SYNTHESIS OF SOME 1-ALKYL-1,4-DIHYDRO-4-OXO-1,7--NAPHTHYRIDINE-3-CARBOXYLIC ACIDS

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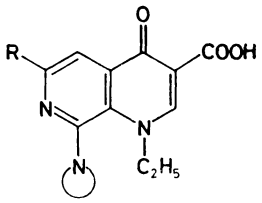
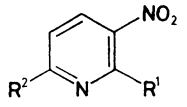
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Reaction of substituted 2-aminopyridines *IIIa*, *IIIb*, *IIIe*, and *IIIf* with ethyl ethoxymethylene malonate provided corresponding pyridylaminomethylenemalonates *Va*—*Vd*, respectively. Thermal cyclization of *Va*, *Vc*, and *Vd* yielded substituted ethyl 4-hydroxy-1,7-naphthyridine-3--carboxylates *VIa*, *VIc*, and *VId*. Compounds *VIc* and *VId* treated with morpholine gave 8-morpholino derivatives *VIe* and *VIf*. These compounds were ethylated to mixtures of N-ethylated (*VIIa*, *VIIb*) and O-ethylated products (*VIIIa*, *VIIIb*). Compound *VIIIb* was also prepared from ethyl 4-chloro-6-fluoro-8-morpholino-1,7-naphthyridine-3-carboxylate *VIIIc* and sodium ethanolate. Esters *VIIa* and *VIIb* wre hydrolyzed under acidic conditions to the respective acids *VIIc* and *VIId*.

Antibacterial quinolones have attracted an increasing attention as a source of potent clinically useful drugs[1,2]. Most active compounds have quinoline or 1,8--naphthyridine skeleton and only little attention has been paid to 1,7-naphthyridine derivatives so far[3,4]. Therefore we decided to prepare such derivatives of a general formula *I* having structural features compatible with antibacterial activity[2]. Since the most active quinolones and 1,8-naphthyridones have a fluorine atom at position 6



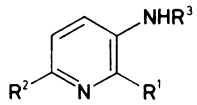
I, R = F, Cl

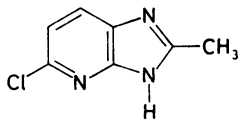


IIa, $R^1 = R^2 = Cl$
IIb, $R^1 = NH_2$; $R^2 = Cl$
IIc, $R^1 = NHCOCH_3$; $R^2 = Cl$
IId, R^1 = 4-ethoxycarbonyl-1-piperazinyl; $R^2 = Cl$
IIe, $R^1 = R^2 = F$

and a substituted amino group at position 7 we were interested in compounds *I* having a halo group at position 6 (R = F, Cl) and a substituted amino group at position 8.

This article describes our synthetic efforts devoted to this direction, including successful synthesis of intermediates *VI* and their further modifications. Using this methodology we have prepared a series of 1,7-naphthyridine derivatives *I*. Their physico-chemical properties and antibacterial activities will be published in detail elsewhere[5].





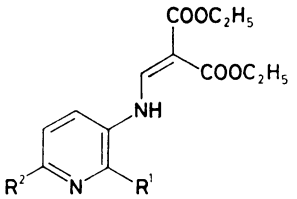
IV

IIIa, R^1 = 4-ethoxycarbonyl-1-piperazinyl ; R^2 = Cl ; R^3 = H
IIIb, R^1 = $NHOCCH_3$, R^2 = Cl ; R^3 = H
IIIc, R^1 = $NHOCCH_3$; R^2 = Cl ; R^3 = CH_3CO
IIId, R^1 = NH_2 ; R^2 = Cl ; R^3 = H
IIIe, R^1 = R^2 = Cl ; R^3 = H
IIIf, R^1 = R^2 = F ; R^3 = H
IIIg, R^1 = R^2 = Cl ; R^3 = C_2H_5

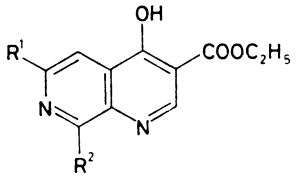
Starting 2,6-dichloro-3-nitropyridine *IIa* (ref.[6]) was treated with ammonia to give *IIb* which was acetylated with acetanhydride yielding *IIc*. Similar treatment of *IIa* with N-ethoxycarbonyl piperazine yielded *IId* which was reduced with iron in acetic acid into *IIIa*. Attempts to prepare compound *IIIb* by this way from *IIc* provided a mixture of *IIIc* and *IV*. Successful reduction of *IIc* was accomplished by aluminium amalgam. Compounds *IIIa* and *IIIb* were easily transferred by a previously described treatment with ethyl ethoxymethylenemalonate[7] into *Va* and *Vb*, respectively. Thermal cyclization of *Va* provided the respective 1,7-naphthyridine *VIa* but we failed to prepare *VIb* in this way. Attempts to accomplish the cyclization of *Vb* with polyphosphoric acid yielded 2,3-diamino-6-chloropyridine *IIId*.

