PREPARATION OF SOME SUBSTITUTED 9,10-DIHYDRO-1-HYDROXY-9--OXOACRIDINE DERIVATIVES

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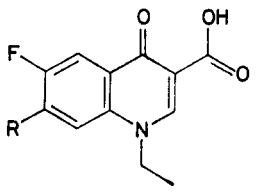
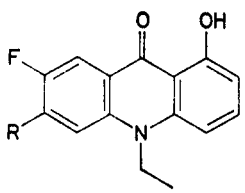
In connection with our research into antibacterial fluoroquinolones[1] of a general formula *I* we were interested in similar 1-hydroxy-acridines *II*. Our synthetic strategy was based on a recent finding[2] that ethyl 2-(1,4-dihydro-4-oxoquinolin-2-yl) acetate reacted at 180°C with diethyl ethoxymethylene-malonate providing diethyl 9,10-dihydro-1-hydroxy-9-oxoacridine-2,4- dicarboxylate.



I



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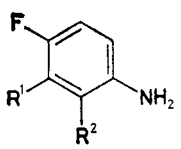
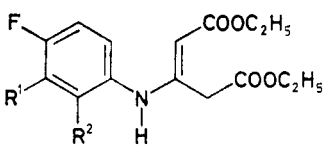
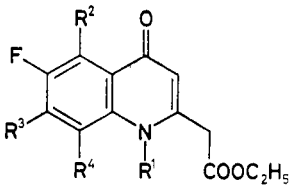


IIIa, $R^1 = R^2 = F$
IIIb, $R^1 = Cl$; $R^2 = H$



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

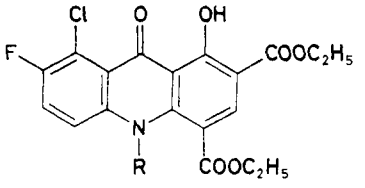


Va, $R^1 = R^2 = H$; $R^3 = R^4 = F$
Vb, $R^1 = R^2 = H$; $R^3 = Cl$; $R^4 = H$
Vc, $R^1 = H$; $R^2 = Cl$; $R^3 = R^4 = H$
Vd, $R^1 = C_2H_5$; $R^2 = H$; $R^3 = R^4 = F$
Ve, $R^1 = C_2H_5$; $R^2 = H$; $R^3 = Cl$; $R^4 = H$
Vf, $R^1 = C_2H_5$; $R^2 = Cl$; $R^3 = R^4 = H$

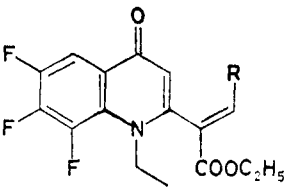
Starting anilines *IIIa* and *IIIb* were treated with diethyl 3-oxoglutarate under Dean–Stark conditions yielding compounds *IVa* and *IVb*, respectively. Cyclization of *IVa* with polyphosphoric acid provided *Va*. Similar cyclization of *IVb* provided

a mixture (TLC on pre-coated silica gel plates Merck, toluene–ethanol–dioxane–concentrated aqueous ammonia 5 : 2 : 4 : 1) of *Vb* (R_F 0·7) and *Vc* (R_F 0·8) in which the latter prevailed. Low solubility of the mixture in suitable solvents did not afford separation by column chromatography. Pure compounds *Vb* and *Vc* were obtained in low yields by a fraction crystallization. N-Ethylation of compounds *Va* – *Vc* with iodoethane in the presence of potassium carbonate in acetone provided compounds *Vd* – *Vf*.

Heating of compounds *Vc* and *Vf* with diethyl ethoxymethylenemalonate afforded acridone derivatives *VIa* and *VIb*, respectively. On the other hand *Vd* under the same conditions yielded an unseparable dark mixture. Compound *Vd* treated with N,N-dimethylformamide dimethyl acetal provided *VIIa*. But we failed to condense the compound with diethyl malonate to *VIIb*, which could serve as an intermediate for the synthesis of corresponding 1-hydroxyacridone derivatives.



VI a, R = H
VI b, R = C_2H_5



VII a, R = $N(CH_3)_2$
VII b, R = $CH(COOC_2H_5)_2$

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. None of the compounds was significantly active.

EXPERIMENTAL

The melting points were determined on a Mettler FP 5 apparatus and were not corrected. ^{1}H NMR spectra (100 MHz) were measured on an apparatus BS-487 (Tesla Brno) 100 MHz in hexadeuterated dimethylsulfoxide, unless otherwise stated. The standard for ^{1}H NMR spectra was 3-trimethyl-silylpropanoic acid, unless otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz.

