A TANDEM *C*-ACYLATION-CYCLIZATION REACTION SEQUENCE FOR THE SYNTHESIS OF NEW *N*-ACYL-3-SUBSTITUTED 1,8-NAPHTHYRIDINE-2,4-DIONES

Alexandros Zografos, Christos Mitsos, and Olga Igglessì-Markopoulou*

Laboratory of Organic Chemistry, Department of Chemical Engineering, National Technical University of Athens, Zografou Campus 157 73 Athens, Greece

Abstract- The 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-ones (**1a, b**) react with active methylene compounds, under mild conditions, to produce *N*-acyl-3-substituted 1,8-naphthyridine-2,4-diones (**3-12**). In addition the *C*-acylation key intermediates (**3a**), (**13**) and (**14**) have been isolated and subsequently cyclized to the corresponding 3-substituted 1,8-naphthyridine-2,4-diones (**3**) and (**15**).

The 3-substituted 1,8-naphthyridine-2,4-diones (Figure 1, X=N) constitute an expanding class of fused ring heterocycles, which display a range of interesting pharmacological and biological properties.[1-8]

1,8-Naphthyridinone-3-carboxylic acid derivatives were investigated thoroughly in the past years and many representatives were found to show antiallergic and gastric antisecretory properties.[1]

In recent years many clinically important antibacterials, collectively known as "*quinolones*" have become a significant class of chemotherapeutic agents.[2] The influence of the structure activity relationship of varying substituents in the naphthyridinone (Figure 1, X=N) or quinolinone (X=C) skeleton was extensively studied.[3]

A particularly potent member of this class of compounds is nalidixic acid (Figure 2, i). In addition, these agents selectively inhibit bacterial DNA *gyrase* relative to mammalian topoisomerase II [4,5] and this mode of action is characteristic of "*quinolones*" as excellent antibacterial agents.

A series of 1,8-naphthyridin-2-one derivatives with appropriate substituents, represent a new class of potent and highly selective *N*-methyl-D-aspartate (NMDA) receptor glycine site antagonists.[6] Moreover, *N*-phenyl-1,8-naphthyridin-2-one derivatives have been shown to exhibit extremely potent anti-inflammatory or antiasthmatic activities.[6] Suzuki *et al.*[7] have described the 5-HT_3 receptor antagonistic

activity of a series of quinolinone and naphthyridinone-3-carboxylic acid derivatives.

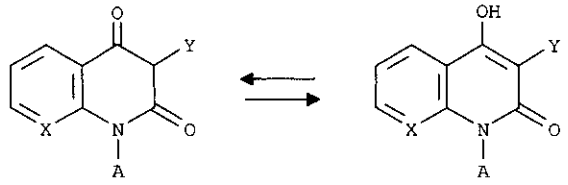
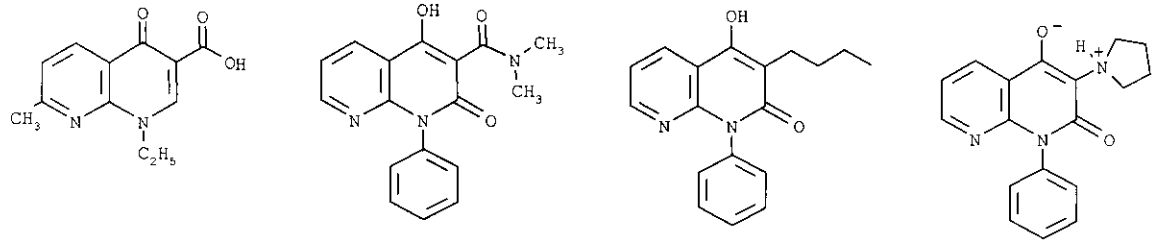


Figure 1

Furthermore, 4-hydroxy-1,8-naphthyridin-2-one-3-carboxamide derivatives (Figure 2, ii) possess a broader spectrum of anti-inflammatory activities than the classical non steroidal anti-inflammatory drugs (NSAIDS).[8]

The 1,8-naphthyridine skeleton in immunomodulator Sch 12223 (Figure 2, iii) is known to be a bioisostere of quinoline.[8]