Because we intended to modify substituents at position 8 we needed to prepare 6,8-dihalo derivatives by similar way. Starting compound *IIa* was transferred into *IIe* (ref.[8]) by potassium fluoride in dimethyl sulfone. Reduction of *IIa* and *IIe* with iron in acetic acid yielded *IIIe* and *IIIf*, respectively. Compound *IIIe* was N-ethylated into *IIIg* using ethyl orthoformate method[9]. Both anilines and aminopyridines usually smoothly react with ethoxymethylenemalonates providing corresponding arylaminomethylenemalonates. In this way compounds *Va* and *Vb* were prepared. Nevertheless we found that 2,6-dihalo-3-aminopyridines reacted with ethyl ethoxymethylenemalonate very slowly under usual conditions, e.g. after such a treatment of *IIIe*

or *IIIf* at 130°C for 8 h yields of *Vc* and *Vd* were about 20%. High yields of these compounds were achieved when the reaction was performed in refluxing toluene solution using boron trifluoride etherate as a catalyst. But we failed to perform this reaction with N-ethyl derivative *IIIg*. Thermal cyclization of *Vc* and *Vd* provided *VIc* and *VId* in good yields but the reaction time was substantially longer than in the case of *Va*.



Va, R^1 = 4-ethoxycarbonyl-1-piperazinyl ; R^2 = Cl
Vb, R^1 = $NHOCCH_3$; R^2 = Cl
Vc, R^1 = R^2 = Cl
Vd, R^1 = R^2 = F

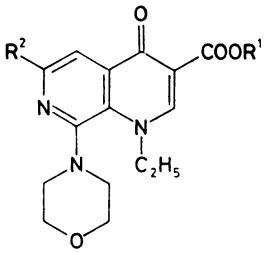


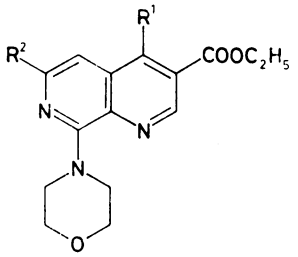
VIa, R^1 = Cl ; R^2 = 4-ethoxycarbonyl-1-piperazinyl
VIb, R^1 = Cl ; R^2 = $NHOCCH_3$
VIc, R^1 = R^2 = Cl
VId, R^1 = R^2 = F
VIe, R^1 = Cl ; R^2 = morpholino
VIf, R^1 = F ; R^2 = morpholino

Compounds *VIc* and *VId* were found to be suitable intermediates for the planned synthesis of 8-substituted 1-alkyl-1,4-dihydro-6-halo-4-oxo-1,7-naphthyridine-3-carboxylic acid derivatives of a general formula *I*. Compounds *VIc* and *VId* treated with secondary amines provided products of nucleophilic displacement reaction at position 8, e.g. morpholine compounds *VIe* and *VIf*, respectively.

Attempts to ethylate 6,8-dihalo derivatives *VIc* and *VId* to the position 1 was unsuccessful under various conditions used usually for this type of reaction, i.e. using sodium hydride or potassium carbonate in N,N-dimethylformamide or dimethyl sulfoxide and iodoethane as an alkylation reagent. Nevertheless 8-substituted

derivatives *VIe* and *VIf* could be alkylated by this way using substantial excess of both potassium carbonate and iodoethane. According to TLC (Silufol UV 254, toluene–ethyl acetate–formic acid 25 : 25 : 1) the reaction mixture contained both products of N-alkylation *VIIa* and *VIIb* (R_F values of about 0·4), and products of O-alkylation *VIIIa* and *VIIIb* (R_F values of about 0·9) besides a substantial amounts of the starting compounds (R_F values of about 0·6). Crude mixtures were subjected to column chromatography on silica gel (toluene–ethyl acetate 1 : 1) followed by crystallization from ethanol. Compound *VIIIb* was prepared independently from *VIf* which was treated with phosphorous oxychloride yielding *VIIIc* and its following treatment with sodium ethoxide provided the desired compound *VIIIb*. Esters *VIIa* and *VIIb* were saponified under acidic conditions yielding *VIIc* and *VIId* respectively.





