Reactions of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one with active methylene compounds: a new efficient route to 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones

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3-Substituted 1,8-naphthyridine-2,4-diones, compounds of very important pharmaceutical use, have been synthesized using a new efficient route. The reaction of 2-methyl-4*H*-pyrido-[2,3-*d*][3,1]oxazin-4-one, 1b, with active methylene compounds furnishes the 1-acetyl-3-substituted-4-hydroxy-1,8-naphthyridin-2-ones 3–5, in good yields. In the case of cyanoacetic esters the intermediate *C*-acylation compounds 7 and 8 were isolated and subsequently cyclized to 1-acetyl-3-cyano-4-hydroxy-1,8-naphthyridin-2-one 6. Spectral data and physical characteristics for all compounds are reported.

1,8-Naphthyridine-2,4-dione derivatives (X = N, Fig. 1), substituted at position 3, form a class of fused ring heterocycles which present interesting pharmacological and biological properties. These compounds occur widely among natural products and have importance in medicine. A series of substituted 1,8-naphthyridin-2(1*H*)-ones are orally active, potent inhibitors of allergic and non-allergic bronchospasm in animal models.[1] Recent reports describe a class of 1-aryl-1,8-naphthyridinone derivatives as potent, orally active inhibitors of the release of the leukotriene mediators of anaphylaxis *in vitro* and *in vivo*.[2] Moreover, 3-carboxy-1,8-naphthyridin-2-one derivatives showed potent gastric anti-secretory properties in rat models.[3]

Recently, novel anti-inflammatory drugs having the 1,8-naphthyridine structure, with a mode of action different from that of the classical acidic nonsteroidal anti-inflammatory drugs (NSAIDs), were designed and synthesized by Suzuki *et al*.[4] Several immunomodulators such as roquinimex and Sch 12 223 (Fig. 2), containing the 4-hydroxyquinolinone and 4-hydroxynaphthyridinone system have been reported.[5] The 1,8-naphthyridine skeleton in Sch 12 223 is known to be a bioisostere of quinoline.[4]

1,8-Naphthyridine derivatives have proved to inhibit type IV phosphodiesterase and are therefore useful in the treatment of respiratory, inflammatory, systemic or local joint diseases, inflammations accompanying organ transplantation, diseases associated with urination and those involving tumour necrosis factors and other cytokines.[6a] Numerous 1,8-naphthyridine derivatives are useful as modulators of cytokine synthesis, immunomodulatory and anti-inflammatory agents.[6b]

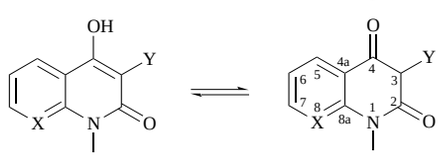
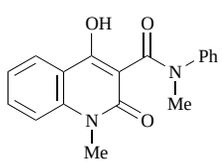
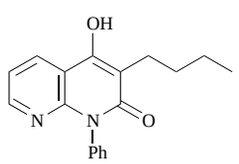


Fig. 1



Roquinimex (LS-2616)



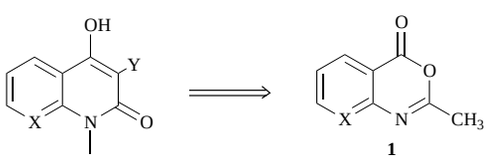
Sch 12223

Fig. 2

The importance of these fused ring heterocycles has encouraged the development of numerous routes for their preparation. The 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones have been prepared by a standard Dieckmann condensation using azaisatoic anhydride derivatives[4,7] or 2-aminonicotinic acid esters as starting material.[1,2c,3,8] Alternatively, 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones have been synthesized by thermal condensation of 2-aminopyridines with malonic esters.[9] However, most of the above methods are less than convenient, since they require several steps and vigorous conditions.

As part of our program for the synthesis and evaluation of nitrogen heterocycles containing the 'enolic β-dicarbonyl moiety', such as 3-substituted 4-hydroxypyrrolin-2-ones (tetramic acids)[10a] we have recently described a new approach for the synthesis of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones (X = CH, Fig. 1).[10b] Our interest in 1,8-naphthyridinones arose from their gross similarity to quinolinones and our desire to prepare 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones possessing the 'enolic β-dicarbonyl moiety'.