Diethyl 3-(2,3,4-Trifluoroanilino)-2-pentendioate (*IVa*)

A mixture of 2,3,4-trifluoroaniline *IIIa* (13·3 g, 0·09 mol), diethyl 3-oxoglutarate (20·2 g, 0·1 mol)

and benzene (100 ml) containing a drop of concentrated hydrochloric acid was heated under Dean–Stark apparatus for 3 h. The reaction mixture was evaporated and the residue was crystallized from hexane yielding 23·6 g (79%) of *IVa*, m.p. 51—52°C. For $C_{15}H_{16}F_3NO_4$ (331·3) calculated: 54·38% C, 4·87% H, 17·20% F, 4·23% N; found: 54·33% C, 4·87% H, 17·12% F, 4·37% N.

Diethyl 3-(3-Chloro-4-fluoroanilino)-2-pentendioate (*IVb*)

Equimolar quantities (10 mmol) of 3-chloro-4-fluoroaniline *IIIb* and diethyl-3-oxoglutarate were treated according to the procedure described for the preparation of *IVa* yielding 90% of *IVb*, m.p. 47—51°C. For $C_{15}H_{17}ClFNO_4$ (329·9) calculated: 54·64% C, 5·20% H, 10·75% Cl, 5·76% F, 4·29% N; found: 54·33% C, 5·12% H, 11·11% Cl, 5·90% F, 4·19% N.

Ethyl 2-(6,7,8-Trifluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Va*)

A mixture of *IVa* (14 g, 42 mmol) and 83% polyphosphoric acid (100 g) was stirred at 110°C for 2 h, the mixture was cooled to 40°C and then mixed with ice (500 g) and the pH was taken to 5—6 with 10% aqueous solution of sodium hydroxide. The precipitate was filtered off, washed with cold water and dried. Crystallization from ethanol yielded 8·1 g (67%) of *Va*, m.p. 244 to 245°C. For $C_{13}H_{10}F_3NO_3$ (285·2) calculated: 54·74% C, 3·53% H, 19·98% F, 4·91% N; found: 54·73% C, 3·49% H, 19·74% F, 4·96% N.

Ethyl 2-(7-Chloro-6-fluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Vb*) and Ethyl 2-(5-Chloro-6-fluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Vc*)

A mixture of *IVb* (15 g, 45·5 mmol) and 83% polyphosphoric acid (100 g) was stirred at 120°C for 2 h. Ice (200 g) was added to the cold mixture which was thoroughly trituated and the pH was taken to 4—5 with 20% aqueous solution of sodium hydroxide. The insoluble portion was filtered off and three times crystallized from ethanol yielding 6·2 g (48%) of *Vc*, m.p. 235—238°C. For $C_{13}H_{11}ClFNO_3$ (283·7) calculated: 55·04% C, 3·91% H, 12·50% Cl, 6·70% F, 4·94% N; found: 54·61% C, 3·82% H, 12·50% Cl, 6·70% F, 4·86% N. ^{1}H NMR spectrum: 1·28 t, 3 H (CH_3); 3·55 s, 2 H (CH_2); 4·16 q, 2 H (CH_2 of ester); 5·90 bs, 1 H (H-3); 7·55 m, 2 H (H-7, H-8). The combined mother liquers were evaporated to dryness and crystallized from ethyl acetate yielding 1·8 g (14%) of *Vc*, m.p. 220—222°C. For $C_{13}H_{11}ClFNO_3$ (283·7) calculated: 55·04% C, 3·91% H, 12·50% Cl, 6·70% F, 4·94% N; found: 54·89% C, 3·87% H, 12·45% Cl, 6·80% F, 4·83% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3); 3·74 s, 2 H (CH_2); 4·18 q, 2 H (CH_2 of ester); 5·93 s, 1 H (H-3); 7·67 d, 1 H (H-8, $J_{H,F} = 6$);7·84 d, 1 H (H-5, $J_{H,F} = 10$).

Ethyl 2-(1-Ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Vd*)

A mixture of *Va* (2·85 g, 10 mmol), potassium carbonate (2·76 g, 20 mmol), iodoethane (1·7 g, 11 mmol) and acetone (50 ml) was stirred at room temperature for 8 h, then additional portion of iodoethane (0·3 g, 2 mmol) was added and the mixture was stirred for another 8 h. The mixture was evaporated in vacuo, the residue was triturated with water (20 ml) and extracted with dichloromethane. The extract was dried with magnesium sulfate and the filtrate was evaporated. The residue (3·1 g) was crystallized from hexane; yield 2·9 g (93%), m.p. 68—69°C. For $C_{15}H_{14}F_3NO_3$ (313.3) calculated: 57·51% C, 4·50% H, 18·19% F, 4·47% N; found: 57·45% C, 4·63% H, 18·20% F, 4·34% N.