VIIa, $R^1 = C_2H_5$; $R^2 = Cl$
VIIb, $R^1 = C_2H_5$; $R^2 = F$
VIIc, $R^1 = H$; $R^2 = Cl$
VIId, $R^1 = H$; $R^2 = F$

VIIIa, $R^1 = OC_2H_5$; $R^2 = Cl$
VIIIb, $R^1 = OC_2H_5$; $R^2 = F$
VIIIc, $R^1 = Cl$; $R^2 = F$

EXPERIMENTAL

The melting points were determined on a Kofler block, and were not corrected. IR spectra were taken on a Philips 9700 spectrometer in KBr pellets, unless otherwise stated; wavenumbers are given in cm^{-1}. UV spectra were taken on a Shimadzu UV 260 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. ^1H NMR spectra (100 MHz) and ^{13}C NMR spectra (25·14 MHz) were measured on an apparatus BS-487 (Tesla Brno) in hexadeuterated dimethyl sulfoxide (^{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. The assignments indicated by an asterisk may be interchanged.

2-Amino-6-chloro-3-nitropyridine (*IIb*)

To a solution of *IIa* (25 g, 0·13 mol) in ethanol (100 ml) was added a solution of anhydrous ammonia (10 g, 0·59 mol) in ethanol (20 ml) and the mixture was let to stand overnight. Then the mixture was evaporated to half of its volume under reduced pressure and diluted with water

(100 ml), insoluble portion was filtered off and crystallized from ethanol: yields 17 g (75%), m.p. 194—196°C. Ref.[10] gave m.p. 195—196°C.

2-Acetamido-6-chloro-3-nitropyridine (*IIc*)

To a solution of *IIb* (1·74 g, 10 mmol) in a mixture of acetic acid (20 ml) and acetanhydride (10 ml) was added concentrated sulfuric acid (0·1 ml) and the mixture was refluxed for 2 h, then it was evaporated to dryness and crystallized from acetone and ethyl acetate; yields 2 g (92%), m.p. 148°C. For $C_7H_6ClN_3O_3$ (215·6) calculated: 39·00% C, 2·81% H, 16·44% Cl, 19·49% N; found: 38·83% C, 2·75% H, 16·50% Cl, 19·56% N.

6-Chloro-2-(4-ethoxycarbonyl-1-piperazinyl)-3-nitropyridine (*IId*)

To a mixture of *IIa* (5 g, 26 mmol) and triethylamine (2·9 g, 28·5 mmol) in chloroform (100 ml) was at −5°C added a solution of N-ethoxycarbonylpiperazine (4·8 g, 30 mmol) in chloroform (20 ml) during 40 min and then the mixture was stirred at this temperature for additional 2 h. Then the mixture was washed twice with 40 ml of 5% hydrochloric acid and then with water and dried with sodium sulfate. The solution was evaporated and purified by column chromatography (silica gel; cyclohexane–isopropanol 25 : 3) followed by crystallization from ethanol yielded 6·3 g (77%) of yellow crystals, m.p. 78—80°C. Ref.[11] gave m.p. 80—81°C.

2,6-Difluoro-3-nitropyridine (*IIe*)

A mixture of dimethylsulfone (19 g), potassium fluoride (31·3 g, 0·54 mol), and toluene (30 ml) was stirred at 150°C and toluene was distilled off. Then 2,6-dichloro-3-nitropyridine (19·3 g, 0·1 mol) was added at once and the mixture was stirred at 150°C for 1 h and without cooling dry toluene (150 ml) was added and then the mixture was cooled down and the insoluble portion was filtered off through a layer (3 cm) of silica gel and washed with toluene. The combined solutions were evaporated under reduced pressure and resulting yellowish oil (13 g, 81%) was used for further reaction without any purification.