(i) *nalidixic acid* (ii) *4-hydroxy-1,8-naphthyridin-2-one-3-carboxamide* (iii) *Sch 12223* (iv) *Sch 37224*

Figure 2

3-Substituted 1,8-naphthyridine-2,4-diones form a unique class of potent inhibitors of allergic and nonallergic bronhospasm in animal models. The mechanism of antiallergy activity may involve inhibition of the release of the sulfopeptide leukotrienes (LTs).[9,10] A class of tricyclic derivatives of the 4-hydroxy-1,8-naphthyridin-2-one system (Figure 2, iv) have been potent, orally active inhibitors of the release of the leukotriene mediators of anaphylaxis *in vivo* and *in vitro*.[11,12]

Although many methods are now available for the synthesis of 1,8-naphthyridine-2,4-diones,[13] the searches for new methodologies continue, mainly with a view to their use in the synthesis of new potential agents with a wide range of biological and pharmaceutical activities.

The 3-substituted 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones were prepared in most cases by treating of 2-substituted amino nicotinic acid esters with ethyl malonyl chloride followed by Dieckmann-like ring closure of the *N*-acylated intermediate.[12]

Similarly, 3-alkyl-4-hydroxy-7-methyl-1,8-naphthyridin-2-ones have been prepared by an alternative route involving the thermal condensation of 2-aminopyridines with malonic esters.[14] Significant contributions to the methodology of 1,8-naphthyridinone ring construction have been made by a number of workers[15] who investigated the reaction of aza-isatoic anhydride with the anions of active methylene compounds.

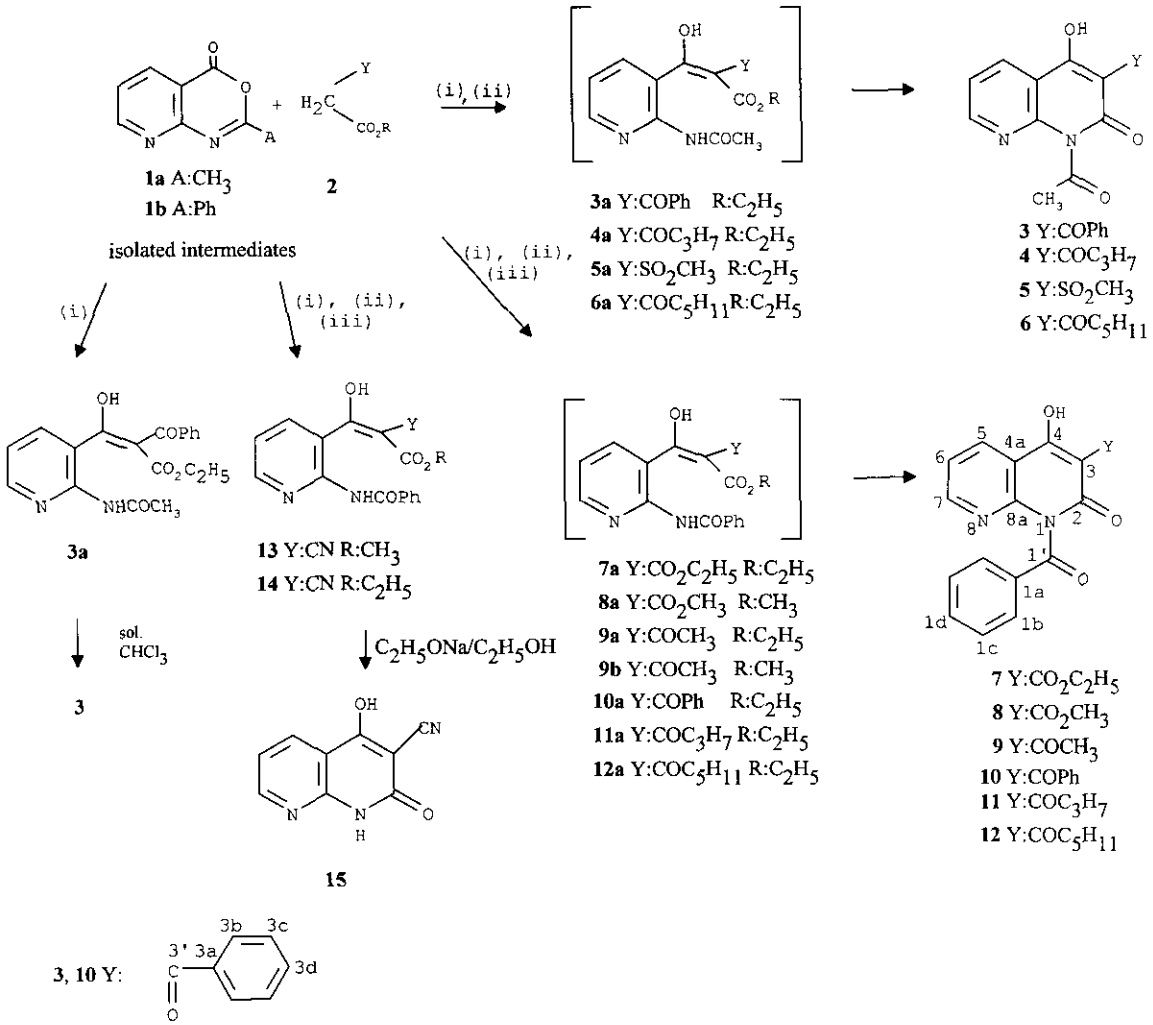
In continuation of our interest in the synthesis of novel functionally substituted nitrogen fused heterocycles of expected biological importance,[16] we wish to report here the successful application of our previously described methodology to the synthesis of 3-substituted 4-hydroxy-1,8-naphthyridin-2-ones, using a simple heterocycle, the 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one, as starting material.