In the 3-substituted 4-hydroxyquinolin-2(1*H*)-one (X = CH) series we used the 2-methyl-3,1-benzoxazin-4-one **1a** as starting material (Scheme 1). This compound was replaced by the 2-



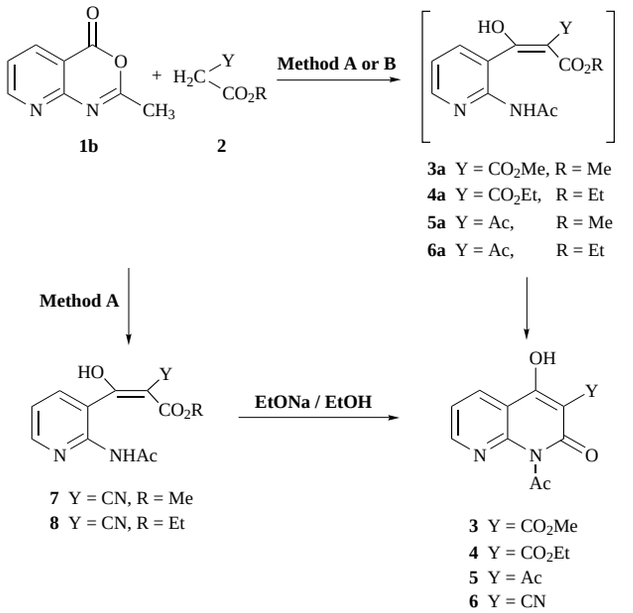
X=CH or N

1

a X=CH
b X=N

Scheme 1

methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one **1b** in order to synthesize the corresponding 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones. The new synthetic approach includes the *C*-acylation of an active methylene compound with an oxazinone, the 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one, **1b**. The intermediate **3a**, **4a** or **5a,b** (not isolated) undergoes an *in situ* intramolecular cyclization to a 3-substituted 4-hydroxy-1,8-



Scheme 2 *Reagents and conditions:* Method A: Bu^{t}OK–Bu^{t}OH, room temp.; Method B: NaH–anhydrous benzene, room temp.

naphthyridin-2(1*H*)-one (Scheme 2). In a typical *C*-acylation–cyclization the active methylene compound **2** (3 mol equiv.) was treated with potassium *tert*-butoxide (2 mol equiv.) in *tert*-butyl alcohol or sodium hydride (3 mol equiv.) in anhydrous benzene at room temperature. After *ca*. 15 min, 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one **1b** (1 mol equiv.) was added to the mixture which was then stirred for 30 min–1 h before treatment with water and diethyl ether; the aqueous layer on acidification gave the 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones, in good yields (60–80%, see Experimental section).

The active carbon of the methylene compound ultimately becomes the 3-carbon of the naphthyridine ring and any substituents attached to this carbon will subsequently reside in the correct position, while the azabenzoxazinone ring supplies the remainder of the molecule. The 2-methyl-4*H*-pyrido[2,3-*d*]-[3,1]oxazin-4-one has been known to be a useful synthon as an acylating agent in which both the carboxylate activation and the amino group protection are achieved simultaneously.

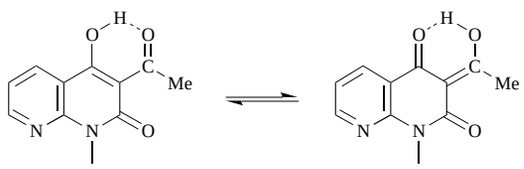
It is suggested that the *in situ* conversion of compound **1b** into **3**, **4** or **5** involves the intermediate formation of **3a**, **4a** or **5a,b**, respectively. Attempts to isolate such intermediates in a pure form were unsuccessful. However, reinvestigation by ^{1}H NMR of the transformation of compound **1b** into the cyclized compounds revealed, in addition to the signals of the final product, the presence of signals which are attributed to the formation of the intermediate compounds **3a**, **4a** or **5a,b** during the course of the *C*-acylation–cyclization reactions.

In the case of cyanoacetic esters the *C*-acylation compounds **7** and **8** were isolated in their enolic form, in good yields (60–70%) without further cyclization under the reaction conditions (Scheme 2) . In an attempt to induce cyclization, compounds **7** and **8** were heated in refluxing ethanol–benzene using sodium ethoxide (2 equiv.). After 3 h, consumption of the *C*-acylation compound was completed and a new product, the 1-acetyl-3-cyano-4-hydroxy-1,8-naphthyridin-2-one, **6**, was formed.