2-Acetamido-3-amino-6-chloropyridine (*IIIb*)

To a solution of *IIc* (5 g, 23·2 mmol) in ethanol (300 ml) was added amalgamated aluminium foil (5 g) and water (3·5 ml) and the mixture was stirred at 40°C for 4 h. The insoluble portion was filtered off, washed with ethanol (100 ml) and the combined filtrates were evaporated. The residue was used for further reaction without any purification.

2,3-Diamino-6-chloropyridine (*IIId*)

A mixture of *Vb* (0·1 g, 0·3 mmol) and 85% polyphosphoric acid (2 g) was stirred at 80°C for 10 min, then the mixture was poured into water and neutralized with aqueous ammonia. The solution was extracted with ethyl acetate and the solution was proved to contain only *IIId* according to TLC (toluene–ethyl acetate–formic acid 25 : 25 : 1) compared with an authentic sample prepared by reduction of *IIb* with amalgamated aluminium foil adhering to the procedure described for the preparation of *IIIb*.

3-Amino-2,6-dichloropyridine (*IIIe*)

To a boiling solution of *IIa* (19·3 g, 0·1 mol) in acetic acid (75 ml) and ethanol (150 ml) was added iron powder (24 g, 0·44 mol) in several portions during 2 h and then the mixture was

refluxed for additional 1 h. The cold mixture was filtered, the filtration cake was washed with ethyl acetate (50 ml). The filtrate was concentrated to dryness, the residue was dissolved in ethanol and 10% ethanolic solution of ammonia (20 ml) was added, the formed precipitate was filtered off and the filtrate was again evaporated. The residue was dissolved in toluene and filtered through a short column of silica gel, filtrate was evaporated (14 g) and the residue was used for further reaction without purification. Analytical sample was purified by crystallization from ethanol, m.p. 119°C. Ref.[11] gave m.p. 119–121°C.

3-Amino-2,6-difluoropyridine (*IIIf*)

This compound was prepared from *IIe* according to the procedure described for *IIIe*, reaction time was 4 h. The compound was used for further reaction without purification; an analytical sample was purified by sublimation in vacuo, m.p. 58–60°C. For $C_5H_4F_2N_2$ (130·1) calculated: 46·16% C, 3·10% H, 29·21% F, 21·53% N; found: 45·94% C, 2·98% H, 29·40% F, 21·47% N.

2,6-Dichloro-3-ethylaminopyridine (*IIIg*)

To a mixture of *IIIe* (5 g, 31 mmol) and ethyl orthoformate (11 g, 74 mmol) were added 2 drops of concentrated sulfuric acid and the mixture was heated while volatile product was distilled off. During 3 h the temperature of the mixture raised to 190°C and the temperature was maintained for additional 2 h. The dark oil was cooled down and then dilute hydrochloric acid (20%, 20 ml) was added and the mixture was refluxed for 1 h. The cold mixture was poured into 10% aqueous solution of sodium hydroxide (100 ml), the mixture was extracted with ethyl acetate (100 ml), the extract was dried with magnesium sulfate, the solvent was distilled off and the residue was distilled in vacuo; yields 2·5 g (43%), b.p. 142°C/1·3 kPa, $n_D^{20} = 1·5869$. For $C_7H_8Cl_2N_2$ (191·1) calculated: 44·01% C, 4·22% H, 37·11% Cl, 14·66% N; found: 43·89% C, 4·24% H, 37·17% Cl, 14·57% N.

2,3-Diacetamido-6-chloropyridine (*IIIc*) and 5-Chloro-2-methylimidazo[4,5-*b*]pyridine (*IV*)

To a solution of *IIc* (1 g, 4·7 mmol) in acetic acid (10 ml) was added iron powder (1·1 g, 20 mmol) and the mixture was stirred under reflux for 2 h, the insoluble portion was filtered off and washed with ethanol (20 ml). The filtrate was evaporated under reduced pressure, the residue was dissolved in ethyl acetate and purified by column chromatography on silica gel yielding two products. The first was identified as *IV* (0·5 g, 63%), m.p. 259–264°C. For $C_7H_6ClN_3$ (167·6) calculated: 50·17% C, 3·61% H, 21·15% Cl, 25·07% N; found: 49·63% C, 3·54% H, 20·79% Cl, 24·81% N. Mass spectrum *m/z*: 167 (M^+). The second compound was identified as *IIIc* (0·2 g, 19%), m.p. 189–191°C. For $C_9H_{10}ClN_3O_2$ (227·6) calculated: 47·48% C, 4·43% H, 15·57% Cl, 18·46% N; found: 47·07% C, 4·33% H, 14·99% Cl, 18·31% N. Mass spectrum *m/z*: 227 (M^+).