The synthetic routes leading to the novel 3-substituted 1,8-naphthyridine-2,4-diones are summarized in Scheme 1. Our strategy involves the condensation of 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one (**1a, b**) with the anion of active methylene compounds (**2**). Under the basic reaction conditions, the non isolated *C*-acylation intermediates (**3a-12a**) were converted *in situ* into the corresponding *N*-acetyl- or *N*-benzoyl-3-substituted 4-hydroxy-1,8-naphthyridin-2-ones (**3-12**) *via* an intramolecular condensation mechanism, without loss of the acetyl or benzoyl group itself. In the case of cyanoacetic esters, the important intermediates (**13**) and (**14**) were isolated and then cyclized using sodium ethoxide in ethanol. In addition, the intermediate (**3a**) was isolated as a solid product, which was cyclized rapidly to the corresponding *N*-acetyl-3-benzoyl-4-hydroxy-1,8-naphthyridin-2-one (**3**).

A systematic exploration of the base-solvent system, the ratio of reactants and the reaction times, provided conditions where the *N*-acyl-1,8-naphthyridine-2,4-diones (**3-12**) and the *C*-acylation compounds (**13**), and (**14**) were isolated in reasonable yields. Extrapolation of these reaction conditions to the isolation of the *C*-acylation products (**3a-12a**), produces messy reactions and only minor amount of the product (**3a**) being isolated. Nevertheless, the isolation of the ethyl [(2-acetylamino-3-pyridyl)hydroxy-methylidene]benzoyl acetate (**3a**) even in low yield (*ca.* 30%) was encouraging and provided a basis for potential optimization of the *C*-acylation reaction **1→3a-12a**. Furthermore, transformation of (**3a**) into the corresponding 1-acetyl-3-benzoyl-4-hydroxy-1,8-naphthyridin-2-one (**3**) was achieved by treatment of (**3a**) with 10% hydrochloric acid in few seconds. In addition the cyclization process **3a→3** took place smoothly in chloroform solution in several hours at ambient temperature. This transformation was readily monitored by ^{1}H NMR (Figure 3). Complete disappearance of the *C*-acylation compound (**3a**) served to indicate the complete transformation into compound (**3**).

