REACTIONS OF N-PROPADIENYL-4-QUINOLONES

Stanislav RÁDL and Lenka KOVÁŘOVÁ

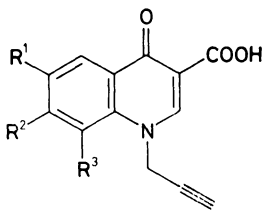
Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

Received November 21, 1990
Accepted January 19, 1991

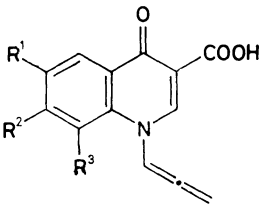
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

N-Alkylation of ethyl 6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (*Vg*) with 3-bromopropyne followed by acidic hydrolysis provided N-propynyl derivative *Ic* which in alkaline media yielded N-propadienyl derivative *IId*. Propadienyl derivatives *IIa* and *IIb* treated with primary or secondary amines provided intermediates *IIIa*—*IIIc* which were hydrolyzed to N-acetonyl derivatives *IVa* and *IVb*, respectively. N-Benzylation of ethyl 7-chloro-6-fluoro--1,4-dihydro-4-oxoquinoline-3-carboxylate (*Va*) followed by hydrolysis yielded 1-benzyl-7--chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (*Vd*) which upon a treatment with N-methylpiperazine provided *Ve*. Compound *Ve* was hydrogenated on Pd to 6-fluoro-1,4--dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (*Vf*).

Recently[1] we have described preparation of N-(2-propynyl) derivatives *Ia* and *Ib*, and their base-catalyzed rearrangement into N-propadienyl quinolones *IIa* and *IIb*, respectively. These N-propadienyl derivatives have been found more active than the corresponding N-(2-propynyl) derivatives *I*. Structure–activity relationships in the field[2] revealed that the most active quinolones have a fluorine atom at position 6 and a cyclic amine (mainly piperazine or N-methylpiperazine) at position 7. Therefore we tried to prepare N-propadienyl compound *IIc*. This compound cannot be

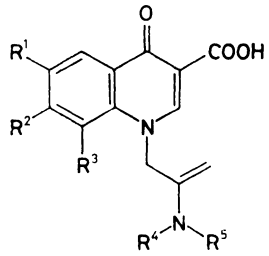


I a, $R^1 + R^2 = OCH_2O$; $R^3 = H$
I b, $R^1 = F$; $R^2 = Cl$; $R^3 = H$
I c, $R^1 = R^2 = R^3 = F$

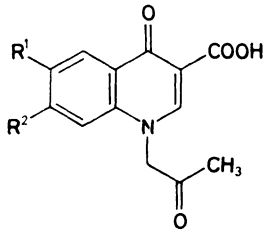


II a, $R^1 + R^2 = OCH_2O$; $R^3 = H$
II b, $R^1 = F$; $R^2 = Cl$; $R^3 = H$
II c, $R^1 = F$; $R^2 = 4$-methyl-1-piperazinyl ; $R^3 = H$
II d, $R^1 = R^2 = R^3 = F$

prepared by a direct nucleophilic reaction of *IIb* with N-methylpiperazine due to high reactivity of the propadienyl group. Addition of primary and secondary amines to various N-propadienyl pyridinium salts is well known[3,4]. We have examined the additions to N-propadienyl quinolones *IIa* and *IIb*. These compounds reacted with both primary and secondary amines to yield corresponding enamines *IIIa*, *IIIb* and *IIIc* which were converted into stable N-acetonyl derivatives *IVa*, and *IVb*, respectively. This way of preparation of N-acetonyl heterocycles provides an alternate access to this type of compounds.



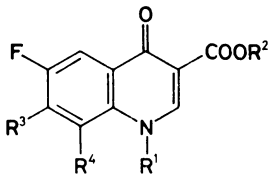
IIIa, $R^1 + R^2 = OCH_2O$; $R^3 = H$; $R^4 = CH_3$; $R^5 = H$
IIIb, $R^1 = F$; $R^2 = Cl$; $R^3 = H$; $R^4 = CH_3$; $R^5 = H$
IIIc, $R^1 = F$; $R^2 = Cl$; $R^3 = H$; $R^4 + R^5 = CH_2CH_2N(CH_3)CH_2CH_2$
IIId, $R^1 = R^2 = R^3 = F$; $R^4 + R^5 = CH_2CH_2N(CH_3)CH_2CH_2$
IIIe, $R^1 = F$; $R^2 =$ 4-methyl-1-piperazinyl ; $R^3 = F$; $R^4 + R^5 = CH_2CH_2N(CH_3)CH_2CH_2$



