PREPARATION OF SOME 2,3-DIHYDRO-7-OXO-7*H*-PYRIDO[1,2,3-*de*][1,4]BENZOXAZINE DERIVATIVES

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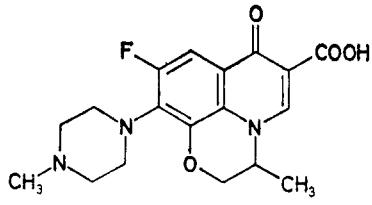
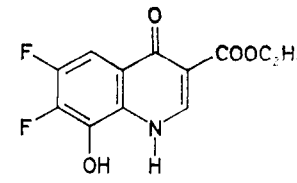
In the last few years interest in analogs of ofloxacin (*I*) has considerably risen. We have recently described[1] a new reaction of 8-hydroxyquinolone *II* with 3-bromopropyne leading to 2,3-dihydro-3-methylene-7-oxo-7*H*-pyridol[1,2,3-*de*][1,4]benzoxazine-6-carboxylate *IIIa*, which could be used as an intermediate for preparation of antibacterically active compound *IIIb* (refs.[1,2]).

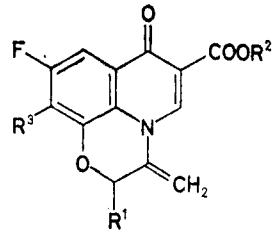
Now we extend the scope of the reaction. Using 3-bromobutyne we obtained 2-methyl derivative *IIIc*. Treatment of *IIIc* with N-methylpiperazine followed by an



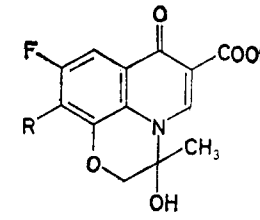
I



II



IIIa, R^1= H ; R^2= C_2H_5 ; R^3= F
IIIb, R^1= R^2= H ; R^3= 4-methylpiperazinyl
IIIc, R^1= CH_3 ; R^2= C_2H_5 ; R^3= F
IIId, R^1= CH_3 ; R^2= H ; R^3= 4-methylpiperazinyl



IVa, R = F
IVb, R = 4-methylpiperazinyl

alkaline hydrolysis provided ofloxacin analog *IIId*. On the other hand we have found that an acidic hydrolysis of *IIIa* provided *IVa* having a tertiary hydroxy group at position 3. When we treated *IIIa* with N-methyl-piperazine and the intermediate *IIIb* subjected the acidic hydrolysis we obtained 3-hydroxy analog of ofloxacin *IVb*.

EXPERIMENTAL

The melting points were determined on a Mettler FP 5 apparatus and were not corrected. IR spectra were taken on a Unicam SP-2006 spectrometer in KBr pellets; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam 8 800 spectrophotometer in ethanol, molar absorption coefficients (ε) are given in m^2mol^{-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, unless otherwise stated). The standard for ^1H NMR spectra was 3-trimethylsilylpropanoic 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.

Ethyl 9,10-Difluoro-2,3-dihydro-3-methylene-2-methyl-7-oxo-7*H*-pyridol[1,2,3-*de*][1,4]benzoxazine-6-carboxylate (*IIIc*)

A solution of 3-bromobutyne (0·73 g, 5·5 mmol) was added dropwise during 1 h to a mixture of *II* (1·35 g, 5 mmol), sodium hydrogen carbonate (0·63 g, 7·5 mmol) and N,N-dimethylformamide (15 ml) at 90°C and then the mixture was stirred at this temperature for additional 2 h. The mixture was cooled down and poured onto ice (200 g). The insoluble portion was filtered off, washed with water and dried. Crystallization from 95% aqueous ethanol provided 0·9 g (56%) of *IIIb*, m.p. 171–173°C. For $C_{16}H_{13}F_2NO_4$ (321·3) calculated: 59·81% C, 4·08% H, 11·83% F, 4·36% N; found: 59·52% C, 4·10% H, 11·42% F, 4·01% N. ^{13}C NMR spectrum: 13·67 q (CH_3 of ethyl), 16·65 q (CH_3), 59·9 t (CH_2 of ethyl), 71·84 t (C-2,) 102·41 t (CH_2=), 103·16 d (C-8, $J_{F,C}$ = 20), 112·75 s (C-6), 122·60 s* (C-7a), 124·50 s* (C-11a), 134·53 s (C-3), 135·60 s (C-11). 140·00 s (C-10), 141·20 d (C-5), 148·20 s (C-9), 163·52 s (COO), 171·35 s (C-7). UV spectrum, λ_{max} (logε): 330 (3·25), 250 (3·05), 229 (3·41).