Ethyl [6-Chloro-2-(ethoxycarbonyl-1-piperazinyl)-3-pyridyl]aminomethylenemalonate (*Va*)

To a solution of *IId* (5·86 g, 18 mmol) in a mixture of acetic acid (30 ml) and ethanol (50 ml) was added iron powder (5 g, 0·09 mol) and the mixture was stirred under reflux for 1 h, insoluble portion was filtered off and washed with ethanol (50 ml). The filtrate was evaporated and diethyl ethoxymethylenemalonate (4 g, 18·5 mmol) was added. The reaction mixture was stirred at 100°C for 2 h, the crude product was crystallized from ethanol yielding 5·7 g (69%), m.p. 144 to 146°C. For $C_{20}H_{27}ClN_4O_6$ (454·9) calculated: 52·81% C, 5·98% H, 7·79% Cl, 12·32% N; found: 52·85% C, 5·98% H, 8·19% Cl, 12·39% N.

Ethyl (2-Acetamido-6-chloro-3-pyridyl)aminomethylenemalonate (*Vb*)

A mixture of crude *IIIb* obtained from 5 g of *IIc* and ethyl ethoxamethylenemalonate (5 g, 23 mmol) was heated at 100°C for 2 h under reduced pressure and the thick product was crystallized from ethanol; yield 4·3 g (52%), m.p. 183°C. For $C_{15}H_{18}ClN_3O_5$ (355·8) calculated: 50·64% C, 5·10% H, 9·96% Cl, 11·81% N; found: 50·58% C, 5·06% H, 10·19% Cl, 11·71% N.

Ethyl (2,6-Dichloro-3-pyridyl)aminomethylenemalonate (*Vc*)

To a toluene solution of crude *IIIe* was added ethyl ethoxymethylenemalonate (21·6 g, 0·1 mol) and boron trifluoride etherate (0·5 ml, 4 mmol) and the mixture was stirred at 100°C for 10 min and then the solution was left to stand for 30 min at room temperature. The solvent was removed by distillation and the residue was crystallized from ethanol; yield 22 g (66%), m.p. 137—138°C. For $C_{13}H_{14}Cl_2N_2O_4$ (333·2) calculated: 46·86% C, 4·24% H, 21·28% Cl, 8·41% N; found: 46·76% C, 4·23% H, 21·20% Cl, 8·34% N.

Ethyl (2,6-Difluoro-3-pyridyl)aminomethylenemalonate (*Vd*)

This was prepared from *IIIf* according to the procedure described for *Vc*. Yield 50% (counted on 2,6-dichloro-3-nitropyridine *IIa*), m.p. 96°C. For $C_{13}H_{14}F_2N_2O_4$ (300·3) calculated: 52·00% C, 4·70% H, 12·65% F, 9·33% N; found: 52·15% C, 4·82% H, 12·84% F, 9·48% N.

Ethyl 6-Chloro-8-(4-ethoxycarbonyl-1-piperazinyl)-4-hydroxy-1,7-naphthyridine-3-carboxylate (*VIa*)

Compound *Va* (1 g, 2·2 mmol) was added into boiling diphenyl ether (5 ml) and the mixture was refluxed for 10 min and then poured into cyclohexane (50 ml), crystalline product was filtered off and washed with cyclohexane. Repeated crystallization from ethanol yielded 0·24 g (27%), m.p. 154°C. For $C_{18}H_{21}ClN_4O_5$ (408·8) calculated: 52·88% C, 5·18% H, 8·67% Cl, 14·70 N; found: 52·78% C, 5·19% H, 8·74% Cl, 14·17% N. IR spectrum: 1 539 (heteroaromat. system), 1 708 (COO).

Ethyl 6,8-Dichloro-4-hydroxy-1,7-naphthyridine-3-carboxylate (*VIc*)

Compound *Vc* (20 g, 0·06 mol) was added into boiling diphenyl ether (200 ml) and the mixture was refluxed for 1 h. cooled down and poured into petroleum ether (250 ml), the precipitate was filtered off and washed with a mixture of petroleum eher and ethyl acetate 1 : 1. Crystallization from N,N-dimethylformamide yielded 9·2 g (53%) of *VIc*, m.p. 298—302°C. For $C_{11}H_8Cl_2N_2O_3$ (287·1) calculated: 46·02% C, 2·81% H, 24·70% Cl, 9·76% N; found: 46·07% C, 2·76% H, 24·69% Cl, 9·75% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 4·24 q, 2 H (CH_2, $J = 7$); 7·95 s, 1 H (H-5); 8·43 s, 1 H (H-2). IR spectrum: 1 528 (heteroaromat. system), 1 707 (COO).