IVa, $R^1 + R^2 = OCH_2O$
IVb, $R^1 = F$; $R^2 = Cl$

Since the N-propadienyl group reacts very easily with cyclic amines it is not possible to receive N-propadienyl-7-cyclic amino derivatives by a nucleophilic displacement reaction of N-propadienyl derivative *IIb*. Reaction of N-(2-propynyl)-derivative *Ib* with piperazine and/or N-methylpiperazine in pyridine yielded only tar products formation. Therefore we decided for an indirect way of the synthesis of *IIc* via N-unsubstituted acid *Vf*. However all attempts to prepare *Vf* by a direct reaction of *Vb* and N-methylpiperazine failed. Thus a benzylation of *Va* provided

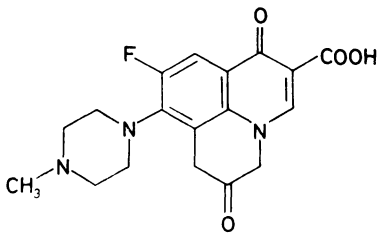
N-benzyl derivative *Vc* which after saponification gave *Vd*. Reaction of *Vd* with N-methylpiperazine in pyridine then yielded *Ve* which after catalytic hydrogenolysis on palladium provided N-unsubstituted derivative *Vf*. Attempts to alkylate this compound with 3-bromopropyne yielded a complex mixture. Thus our attempts to prepare the target compound *IIc* were unsuccessful.



Va, R^1= H ; R^2= C_2H_5 ; R^3= Cl ; R^4= H
Vb, R^1= R^2= H ; R^3= Cl ; R^4= H
Vc, R^1= benzyl ; R^2= C_2H_5 ; R^3= Cl ; R^4= H
Vd, R^1= benzyl ; R^2= H ; R^3= Cl ; R^4= H
Ve, R^1= benzyl ; R^2= H ; R^3= 4-methyl-1-piperazinyl ; R^4= H
Vf, R^1= R^2= H ; R^3= 4-methyl-1-piperazinyl ; R^4= H
Vg, R^1= H ; R^2= C_2H_5 ; R^3= R^4= F
Vh, R^1= $CH_2C{\equiv}CH$; R^2= C_2H_5 ; R^3= R^4= F

High reactivity of enamines is well known. The most versatile reactions of this class of compounds are alkylation and acylation reactions. However, similar arylation reactions have been also described[5]. Since the fluorine substituent at position 8 of quinolones is known to be able of nucleophilic displacement reactions[6-9] we decided to try to prepare *VI* by this way from *IId* via possible intermediates *IIId* or *IIIe*. Compound *VI* could be of interest since compounds with similar 1,8 bridges on the quinolone skeleton are known or claimed as good antibacterials[2]. For this reason we prepared N-propadienyl derivative *IId* by the following reaction steps. Alkylation of *Vg* with bromopropyne provided *Vh* which was hydrolyzed under acidic conditions to *Ic*. An alkaline isomerization then provided N-propadienyl derivative *IId*. We failed to prepare compound *VI*, attempts of its preparation by a reaction of *IId* with N-methylpiperazine and following acidic hydrolysis yielded a complex mixture.

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 Ic* 128, *IId* 64, *Vd* 32, *Ve* 4;



VI

S. pyogenes IId 64, *IVb* 128, *Vd* 64, *Ve* 64; *S. faecalis Vd* 64, *Ve* 64; *E. coli Ic* 128, *IId* 128, *IVb* 128, *Ve* 4; *P. vulgaris Ic* 16, *IId* 4, *IVa* 32, *IVb* 32, *Vd* 8, *Ve* ≦ 1; *P. aeruginosa Ve* 8.

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-2006 spectrometer in KBr pellets, unless otherwise stated; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam PU 8800 spectrophotometer in ethanol, molar absorption 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. ^{1}H 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 ^{1}H NMR spectra was 3-trimethyl-silylpropanoic acid, unless otherwise stated, the ^{13}C NMR spectra were referenced to tetramethylsilane. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz.