The structure of the newly prepared *C*-acylation compounds **7** and **8** was assigned on the basis of their analytical and spectral data (see Experimental section). Characteristically, the IR spectra of the above *C*-acylation compounds show a sharp nitrile absorption at 2210 cm^{-1} and two absorption bands for the β-keto ester in the 1720–1670 cm^{-1} range, attributable to the carbonyl of the keto and enol forms. It is noteworthy that the IR spectrum of the cyclization product **6** still exhibits a characteristic prominent nitrile absorption at 2200 cm^{-1}, therefore ruling out cyclization with the nitrile.

The ^{1}H NMR spectra of the cyclization products **3**, **4** and **5** show an enol hydrogen at 15.56–15.70 ppm as a broad signal. The 2,4-diketone form (Fig. 1) can be readily ruled out on the basis of ^{1}H NMR spectral data by the lack of the methinyl proton at position 3. All the aromatic protons are sharply differentiated with the expected multiplicity, H-5 being observed at 8.98–9.06 ppm, H-6 at 7.48–7.73 ppm and H-7 at 9.26–9.93 ppm. Integration of these signals gave the ratio 1:1:1. Structure assignment was made by comparison with data reported in the literature for products of similar structure.[11]

Compounds **3**, **4** and **5** are of additional interest since they have the potential to exist in the tautomeric enolic forms **a** and **b**, as shown in Scheme 3. Since only one set of signals is



Scheme 3

observed in the ^{1}H NMR spectra, in $CDCl_3$ solution, it is assumed that if tautomerism exists, it is fast on the NMR time-scale.[10a]

In conclusion, we have described a new and efficient route to the preparation of 3-substituted 1,8-naphthyridine-2,4-diones using the 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one as starting material. Current research is dedicated towards further application of the proposed method to the synthesis of compounds containing the 1,8-naphthyridine-2,4-dione system bearing various substituents on the aromatic ring and the 3-position, using the suitably substituted oxazinones and the appropriate active methylene compounds.

Experimental

Mps were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 spectrometer. The NMR spectra were recorded on either Varian EM-360 60 MHz or Varian Unity Plus 300 MHz spectrometers, using Me_4Si as internal reference. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

Preparation of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one, 1b

2-Aminonicotinic acid (1.9 g, 0.014 mol) was added to acetic anhydride (10 ml) and the mixture was refluxed at 165–170 °C for *ca*. 1 h. The solution, after being cooled to <80 °C, was evaporated *in vacuo*. Light petroleum was added to the solid residue formed to give 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one **1b** as a solid (2.23 g, 90%), mp 165–166 °C (lit.,[12] mp 175–178 °C). The product thus obtained was used for the *C*-acylation-cyclization reactions without further purification.

General procedures for the reactions of active methylene compounds with 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one

Method A. Potassium *tert*-butoxide (2.24 g, 0.02 mol) was stirred in *tert* butyl alcohol (100 ml) at room temperature until it dissolved (*ca*. 15 min) after which the active methylene compound **2** (0.03 mol) was added dropwise to the mixture. Stirring was continued for 1 h after which compound **1b** (1.4 g, 0.01 mol) was added to the mixture and stirring continued at room temperature for 30 min–1 h. Water and diethyl ether were added to the reaction mixture and the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice–water bath.

The precipitate thus formed was filtered off and washed with water.

Method B. The active methylene compound **2** (0.03 mol) was added dropwise to a mixture of sodium hydride (55–60% sodium hydride in oil; 0.03 mol) in anhydrous benzene (90 ml) and the thick, white slurry thus formed was stirred at room temperature for 1 h. Compound **1b** (1.4 g, 0.01 mol) was added to the mixture and stirring continued for 1–2.5 h. Water and diethyl ether were added to the reaction mixture, and the aqueous layer was separated and acidified with 10% hydrochloric acid, in an ice–water bath. The precipitate thus formed was filtered off and washed with water.

1-Acetyl-3-methoxycarbonyl-4-hydroxy-1,8-naphthyridin-2-one 3. *Following method A*.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), dimethyl malonate **2** (Y = CO_2Me, R = Me) (4 g, 0.03 mol) and potassium *tert*-butoxide (2.24 g, 0.02 mol) in *tert*-butyl alcohol 100 ml)] was stirred for 30 min after which it was acidified with 10% hydrochloric acid to give a coloured precipitate. This was filtered off and washed with water to afford the product **3** (2.13 g, 82%), mp 175–176 °C (from $CHCl_3$).