In a typical *C*-acylation-cyclization reaction, (Scheme 1), 2 equiv. of the active methylene compound (**2**) were treated with 2 equiv. of potassium *tert*-butoxide in *tert*-butyl alcohol or sodium hydride in anhydrous benzene or tetrahydrofuran. After *ca.* 60 min, 1equiv. of 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one (**1**) was added to the reaction mixture which was then stirred for 1.5-2 h before treatment with water and

ether. The aqueous layer in acidification gave the products (**3-12**).

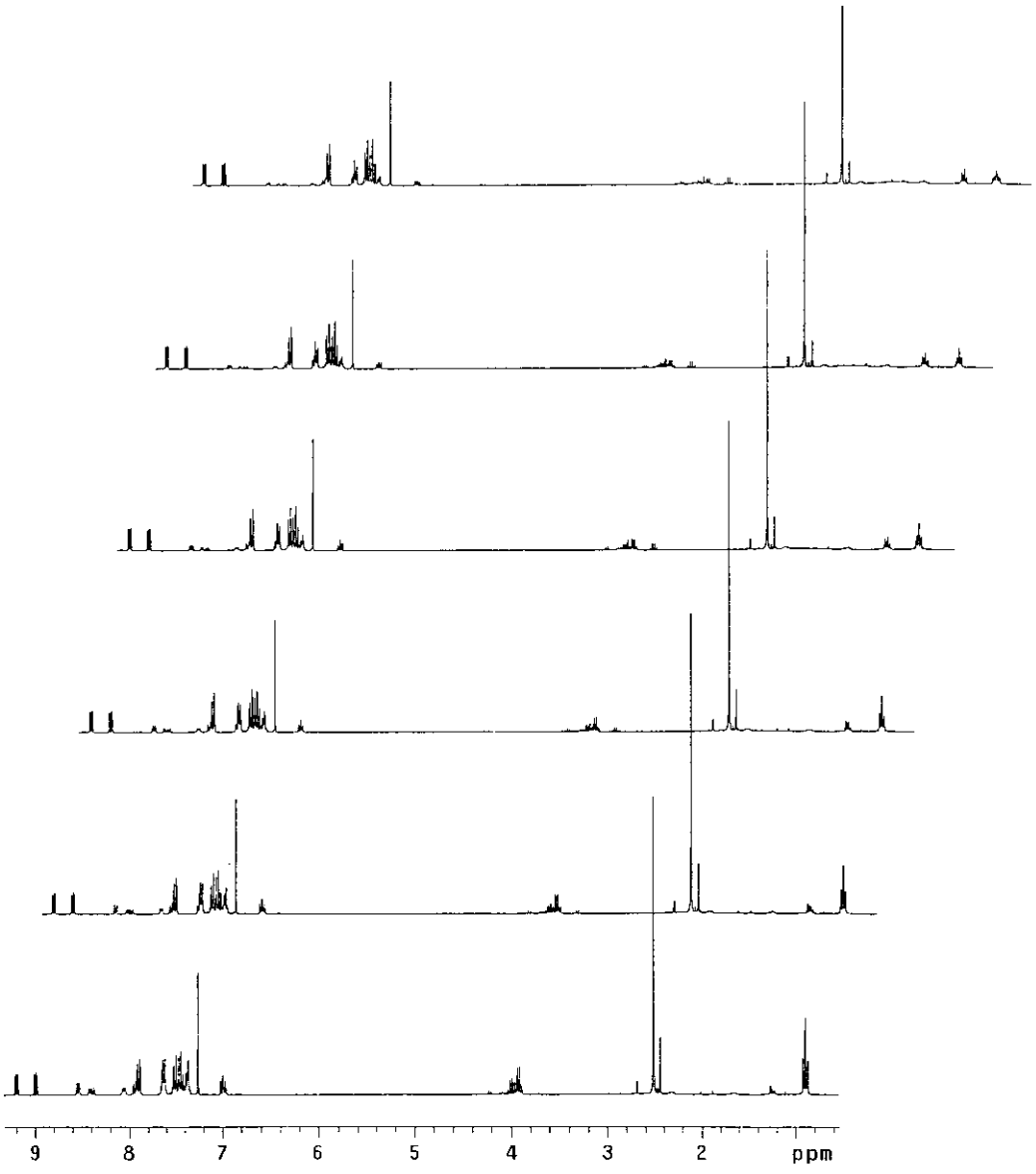


Reagents and condition: (i) Method A: *t*-C_4H_9OK - *t*-C_4H_9OH, rt; (ii) Method B: NaH - anhydrous benzene, rt; (iii) Method C: NaH - anhydrous THF, rt.