1,4-Dihydro-6,7-methylenedioxy-4-oxo-1-(2-oxopropyl)quinoline-3-carboxylic Acid (*IVa*)

A mixture of *IIa* (0·27 g, 1 mmol) and 20% ethanolic solution of methylamine (20 ml) was refluxed for 8 h and then evaporated to dryness. The residue was triturated with 5% hydrochloric acid, the solid was filtered off, washed with water and crystallized from N,N-dimethylformamide; yield 0·22 g (76%), not melting up to 360°C. For $C_{14}H_{11}NO_6$ (289·2) calculated: 58·14% C, 3·83% H, 4·84% N; found: 57·96% C, 3·95% H, 4·80% N. ^{1}H NMR spectrum (150°C): 2·30 s, 3 H (CH_3); 5·50 s, 2 H (N—CH_2); 6·22 s, 2 H (O—CH_2—O); 7·26 s, 1 H (H-8); 7·65 s, 1 H (H-5); 8·70 s, 1 H (H-2).

7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2-oxopropyl)quinoline-3-carboxylic Acid (*IVb*)

A. This compound was prepared from *IIb*, adhering to the procedure described for the preparation of *IVa*; yield 67%, m.p. 254–256°C (ethanol). For $C_{13}H_9ClFNO_4$ (297·7) calculated: 52·46% C, 3·05% H, 11·91% Cl, 6·38% F, 4·71% N; found: 52·43% C, 3·16% H, 11·63% Cl, 6·60% F, 4·76% N. IR spectrum: 1 715 (COOH); 1 700, 1 615 (C=O); 1 565, 1 540, 1 500 (aromat. system). UV spectrum, λ_{max} (log ε): 336 (3·01), 324 (2·97), 260 (3·46), 252 (3·37). Mass spectrum (m/z): 297 (M^+). ^{1}H NMR spectrum: 2·32 s, 3 H (CH_3); 5·62 s, 2 H (N—CH_2); 8·10 d, 1 H (H-8, $J_{H,F} = 6$); 8·17 d, 1 H (H-5, $J_{H,F} = 9$); 8·87 s, 1 H (H-2).

B. A mixture of *IIb* (0·28 g, 1 mmol), N-methylpiperazine (0·5 ml), and acetonitrile (10 ml) was refluxed for 2 h, then evaporated to dryness, the residue was dissolved in ethanol (2 ml) and acidified with a drop of concentrated hydrochloric acid. The solid was filtered off and crystallized from ethanol; yield 0·18 g (60%), m.p. 253—256°C.

Ethyl 1-Benzyl-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (*Vc*)

A mixture of *Va* (13·5 g, 50 mmol), potassium carbonate (10·5 g, 75 mmol), benzylchloride (7·6 g, 60 mmol), and dimethylsulfoxide (100 ml) was stirred at 100°C for 12 h. The reaction mixture was poured into water (750 ml), the precipitate was filtered off and washed with water. Crystallization from ethanol provided 15·5 g (86%) of *Vc*; m.p. 210—213°C. For $C_{19}H_{15}ClFNO_3$ (359·8) calculated: 63·43% C, 4·20% H, 9·85% Cl, 5·28% F, 3·89% N; found: 63·04% C, 4·19% H, 10·27% Cl, 5·31% F, 3·84% N. IR spectrum: 1 725 (COO), 1 610 (C=O), 1 550, 900, 710, 695 (aromat. system). UV spectrum, λ_{max} (log ε): 334 (2·99), 321 (3·01), 310 (2·93), 261 (3·39), 252 (3·37), 216 (2·42). ^{1}H NMR spectrum: 1·32 t, 3 H (CH_3, J = 7); 4·24 q, 2 H (CH_2, J = 7); 5·72 s, 2 H (N—CH_2); 7·30 m, 5 H (phenyl); 7·94 d, 1 H (H-8, $J_{H,F}$ = 7); 8·04 d, 1 H (H-5, $J_{H,F}$ = 9); 8·92 s, 1 H (H-2).

1-Benzyl-7-chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (*Vd*)

A suspension of *Vc* (3·6 g, 10 mmol) in 10% aqueous solution of sodium hydroxide (300 ml) was refluxed for 4 h. The homogenous mixture was acidified with concentrated hydrochloric acid, cooled down and the solid was filtered off and washed with water. Crystallization from ethanol yielded 2·6 g (78%) of *Vd*; m.p. 200—206°C. For $C_{17}H_{11}ClFNO_3$ (331·7) calculated: 61·55% C, 3·34% H, 10·69% Cl, 5·73% F, 4·22% N; found: 60·97% C, 3·34% H, 10·94% Cl, 5·96% F, 3·81% N. IR spectrum: 1 710 (COOH), 1 612 (C=O), 1 565, 1 540, 900, 715, 695 (aromat. system). UV spectrum, λ_{max} (log ε): 335 (3·04), 321 (3·08), 261 (3·33), 252 (3·30), 214 (3·49), λ_{infl} 305 (3·00). ^{1}H NMR spectrum: 5·90 s, 2 H (N—CH_2); 7·34 s, 5 H (phenyl); 8·20 m, 2 H (H-5, H-8); 9·06 s, 1 H (H-2).