Following method B.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), dimethyl malonate **2** (Y = CO_2Me, R = Me) (4 g, 0.03 mol) and sodium hydride (0.03 mol) in anhydrous benzene (100 ml)] was stirred for 1 h after which it was acidified with 10% hydrochloric acid to give a coloured precipitate. This was filtered off and washed with water to afford the product **3** (1.23 g, 48%), mp 173–175 °C (from $CHCl_3$) (Found: C, 54.94; H, 3.97; N, 10.67. $C_{12}H_{10}O_5N_2$ requires C, 54.96; H, 3.84; N, 10.68%); δ_H(60 MHz; $CDCl_3$; Me_4Si) 2.70 (3 H, s, $COCH_3$), 4.00 (3 H, s, CO_2CH_3), 7.50 (1 H, pseudotriplet, 6-H), 9.06 (1 H, dd, $J_{5,6}$ 7, $J_{5,7}$ 1, 5-H), 9.33 (1 H, dd, $J_{6,7}$ 7, $J_{5,7}$ 1, 7-H) and 15.56 (1 H, br, OH).

1-Acetyl-3-ethoxycarbonyl-4-hydroxy-1,8-naphthyridin-2-one 4. *Following method A*.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), diethyl malonate **2** (Y = CO_2Et, R = Et) (4.8 g, 0.03 mol) and potassium *tert*-butoxide (2.24 g, 0.02 mol) in *tert*-butyl alcohol (100 ml)] was stirred for 30 min after which it was acidified with 10% hydrochloric acid to give a coloured precipitate. This was filtered off and washed with water to afford the product **4** (2.37 g, 87%) mp 155–157 °C (from $CHCl_3$).

Following method B.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), diethyl malonate **2** (Y = CO_2Et, R = Et) (4.8 g, 0.03 mol) and sodium hydride (0.03 mol) in anhydrous benzene (100 ml)] was stirred for 1 h after which it was acidified with 10% hydrochloric acid to give a coloured precipitate. This was filtered off and washed with water to afford the product **4** (1.35 g, 40%), mp 157–159 °C (from $CHCl_3$) (Found: C 56.70; H 4.46; N 10.25. $C_{13}H_{12}O_5N_2$ requires C, 56.52; H, 4.38; N, 10.14%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.43 (3 H, t, *J* 7,CH_2CH_3), 2.68 (3 H, s, $COCH_3$), 4.46 (2 H, q, *J* 7, CH_2CH_3), 7.48 (1 H, pseudotriplet, 6-H), 9.00 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,7}$ 1.6, 5-H), 9.28 (1 H, dd, $J_{6,7}$ 6.5, $J_{5,7}$ 1.6, 7-H) and 15.89 (1 H, br, OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 164.51 (CO ester), 163.09 (C-4), 162.22 (C-2), 153.91 ($COCH_3$), 149.30 (C-8a), 144.68 (C-7), 132.05 (C-5), 122.49 (C-4a), 116.22 (C-6), 109.77 (C-3), 62.03 (CH_2CH_3), 23.27 ($COCH_3$) and 14.21 (CH_2CH_3).

1,3-Diacetyl-4-hydroxy-1,8-naphthyridin-2-one 5. *Following method A*.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), methyl acetoacetate **2** (Y = COMe, R = Me) (2.3 g, 0.02 mol) or ethyl acetoacetate **2** (Y = COMe, R = Et) (2.6 g, 0.02 mol) and potassium *tert*-butoxide (2.24 g, 0.02 mol) in *tert*-butyl alcohol (130 ml)] was stirred for 1 h. Compound **5** was obtained as a solid [1.88 g (62%) when methyl acetoacetate was used as the active methylene compound and 1.53 g (50%) when ethyl acetoacetate was used as the active methylene compound] mp 170–171 °C (from $CHCl_3$).

Following method B.—The reaction mixture [compound **1b** (1.4 g, 0.01 mol), methyl acetoacetate **2** (Y = COMe, R = Me) (3.5 g, 0.03 mol) or ethyl acetoacetate **2** (Y = COMe, R = Et) (3.9 g, 0.03 mol) and sodium hydride (0.03 mol) in anhydrous benzene (100 ml)] was stirred for 1 h. Compound **5** was obtained as a solid [2.04 g (67%) when methyl acetoacetate was used as the active methylene compound and 1.64 g (54%) when ethyl acetoacetate was used as the active methylene compound], mp 167–170 °C (from $CHCl_3$) (Found: C, 58.01; H, 4.07; N, 11.38. $C_{12}H_{10}O_4N_2$ requires C, 58.53; H, 4.09; N, 11.38%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.69 (6 H, s, $COCH_3$ and *N*-$COCH_3$), 7.50 (1 H, pseudotriplet, 6-H), 8.98 (1 H, dd, $J_{5,6}$ 7.5, $J_{5,7}$ 1.9, 5-H), 9.26 (1 H, dd, $J_{6,7}$ 7.5, $J_{5,7}$ 1.9, 7-H) and 15.75 (1 H, br, OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 198.81 (C-*C*OCH_3), 163.87 (C-4), 163.00 (C-2), 155.30 (N-*C*OCH_3), 149.18 (C-8a), 144.85 (C-7), 131.90 (C-5), 122.56 (C-4a), 116.37 (C-6), 115.04 (C-3), 31.87 (C-CO*C*H_3) and 23.91 (N-CO*C*H_3).