Scheme 1

In the case of cyanoacetic esters (**2**) (Y=CN) the *C*-acylation intermediates, alkyl [(2-benzoylamino-3-pyridyl)hydroxymethylidene]cyanoacetates (**13**) (R=CH_3) and (**14**) (R=C_2H_5) were isolated as solid products in good yields. Cyclization of the *C*-acylation compounds (**13**) and (**14**) was affected by refluxing them with 2 equiv. of sodium ethoxide in ethanol. Work up of the reaction mixture gave the 3-cyano-4-hydroxy-1,8-naphthyridin-2-one (**15**) as pure solid in good yield (80%).

The structures of the newly obtained compounds were established by elemental analysis and spectroscopic data (see EXPERIMENTAL).



The transfomation of **3a**→**3** by ^{1}HNMR spectra in $CDCl_3$ (spectra every two hours).

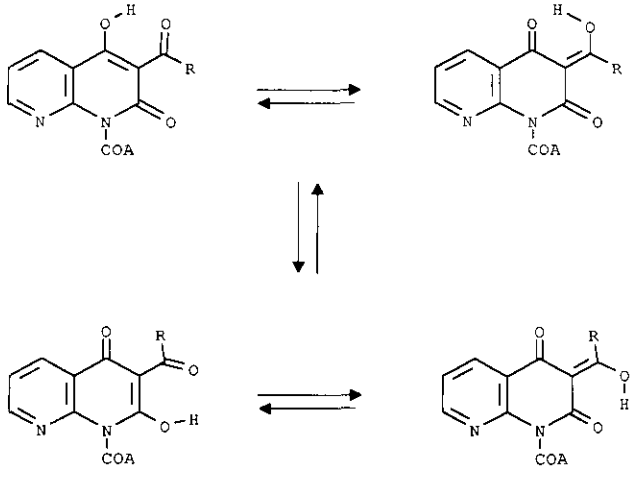
Figure 3

The IR spectra of the newly prepared *N*-acyl-3-substituted 1,8-naphthyridine-2,4-diones (see EXPERIMENTAL section) showed characteristic CO absorption at 1730-1720 cm^{-1} for the β-dicarbonyl system CO-CH-CO (keto form), at 1680-1670 cm^{-1} for the dicarbonyl system C(OH)=C-CO (enol form) and the amide carbonyl. The band at 1570-1560 cm^{-1} is attributed to the carbon-carbon double bond absorption.

The IR spectra of the new *C*-acylation compounds (**13**) and (**14**) are characterized by absorption at 3500 cm^{-1} (OH stretching of water), a strong cyano band at 2200 cm^{-1}, two bands at 1720 and 1670 cm^{-1} for the β-dicarbonyl system CO-CH-CO, C(OH)=C-CO (keto and enol form, respectively) and the amide carbonyl absorption. The band at 1570 cm^{-1} should be assigned to carbon-carbon double bond.

The ^1H NMR spectra indicate that no signals which might correspond to sp^3-CH group for the 1,8-naphthyridine-2,4-dione system could be detected. In addition, these compounds must exist in their enolic form as shown from the enol proton at 15.6-15.9 ppm as a broad signal (exchangeable protons). All the heteroaromatic protons of the cyclization products appear at 7.40-9.40 ppm, 5-H as doublet of doublets at 8.75-9.05 ppm, 6-H as pseudotriplet at 7.40-7.85 ppm and 7-H as doublet of doublets at 9.15-9.40 ppm, in the ratio of 1:1:1.