Ethyl 6,8-Difluoro-4-hydroxy-1,7-naphthyridine-3-carboxylate (*VId*)

The compound was prepared from *Vd* (20 g, 67 mmol) according to the procedure described for the preparation of *VIc*; yield 8·1 g (48%), m.p. 274—275°C. For $C_{11}H_8F_2N_2O_3$ (254·2) calculated: 51·98% C, 3·17% H, 14·95% F, 11·02% N; found: 51·72% C, 3·17% H, 14·78% F, 10·82% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 4·24 q, 2 H (CH_2, $J = 7$); 7·56 d, 1 H (H-5, $J_{H,F} = 3$); 8·45 s, 1 H (H-2). IR spectrum: 1 532, 1 558 (heteroaromat. system), 1 707 (COO).

Ethyl 6-Chloro-4-hydroxy-8-morpholino-1,7-naphthyridine-3-carboxylate (*VIe*)

To a stirred suspension of *VIc* (1·44 g, 5 mmol) in N,N-dimethylformamide (30 ml) was added morpholine (1·75 g, 20 mmol) and the mixture was stirred at 100°C for 1 h. Then most of the solvent was evaporated under reduced pressure, the residue was triturated with water (100 ml) and the solid was filtered off and dried. Column chromatography on silica gel (ethyl acetate) followed by crystallization from ethanol yielded 1·16 g (69%), of yellow crystals, m.p. 169—173°C. For $C_{15}H_{16}ClN_3O_4$ (337·8) calculated: 53·34% C, 4·77% H, 10·50% Cl, 12·44% N; found: 53·05% C, 4·74% H, 10·66% Cl, 12·23% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 3·40 bt, 4 H (H-3′, H-5′ of morpholine); 3·85 bt, 4 H (H-2′, H-6′ of morpholine); 4·24 q, 2 H (CH_2, $J = 7$); 7·54 s, 1 H (H-5); 8·44 s, 1 H (H-2). ^{13}C NMR spectrum: 14·19 q (CH_3), 49·60 t (C-3′, C-5′ of morpholine), 62·52 t (CH_2), 67·08 t (C-2′, C-6′ of morpholine), 105·25 d (C-5), 106·29 s (C-3), 127·91 s (C-4a), 136·89 s (C-8a), 144·46 s (C-6), 146·85 d (C-2), 157·31 s (C-8), 165·00 s (COO), 169·63 s (C-4). IR spectrum: 1 511, 1 543 (heteroaromat. system), 1 717 (COO).

Ethyl 6-Fluoro-4-hydroxy-8-morpholino-1,7-naphthyridine-3-carboxylate (*VIf*)

Reaction of *VId* with morpholine was performed at 60°C under conditions mentioned for the synthesis of *VIe*. The same isolation provided 83% of *VIf*, m.p. 169—171°C. For $C_{15}H_{16}FN_3O_4$ (321·3) calculated: 56·07% C, 5·02% H, 5·91% F, 13·08% N; found: 55·86% C, 5·06% H, 6·01% F, 12·97% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 3·30 bt, 4 H (H-3′, H-5′ of morpholine); 3·84 bt, 4 H (H-2′, H-6′ of morpholine); 4·24 q, 2 H (CH_2, $J = 7$); 7·18 d, 1 H (H-5, $J_{H,F} = 3$); 8·44 s, 1 H (H-2). IR spectrum: 1 548, 1 594 (heteroaromat. system), 1 718 (COO).