Methyl [(2-acetylamino-3-pyridyl)hydroxymethylidene]cyanoacetate 7. *Following method A*.—The reaction mixture was stirred at room temperature for 1 h to give the *C*-acylation product **7** as a solid (1.57 g, 65%), mp 176–178 °C (from EtOH) (Found: C, 55.18; H, 4.36; N, 15.87. $C_{12}H_{11}O_4N_3$ requires C, 55.17; H, 4.24; N, 16.09%); ν_{max}(Nujol)/cm^{-1} 2210s (CN), 1720 and 1700s (CO ester, keto form) and 1600s (C=C ring stretching); δ_H(60 MHz; $CDCl_3$; Me_4Si) 2.80 (3 H, s, $COCH_3$), 3.78 (3 H, s, CO_2CH_3), 7.08 (1 H, dd, $J_{4,5}$ 8, $J_{5,6}$ 5, 5-H), 8.25–8.48 (2 H, m, 4-H and 6-H), 9.30 (1 H, br, NH) and 12.76 (1 H, br, OH).

Ethyl [(2-acetylamino-3-pyridyl)hydroxymethylidene]cyanoacetate 8. *Following method A*.—The reaction mixture was stirred at room temperature for 1 h to give the *C*-acylation product **8** as a solid (1.80 g, 71%), mp 106–108 °C (from $CHCl_3$) (Found: C 56.67; H 4.82; N 15.91. $C_{13}H_{13}O_4N_3$ requires C, 56.72; H, 4.76; N, 15.27%); ν_{max}(Nujol)/cm^{-1} 3500m (OH), 2210w (CN), 1710w (CO ester, keto form), 1670s (CO ester, enol form) and 1600s (C=C ring stretching); δ_H(60 MHz; $CDCl_3$; Me_4Si) 1.36 (3 H, t, *J* 7, CH_2CH_3), 2.83 (3 H, s, $COCH_3$), 4.26 (2 H, q, *J* 7, CH_2CH_3), 7.09 (1 H, dd, $J_{4,5}$ 8, $J_{5,6}$ 5, 5-H), 8.28–8.53 (2 H, m 4-H and 6-H), 7.73 (1 H, br, NH) and 12.83 (1 H, br, OH).

1-Acetyl-3-cyano-4-hydroxy-1,8-naphthyridin-2-one 6. The *C*-acylation compound [0.002 mol **7** (0.50 g) or **8** (0.55 g)] dissolved in a small quantity of ethanol was added to a solution of sodium ethoxide in ethanol [prepared from sodium (0.09 g, 4 mmol) in absolute ethanol (10 ml)] containing anhydrous benzene (10 ml). The reaction mixture was refluxed for 3 h and set aside overnight at room temperature. Water and diethyl ether were then added to the reaction mixture after which the aqueous layer was separated, acidified with 10% hydrochloric acid and extracted with ethyl acetate and diethyl ether. The organic layers were combined, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting red solid was triturated with diethyl ether, filtered off and washed with small amounts of diethyl ether to give the title compound **6** [0.26 g (59%) from **7** and 0.25 g (60%) from **8**], mp 213–214 °C; ν_{max}(Nujol)/cm^{-1} 2210w (CN), 1690m (CO stretching, amide I) and 1610 (C=C ring stretching); δ_H(60 MHz; $CDCl_3$–[$^2H_6$]DMSO; Me_4Si) 2.76 (3 H, s, $COCH_3$), 6.78 (1 H, br, OH), 7.73 (1 H, pseudotriplet, 6-H), 9.00 (1 H, dd, $J_{5,6}$ 8, $J_{5,7}$ 1, 5-H) and 9.93 (1 H, dd, $J_{6,7}$ 8, $J_{5,7}$ 1, 7-H).

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