Ethyl 2-(7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Ve*)

This compound was prepared from *Vb* in 58% yield according to the procedure described for the synthesis of *Vd*, m.p. 81–84°C (hexane). For $C_{15}H_{15}ClFNO_3$ (311·7) calculated: 57·79% C, 4·85% H, 11·37% Cl, 6·09% F, 4·49% N; found: 57·52% C, 4·53% H, 10·98% Cl, 5·93% F, 4·62% N.

Ethyl 2-(5-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinolin-2-yl)acetate (*Vf*)

This compound was prepared from *Vc* in 71% yield from *Vc* according to the procedure described for the synthesis of *Vd*, m.p. 86–90°C (ethanol). For $C_{15}H_{15}ClFNO_3$ (311·7) calculated: 57·79% C, 4·85% H, 11·38% Cl, 6·09% F, 4·49% N; found: 57·73% C, 4·73% H, 11·52% Cl, 6·24% F, 4·64% N. ^{1}H NMR spectrum ($CDCl_3$, tetramethylsilane): 1·28 t, 3 H (CH_3 of ester); 1·60 t, 3 H (CH_3 of N-ethyl); 3·92 s, 2 H (CH_2); 4·22 m, 4 H (CH_2 of ester and N-ethyl); 6·85 s, 1 H (H-3); 7·47 t, 1 H (H-7, $J = 9$); 7·90 dd, 1 H (H-8, $J = 9$; 5).

Diethyl 8-Chloro-7-fluoro-9,10-dihydro-1-hydroxy-9-oxoacridine-2,4-dicarboxylate (*VIa*)

A mixture of *Vc* (1·42 g, 5 mmol) and diethyl ethoxymethylenemalonate (1·19 g, 5·5 mmol) was stirred at 180°C for 2 h. The cold mixture was triturated with acetone (15 ml), the insoluble portion was filtered off, washed with acetone and crystallized from toluene; yield 1·1 g (54%), m.p. 265–270°C. An analytical sample was crystallized twice from ethanol; m.p. 270–274°C. For $C_{19}H_{15}ClFNO_6$ (407·8) calculated: 55·96% C, 3·71% H, 8·69% Cl, 4·66% F, 3·43% N; found: 55·63% C, 3·72% H, 9·06% Cl, 4·10% F, 3·39% N.

Diethyl 8-Chloro-10-ethyl-7-fluoro-9,10-dihydro-1-hydroxy-9-oxoacridine-2,4-dicarboxylate (*VIb*)

This compound was prepared in 67% yield from *Vf* according to the procedure described for the preparation of *VIa*, m.p. 184–186°C. For $C_{21}H_{19}ClFNO_6$ (435·8) calculated: 57·87% C, 4·39% H, 8·13% Cl, 4·36% F, 3·21% N; found: 57·53% C, 4·38% H, 8·59% Cl, 4·20% F, 3·14% N. ^{1}H NMR spectrum: 1·23 t, 3 H and 1·26 t, 3 H (CH_3 of esters); 1·55 t, 3 H (CH_3 of N-ethyl); 4·30 m, 6 H (3 × CH_2); 7·68 dd 1 H (H-6, $J = 9$; $J_{H,F} = 10$).

Ethyl 2-Dimethylaminomethylene-2-(1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinolin-2-yl)-acetate (*VIIa*)

A mixture of *Vd* (1·55 g, 5 mmol), N,N-dimethylformamide dimethyl acetal (1·1 g, 10 mmol) and dioxane (5 ml) was stirred at room temperature for 5 h and then was left to stand at this temperature for 3 days. The mixture was evaporated to dryness and crystallized from methanol; yield 1·05 g (57%), m.p. 171–174°C. For $C_{18}H_{19}F_3N_2O_3$ (368.3) calculated: 58·69% C, 5·20% H, 15·47% F, 7·61% N; found: 58·46% C, 5·14% H, 15·53% F, 7·73% N. ^{1}H NMR spectrum: 1·16 t, 3 H (CH_3 of ester); 1·48 t, 3 H (CH_3 of N-ethyl); 2·76 s, 6 H (N—CH_3); 4·08 q, 2 H (CH_2); 4·26 q, 2 H (CH_2); 7·08 s, 1 H (=CH—N); 7·80 m, 1 H (H-5).

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2. Deady L. W., Werden D. M.: J. Org. Chem. *52*, 3930 (1987).

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