Ethyl 6-Chloro-1-ethyl-1,4-dihydro-8-morpholino-4-oxo-1,7-naphthyridine-3-carboxylate (*VIIa*)

A mixture of *VIe* (1·7 g, 5 mmol), potassium carbonate (5 g, 36 mmol) and N,N-dimethylformamide (30 ml) was stirred at 100°C for 30 min and then iodoethane (6·2 g, 40 mmol) was added and the mixture was stirred at 100°C for 6 h. Then additional potassium carbonate (5 g, 36 mmol) and iodoethane (6·2 g, 40 mmol) were added and the mixture was stirred at 100°C for further 6 h. Most of the solvent was evaporated under reduced pressure, the residue was triturated with water (100 ml), the insoluble portion was filtered off, dissolved in ethyl acetate and dried with sodium sulfate. The solution was purified by column chromatography on silica gel (toluene–ethyl acetate 1 : 1) followed by crystallization from ethanol; yield 0·8 g (44%) of *VIIa*, m.p. 191°C. For $C_{17}H_{20}ClN_3O_4$ (365·8) calculated: 55·82% C, 5·51% H, 9·69% Cl, 11·49% N; found: 55·59% C, 5·44% H, 9·81% Cl, 11·56% N. ^{1}H NMR spectrum: 1·04 t, 3 H (CH_3 of N-ethyl, $J = 7$); 1·30 t, 3 H (CH_3, $J = 7$); 3·30 m, 4 H (H-3′, H-5′ of morpholine); 3·80 bt, 4 H (H-2′, H-6′ of morpholine); 4·24 q, 2 H (CH_2, $J = 7$); 4·65 q, 2 H (CH_2 of N-ethyl, $J = 7$); 7·60 s, 1 H (H-5); 8·65 s, 1 H (H-2). IR spectrum: 1 535, 1 564 (heteroaromat. system), 1 644 (C=O), 1 720 (COO). UV spectrum, λ_{max} (log ε): 210 (3·49), 325 (3·19).

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-8-morpholino-4-oxo-1,7-naphthyridine-3-carboxylate (*VIIb*) and Ethyl 4-Ethoxy-6-fluoro-8-morpholino-1,7-naphthyridine-3-carboxylate (*VIIIb*)

The same conditions as described for the synthesis of *VIIa* were applied. Column chromatography on silica gel (toluene–ethyl acetate 1 : 1) yielded 48% of crude product (17% after double crystallization from ethanol) of *VIIb*, m.p. 135—138°C and 20% of crude product (8% after crystallization from ethanol) of *VIIIb*, m.p. 109—110°C, and about 10% of crude starting compound

VId. For $C_{17}H_{20}FN_3O_4$ (349·4) calculated: 58·42% C, 5·73% H, 5·44% F, 12·03% N. For *VIIb* found: 58·42% C, 5·81% H, 5·81% F, 12·15% N. ^{1}H NMR spectrum: 1·06 t, 3 H (CH_3 of N-ethyl, $J = 7$); 1·31 t, 3 H (CH_3, $J = 7$); 3·30 m, 4 H (H-3′, H-5′ of morpholine); 3·80 bm, 4 H (H-2′, H-6′ of morpholine); 4·26 q, 2 H (CH_2, $J = 7$); 4·66 q, 2 H (CH_2 of N-ethyl, $J = 7$); 7·26 d, 1 H (H-5, $J_{H,F} = 3$); 8·67 s, 1 H (H-2). ^{13}C NMR spectrum: 13·52 q (CH_3 of N-ethyl), 14·34 q (CH_3), 48·03 t (N—CH_2), 49·60 t (C-3′, C-5′ of morpholine), 59·23 t (CH_2), 64·91 (C-2′, C-6′ of morpholine), 94·68 d (C-5, $J_{F,C} = 39$), 110·87 s (C-3), 123·47 s (C-8a), 141·20 s (C-4a), 150·59 d (C-2), 152·60 s (C-8, $J_{F,C} = 15$), 157·23 s (C-6, $J_{F,C} = 246$), 163·43 s (COO), 170·53 (C-4). IR spectrum: 1 548, 1 586 (heteroaromat. system), 1 645 (C=O), 1 675 (COO). UV spectrum, λ_{max}, (log ε): 225 (3·21), 314 (3·14).

6-Chloro-1-ethyl-1,4-dihydro-8-morpholino-4-oxo-1,7-
-naphthyridine-3-carboxylic Acid (*VIIc*)

The mixture of *VIIa* (0·3 g, 1 mmol), ethanol (10 ml), and 20% aqueous hydrochloric acid (5 ml) was refluxed for 30 min. The mixture was evaporated in vacuo and the residue was triturated with water (20 ml), the solid was collected by filtration and crystallized from mixture of ethanol and acetone; yield 0·27 g, (80%), m.p. 278—281°C. For $C_{15}H_{16}ClN_3O_4$ (337·8) calculated: 53·34% C, 4·77% H, 10·50% Cl, 12·44% N; found: 53·14% C, 4·79% H, 10·25% Cl, 12·02% N.