The 4-hydroxy-1,8-naphthyridin-2-ones, bearing an alkoxy carbonyl (**7**), (**8**) or an acyl group (**3**), (**4**), (**6**), (**9-12**) at position 3, have several interesting structural possibilities for enol-enol tautomerism and hydrogen bonding. A single set of signals can be observed in the ^1H and ^{13}C NMR spectra of these compounds, indicating that if the tautomeric interconversion showed in Scheme 2 exist, is fast on the NMR time scale, at room temperature.



Keto-enol tautomeric forms of 3-substituted 1,8-naphthyridine-2,4-dione

Scheme 2

The ^{13}C assignments of the newly prepared compounds are based on the off resonance decoupling.

The chemical shifts are given in the Experimental section. The assignments were made according to data reported in the literature for related molecules.[17]

CONCUSION

In conclusion, we have developed an efficient synthesis of 1,3-disubstituted 1,8-naphthyridine-2,4-diones utilizing simple building blocks as reaction inputs. Our goal in the present study is to employ a tandem *C*-acylation-cyclization reaction sequence that provides direct access to new *N*-acyl-3-substituted 1,8-napthyridine-2,4-diones. The reaction proceeds *via* the formation of novel intermediates which are initially formed and undergo a base-induced intramolecular cyclization.

EXPERIMENTAL

Melting points were determined on a Galenkamp MFB-595 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 267 spectrophotometer. NMR spectra were recorded on a Varian Gemini 2000, 300 MHz spectrometer. 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 at the University of Liverpool.

I. 2-Substituted 4*H*-Pyrido[2,3-*d*][3,1]oxazin-4-ones (1a, b).

The 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-ones were prepared according to earlier publications[16,18] and they were used without further purification.

II. General procedures for the reactions of active methylene compounds with 2-substituted 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-ones.

Method A: Potassium *tert*-butoxide (0.5 g, 4.5 mmol) was stirred in *tert*-butyl alcohol (25 mL) at rt until it dissolved, after which the appropriate active methylene compound (4.5 mmol) was added dropwise to the solution and the mixture was stirred for 1 h. Compound (**1**) (2.2 mmol) was then added to the mixture and stirring continued at rt for 1.5-2 h. Water was added until the salt was dissolved. The colored solution was extracted with ether 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 cold water.

Method B or C: To a suspension of sodium hydride (55-60% sodium hydride in oil) (0.5 g, 11 mmol) in 20 mL of anhydrous benzene (Method B) or in 20 mL of anhydrous THF (Method C) was added dropwise, the appropriate methylene compound (11 mmol). The mixture was stirred for 1 h at rt. Compound (**1**) (5.5 mmol) was then added to the mixture and stirring continued for 1.5-2 h. The solvent was evaporated *in vacuo* and the residue was dissolved with water, extracted with ether and the aqueous layer acidified with 10% aqueous hydrochloric acid and extracted with chloroform. The chloroform layer was evaporated *in vacuo* to give an oily residue which triturated with light petroleum ether. The solid was filtered off and washed with petroleum ether.

1-Acetyl-3-benzoyl-4-hydroxy-1,8-naphthyridin-2-one (3). *Following method A.*-The reaction mixture [compound (**1a**) (0.36 g, 2.2 mmol), ethyl benzoylacetate (**2**) (Y=COPh, R=C_2H_5) (0.86 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**3**) (0.32 g, 48%).

Following method B.- The reaction mixture [compound (**1a**) (0.89 g, 5.5 mmol), ethyl benzoylacetate (**2**) (Y=COPh, R= C_2H_5) (2.10 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**3**) (0.19 g, 11%), mp 206-211 °C (from $CHCl_3$/petroleum ether). Anal. Calcd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.90; N, 9.09. Found: C, 65.96; H, 3.86; N, 9.01. IR (Nujol) cm^{-1}: 1700s (C=O ester, keto form), 1670m (C=O ester, enol form and CO, amide) and 1560 (C=C ring streching). ^{1}HNMR ($CDCl_3$) δ: 2.50 (3H, s, $COCH_3$), 7.44 (1H, pseudotriplet, 6-H), 7.46-7.92 (5H, m, COPh), 8.98 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 7, 5-H), 9.19 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 7, 7-H) and 15.87 (1H, br, OH). ^{13}CNMR ($CDCl_3$) δ: 192.8 (*C*OPh), 163.3 (C-4), 161.3 (C-2), 154.6 (N-*C*OCH_3), 149.5 (C-8a), 144.5 (C-7), 136.7 (C-3a), 134.3 (C-5), 131.9 (C-3d), 129.4 (C-3b), 129.0 (C-3c), 122.6 (C-4a), 116.1 (C-6), 115.5 (C-3), 22.4 ($COCH_3$).