1-Benzyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid (*Ve*)

A mixture of *Vd* (6·6 g, 20 mmol), N-methylpiperazine (10 ml), and pyridine (100 ml) was stirred at 100°C for 30 h, then the mixture was evaporated to dryness, the residue was boiled with ethanol (50 ml) and cooled down. The solid was filtered off, washed with cold ethanol and crystallized from ethanol; yield 6·3 g (80%), m.p. 251—253°C. For $C_{22}H_{22}FN_3O_3$ (395·4) calculated: 66·82% C, 5·61% H, 4·80% F, 10·63% N; found: 66·49% C, 5·61% H, 4·75% F, 10·56% N. IR spe'trum: 1 702 (COOH), 1 626 (C=O), 1 505, 695 (aromat. system). UV spectrum, λ_{max} (log ε): 320 (3·08), 281 (3·61). ^{1}H NMR spectrum (100°C): 2·22 s, 3 H (N—CH_3); 2·44 t, 4 H (H-3′, H-5′ of piperazine); 3·20 t, 4 H (H-2′, H-6′ of piperazine); 5·80 s, 2 H (N—CH_2); 7·08 d, 1 H (H-8, $J_{H,F}$ = 8); 7·34 s, 5 H (phenyl); 7·84 d, 1 H (H-5, $J_{H,F}$ = 12); 8·84 s, 1 H (H-2). ^{13}C NMR spectrum (100°C): 48·70 q (N—CH_3), 48·72 t (C-3′, C-5′ of piperazine), 53·56 t (C-2′, C-6′ of piperazine), 56·62 t (N—CH_2), 106·22 d (C-8), 107·11 s (C-3), 110·74 d (C-5, $J_{C,F}$ = 24), 118·58 s (C-4a), 126·53 d (C-2′, C-6′ of phenyl), 127·65 d (C-4′ of phenyl), 128·48 d (C-3′, C-5′ of phenyl), 134·75 s (C-8a), 137·29 s (C-1′ of phenyl), 144·61 s (C-7), 148·89 d (C-2), 152·27 s (C-6, $J_{C,F}$ = 249), 165·30 (COOH), 176·06 s (C-4).

6-Fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid (*Vf*)

A mixture of *Ve* (3·95 g, 10 mmol), acetic acid (300 ml) and 5% palladium catalyst on charcoal (1 g) was hydrogenated during vigorous shaking until a consumption of hydrogen was registered. Then the catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from N,N-dimethylformaldehyde; yield 2·1 g (69%), m.p. 223–225°C. For $C_{15}H_{16}FN_3O_3$ (305·3) calculated: 59·01% C, 5·28% H, 6·22% F, 13·76% N; found: 59·21% C, 5·70% H, 5·85% F, 13·61% N. IR spectrum: 1 678 (COOH), 1 636 (C=O), 1 590, 1 506, 1 486 (aromat. system). UV spectrum, λ_{max} (log ε): 271 (3·51), 222 (3·16). ^{1}H NMR spectrum: 2·08 s, 3 H (N—CH_3); 2·55 bs, 4 H (H-3′, H-5′ of piperazine); 3·20 bs, 4 H (H-2′, H-6′ of piperazine); 7·20 bd, 1 H (H-8); 7·78 d, 1 H (H-5, $J_{H,F}$ = 12); 8·80 s, 1 H (H-2).