9-Fluoro-2,3-dihydro-2-methyl-3-methylene-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido-[1,2,3-*de*][1,4]benzoxazine-6-carboxylic Acid (*IIId*)

A mixture of *IIIc* (0·6 g, 1·9 mmol), N-methylpiperazine (1 g, 10 mmol) and dimethyl sulfoxide (15 ml) was stirred at 110–120°C for 13 h. The solution was evaporated in vacuo, the residue was suspended in ethanol (90 ml) and a solution of sodium hydroxide (0·4 g, 10 mmol) in water (10 ml) was added dropwise and the mixture was stirred at 50°C for 30 min. The formed solution was evaporated, the residue was dissolved in water (10 ml), acidified with hydrochloric acid, treated with charcoal and neutralized with 5% aqueous solution of sodium hydrogen carbonate. The mixture was extracted with trichloromethane, dried with magnesium sulfate and the residue after evaporation was crystallized from 95% aqueous ethanol: yields 0·4 g (50%), m.p. 271–273°C. For $C_{19}H_{20}FN_3O_4 \cdot 2{\cdot}5\,H_2O$ (418·4) calculated: 54·54% C, 6·02% H, 4·54% F, 10·04% N; found: 54·56% C, 5·24% H, 4·58% F, 9·96% N. IR spectrum: 2 407 (OH), 1 719 (COOH), 1 660 (CH_2=), 1 617 (C=O). UV spectrum, λ_{max} (log ε): 336 (3·07), 299 (3·40), 244 (3·04), 220 (3·25).

^{1}H NMR spectrum (90°C): 1·65 d, 3 H (CH_3); 2·48 bt, 4 H (H-3′, H-5′, of piperazine); 2·84 s, 3 H (CH_3 of piperazine); 3·32 bt, 4 H (H-2′, H-6′ of piperazine); 5·14 m, 1 H (C-2); 5·54 d, 5·98 d, 2 H (CH_2=); 7·62 d, 1 H (H-8, $J_{H,F}$ = 11); 8·90 s, 1 H (H-5). Mass spectrum, m/z = 373.

9,10-Difluoro-2,3-dihydro-3-hydroxy-3-methyl-7-oxo-7*H*-pyridol[1,2,3-*de*][1,4]benzoxazine-6--carboxylic Acid (*IVa*)

A suspension of *IIIa* (0·25 g, 0·8 mmol) in a mixture of concentrated hydrochloric acid (2 ml) and acetic acid (2 ml) was refluxed for 4 h. The mixture was cooled down and the separated crystals were filtered off and crystallized from N,N-dimethylformamide; yield 0·15 g (62%), m.p. 253—257°C. For $C_{13}H_9F_2NO_5$ (297·2) calculated 52·53% C, 3·05% H, 12·78% F, 4·71% N; found: 52·20% C, 3·15% H, 12·82% F, 4·49% N. IR spectrum: 3 180 (OH), 1 680 (COOH), 1 570, 1 520 (aromat. system). UV spectrum, λ_{max} (log ε): 317 (3·08), 232 (3·37). ^{1}H NMR spectrum (110°C): 1·76 s, 3 H (CH_3); 4·48 s, 2 H (C-2); 7·83 dd, 1 H (H-8, $J_{H,F}$ = 1 000, 10); 9·10 s, 1 H (H-5). Mass spectrum, m/z = 297 (M^+).

9-Fluoro-2,3-dihydro-3-hydroxy-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3--de][1,4]benzoxazine-6-carboxylic Acid (*IVb*)

A mixture of *IIIa* (1 g, 3·25 mmol), N-methylpiperazine (1 g, 10 mmol) and dimethyl sulfoxide (20 ml) was stirred at 110—120°C for 10 h. The solution was evaporated in vacuo, the residue was suspended in a mixture of 10% hydrochloric acid (10 ml) and acetic acid (10 ml) and the mixture was refluxed for 4 h. The mixture was evaporated to dryness, the residue was triturated with methanol (5 ml) and left to stand overnight in a refrigerator, insoluble portion was filtered off and crystallized from methanol; yield 0·4 g (28%), m.p. 251—253°C. For $C_{18}H_{20}FN_3O_5$ . . HCl . H_2O (431·8) calculated: 50·06% C, 5·37% H, 8·21% Cl, 4·40% F, 9·73% N; found: 50·02% C, 5·03% H, 8·45% Cl, 4·79% F, 9·88% N. IR spectrum: 2 679 (OH), 1 682 (COOH), 1 618 (C=O). UV spectrum, λ_{max} (log ε): 297 (3·52). ^{13}C NMR spectrum: 24·43 q (CH_3), 41·98 q (N—CH_3), 46·46 t, 46·61 t (C-2′, C-6′ of piperazine), 52·81 t (C-3′, C-5′ of piperazine). 70·81 t (C-2), 83·62 s (C-3), 103·19 d (C-8, $J_{F,C}$ = 24), 106·67 s (C-6), 119·85 s (C-7a), 124·68 s (C-11a), 129·79 s (C-10), 139·90 s (C-11), 140·05 d (C-5), 154·57 s (C-9, $J_{H,F}$ = 247), 165·23 s (COO), 175·94 s (C-7). Mass spectrum, m/z = 377.

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