1-Acetyl-3-butanoyl-4-hydroxy-1,8-naphthyridin-2-one (4). *Following method A.*-The reaction mixture [compound (**1a**) (0.36 g, 2.2 mmol), ethyl butanoylacetate (**2**) (Y=COC_3H_7, R=C_2H_5) (0.71 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**4**) (0.28 g, 47%).

Following method B.- The reaction mixture [compound (**1a**) (0.89 g, 5.5 mmol), ethyl butanoylacetate (**2**) (Y=COC_3H_7, R= C_2H_5) (1.74 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**4**) (0.12 g, 8%), mp 182-186 °C (from $CHCl_3$/ petroleum ether). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.48; H, 5.12; N, 10.18. IR (Nujol) cm^{-1}: 1730s (C=O ester, keto form), 1680m (C=O ester, enol form and CO, amide) and 1570 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 0.96 (3H, t, J = 2, $CH_2CH_2CH_3$), 1.69 (2H, m, $CH_2CH_2CH_3$), 2.56 (3H, s, $COCH_3$), 2.99 (2H, t, J = 7, $CH_2CH_2CH_3$), 7.70 (1H, pseudotriplet, 6-H), 8.96 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 7, 5-H) and 9.32 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 7, 7-H). ^{13}CNMR ($(CD_3)_2CO$) δ: 203.1 (COC_3H_7), 164.0 (C-4), 162.8

(C-2), 156.6 (N-*C*OCH_3), 150.8 (C-8a), 145.7 (C-7), 133.3 (C-5), 123.3 (C-4a), 117.6 (C-6), 116.2 (C-3),

45.9 ($CH_2CH_2CH_3$), 23.1 ($COCH_3$), 18.1 ($CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_3$).

1-Acetyl-3-methylsulfonyl-4-hydroxy-1,8-naphthyridin-2-one (5). *Following method A.*-The reaction mixture [compound (**1a**) (0.36 g, 2.2 mmol), ethyl methylsulfonylacetate (**2**) (Y=SO_2CH_3, R=C_2H_5) (0.74 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**5**) (0.26 g, 42%), mp 197-199 °C (from $CHCl_3$/ petroleum ether). Anal. Calcd for $C_{11}H_{10}N_2O_5S \cdot 1/3\ H_2O$: C, 45.83; H, 3.47; N, 9.72. Found: C, 45.68; H, 3.50; N, 9.49. IR (Nujol) cm^{-1}: 1730s (C=O ester, keto form), 1620m (C=O ester, enol form and CO, amide) and 1570 (C=C ring streching), 1130m (S=O streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 2.90 (3H, s, $COCH_3$), 3.35 (3H, s, SO_2CH_3), 7.81 (1H, pseudotriplet, 6-H), 9.06 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 7, 5-H) and 9.37 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 7, 7-H). ^{13}CNMR (DMSO-d_6) δ: 163.9 (C-4), 163.5 (C-2), 154.1 (N-$COCH_3$), 149.2 (C-8a), 144.4 (C-7), 132.2 (C-5), 124.2 (C-4a), 117.9 (C-6), 114.6 (C-3), 43.2 (SO_2CH_3), 24.1 ($COCH_3$).