Ethyl 6,7,8-trifluoro-1,4-dihydro-4-oxo-1-(2-propynyl)quinoline-3-carboxylate (*Vh*)

A mixture of *Vg* (2·7 g, 10 mmol), potassium carbonate (2·1 g, 15 mmol), and dimethylsulfoxide (20 ml) was stirred at 70°C, then 3-bromopropyne (2·4 g, 20 mmol) was added over 1 h followed by stirring for additional 6 h at this temperature. The mixture was poured into water (100 ml), the separated dark solid (2·1 g) was filtered off and crystallized twice from ethanol using charcoal; yield 1·1 g (36%), m.p. 170–172°C. For $C_{15}H_{10}F_3NO_3$ (309·2) calculated: 58·26% C, 3·26% H, 18·43% F, 4·53% N; found: 58·13% C, 3·24% H, 18·28% F, 4·40% N. IR spectrum: 3 250 (≡C—H), 2 120 (C≡C), 1 680 (COO), 1 600 (C=O), 1 635, 1 560, 1 510 (aromat. system). UV spectrum, λ_{max} (log ε): 310 (3·09), 244 (3·16), 213 (3·38); λ_{infl} (log ε): 322 (3·02), 251 (3·07). ^{1}H NMR spectrum: 1·32 t, 3 H (CH_3, J = 7); 3·72 bs, 1 H (≡C—H); 4·26 q, 2 H (CH_2, J = 7);, 5·36 bs, 2 H (N—CH_2); 8·04 m, 1 H (H-5); 8·84 bs, 1 H (H-2).

6,7,8-Trifluoro-1,4-dihydro-4-oxo-1-(2-propynyl)quinoline-3-carboxylic Acid (*Ic*)

A mixture of *Vh* (1·1 g, 3·6 mmol), acetic acid (6 ml), and concentrated hydrochloric acid (6 ml) was refluxed for 4 h, then water (10 ml) was added into the reaction mixture and the separated solid was filtered off and crystallized from ethanol; yield 0·7 g (70%), m.p. 225–229°C (decomp.). For $C_{13}H_6F_3NO_3$ (281·2) calculated: 55·53% C, 2·15% H, 20·27% F, 4·98% N; found: 54·98% C, 2·20% H, 20·08% F, 4·83% N. IR spectrum: 3 260 (≡C—H), 2 120 (C≡C), 1 710 (COOH), 1 620 (C=O), 1 560, 1 520, 1 490 (aromat. system). UV spectrum λ_{max} (log ε): 312 (3·06), 244 (3·22), 215 (3·34), λ_{infl} 322 (2·99). ^{1}H NMR spectrum: 3·78 bs, 1 H (≡C—H); 5·54 bs, 2 H (N—CH_2); 8·22 m, 1 H (H-5); 9·12 bs, 1 H (H-2).

6,7,8-Trifluoro-1,4-dihydro-4-oxo-1-propadienylquinoline-3-carboxylic Acid (*IId*)

A mixture of *Ic* (0·56 g, 2 mmol), sodium hydrogen carbonate (0·84 g, 10 mmol), water (4 ml) and ethanol (4 ml) was stirred at room temperature for 1 h and then refluxed for 5 h. The mixture was cooled down and acidified with acetic acid, the precipitate was filtered off, washed with small amount of cold water and crystallized from 50% aqueous ethanol; yield 0·36 g (64%), m.p. 118–121°C. For $C_{13}H_6F_3NO_3$ (281·2) calculated: 55·53% C, 2·15% H, 20·27% F, 4·98% N; found: 55·70% C, 2·61% H, 19·87% F, 4·68H N. IR spectrum: 1 710 (COOH), 1 605 (C=O), 1 560, 1 515 (aromat. system). UV spectrum, λ_{max} (log ε): 324 (2·97), 315 (2·97), 252 (3·22), 246 (3·22), 218 (3·31).

REFERENCES

1. Rádl S., Kovářová L., Holubek J.: Collect. Czech. Chem. Commun. *56*, 439 (1991).

2. Rádl S.: Pharmacol. Ther. *48*, 1 (1990).
3. Katritzky A. R., Schwartz O. A., Rubio O., Markees D. G.: Helv. Chim. Acta *67*, 939 (1984).
4. Katritzky A. R., Ramer W. H.: J. Org. Chem. *50*, 852 (1985).
5. Kuehne M. E.: J. Org. Chem. *84*, 837 (1962).
6. Kiely J. S., Schroeder M. C., Sesnie J. C.: J. Med. Chem. *31*, 2004 (1988).
7. Egawa H., Miyamoto T., Matsumoto J.: Chem. Pharm. Bull. *34*, 4098 (1986).
8. Chu D. T. W., Maleczka R. E.: J. Heterocycl. Chem. *24*, 453 (1987).
9. Nishimura Y., Minamida A., Matsumoto J.: J. Heterocycl. Chem. *25*, 479 (1988).

Translated by the author (S.R.).