1-Ethyl-6-fluoro-1,4-dihydro-8-morpholino-4-oxo-1,7-
-naphthyridine-3-carboxylic Acid (*VIId*)

Using the same conditions as for the synthesis of *VIIc* we recieved *VIId* from *VIIb* in 82% yields, m.p. 257—265°C. For $C_{15}H_{16}FN_3O_4$ (321·3) calculated: 56·07% C, 5·02% H, 5·91% F, 13·08% N; found: 55·79% C, 5·05% H, 5·75% F, 13·03% N.

Ethyl 4-Chloro-6-fluoro-8-morpholino-1,7-naphthyridine-3-carboxylate (*VIIIc*)

A mixture of *VIf* (0·4 g, 1·1 mmol) and phosphorus oxychloride (3 ml) was refluxed for 2 h, evaporated under reduced pressure and the residue was triturated with water and then extracted with ethyl acetate (50 ml). The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (toluene–ethyl acetate 1 : 1) and crystallization from ethanol yielded 0·25 g (66%), m.p. 134—136°C. For $C_{15}H_{15}ClFN_3O_3$ (339·8) calculated: 53·03% C, 4·45% H, 10·43% Cl, 5·59% F, 12·37% N; found: 52·89% C, 4·43% H, 10·49% Cl, 5·87% F, 12·70% N. ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3, $J = 7$); 3·78 bt, 4 H (H-3′, H-5′ of morpholine); 4·16 bt, 4 H (H-2′, H-6′ of morpholine); 4·46 q, 2 H (CH_2, $J = 7$); 6·91 d, 1 H (H-5, $J_{H,F} = 3$); 8·92 s, 1 H (H-2). IR spectrum: 1 545, 1 589 (heteroaromat. system), 1 732 (COO).

Ethyl 4-Ethoxy-6-fluoro-8-morpholino-1,7-naphthyridine-3-crboxylate (*VIIIb*)

Compound *VIIIc* (0·3 g, 0·9 mmol) was added to ethanol (20 ml) in which sodium (0·023 g, 1 mmol) had been dissolved. The mixture was stirred at 60°C for 2 h, evaporated in vacuo and purified by column chromatography on silica gel (toluene–ethyl acetate 1 : 1) and crystallized from ethanol; yield 0·2 g (64%), m.p. 110°C. For $C_{1'}H_{20}FN_3O_4$ calculated: (349·4) 58·42% C, 5·73% H, 5·44% F, 12·03% N; found: 58·42% C, 5·75% H, 5·53% F, 11·89% N. ^{1}H NMR spectrum: 1·37 t, 3 H (CH_3, $J = 7$); 1·40 t, 3 H (CH_3 of ethoxy, $J = 7$); 3·30 bt, 4 H (H-3′, H-5′ of morpholine); 3·75 bt, 4 H (H-2′, H-6′ of morpholine); 4·22 q, 2 H (CH_2, $J = 7$); 4·40 q, 2 H (CH_2 of ethoxy, $J = 7$); 6·84 d, 1 H (H-5, $J_{H,F} = 3$); 8·82 s, 1 H (H-2). ^{13}C NMR spectrum: 13·37 q* (CH_3), 14·71 q* (CH_3 of ethoxy), 48·48 t (C-3′, C-5′ of morpholine), 61·10 t (CH_2),

65·81 t (C-2′, C-6′ of morpholine), 71·04 t (CH_2 of ethoxy, 85·38 d (C-5, $J_{F,C} = 41$), 116·97 s (C-3), 132·51 s (C-4a, $J_{H,F} = 10$), 135·42 s (C-8a, $J_{F,C} = 4$), 146·03 d (C-2), 155·34 s (C-8, $J_{C,F} = 18$), 158·62 s (C-6, $J_{F,C} = 231$), 160·74 s (C-4), 163·96 s (COO). IR spectrum: 1 847, 1 546, 1 592 (heteroaromat. system), 1 720 (COO). UV spectrum, λ_{max}, (log ε): 245 (3·32), 312 (2·90), 371 (2·83).

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