1-Acetyl-3-hexanoyl-4-hydroxy-1,8-naphthyridin-2-one (6). *Following method A.*-The reaction mixture [compound (**1a**) (0.36 g, 2.2 mmol), ethyl hexanoylacetate (**2**) (Y=COC_5H_{11}, R=C_2H_5) (0.84 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**6**) (0.20 g, 30%), mp 179-182 °C (from $CHCl_3$/ petroleum ether). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 5.97; N, 9.24. IR (Nujol) cm^{-1}: 1710s (C=O ester, keto form), 1660m (C=O ester, enol form and CO, amide) and 1540 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 0.89 [3H, t, J = 2, $(CH_2)_4CH_3$], 1.34 [4H, m, $(CH_2)_2(CH_2)_2CH_3$], 1.69 [2H, m, $CH_2CH_2(CH_2)_2CH_3$], 2.56 (3H, s, N-$COCH_3$), 3.01 [2H, t, J = 3, $CH_2(CH_2)_3CH_3$], 7.70 (1H, pseudotriplet, 6-H), 8.96 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 5, 5-H), 9.33 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 5, 7-H) and 15.64 (1H, br, OH). ^{13}CNMR ($(CD_3)_2CO$) δ: 203.2 (COC_5H_{11}), 164.0 (C-4), 162.8 (C-2), 156.6 (N-$COCH_3$), 150.8 (C-8a), 145.7 (C-7), 133.4 (C-5), 123.3 (C-4a), 117.6 (C-6), 116.3 (C-3), 44.0 [$COCH_2(CH_2)_3CH_3$], 32.3 [$COCH_2CH_2(CH_2)_2CH_3$], 24.4 [$CO(CH_2)_2CH_2CH_2CH_3$], 23.2 [$CO(CH_2)_3CH_2CH_3$], 23.1 ($COCH_3$), 14.1 [$CO(CH_2)_4CH_3$].

1-Benzoyl-3-ethoxycarbonyl-4-hydroxy-1,8-naphthyridin-2-one (7). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), diethyl malonate (**2**) (Y=$CO_2C_2H_5$, R=C_2H_5) (0.72 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**7**) (0.52 g, 70%).

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), diethyl malonate

(**2**) (Y=$CO_2C_2H_5$, R=C_2H_5) (1.76 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 mL) (method C)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**7**), (0.48 g, 26%) for method B, and (1.15 g, 62%) for method C, mp 188-190 °C (from methanol). Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.73; H, 4.14; N, 8.28. IR (Nujol) cm^{-1}: 1710s (C=O ester, keto form), 1650m (C=O ester, enol form and CO, amide) and 1570 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) *δ:* 1.11 (3H, t, *J* = 7, CH_2CH_3), 4.20 (2H, q, *J* = 7, CH_2CH_3), 7.58-7.75 (6H, m, COPh and 6-H), 8.99 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 9.32 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H); ^{13}CNMR ($(CD_3)_2CO$) *δ:* 165.0 ($CO_2CH_2CH_3$), 164.0 (C-4), 158.5 (C-2), 155.0 (C-1′), 149.4 (C-8a), 143.4 (C-7), 136.6 (C-1a), 132.0 (C-5), 131.0 (C-1d), 129.2 (C-1b), 127.9 (C-1c), 124.1 (C-4a), 117.1 (C-6), 108.9 (C-3), 61.4 (CH_2CH_3), 13.5 (CH_2CH_3).

1-Benzoyl-3-methoxycarbonyl-4-hydroxy-1,8-naphthyridin-2-one (8). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), dimethyl malonate (**2**) (Y=CO_2CH_3, R= CH_3) (0.59 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**8**) (0.46 g, 65%).

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), dimethyl malonate (**2**) (Y=CO_2CH_3, R= CH_3) (1.45 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 mL) (method C)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**8**), (0.21 g, 12%) for method B, and (0.68 g, 38%) for method C, mp 209-212 °C (from methanol). Anal. Calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.73; N, 8.64. Found: C, 63.01; H, 3.71; N, 8.62. IR (Nujol) cm^{-1}: 1710s (C=O ester, keto form), 1640m (C=O ester, enol form and CO, amide) and 1570 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) *δ:* 3.73 (3H, s, CO_2CH_3), 7.60-7.76 (6H, m, COPh and 6-H), 8.99 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 6, 5-H) and 9.33 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ =6, 7-H). ^{13}CNMR ($(CD_3)_2CO$) *δ:* 166.4 (CO_2CH_3), 164.0 (C-4), 159.2 (C-2), 155.9 (C-1′), 151.3 (C-8a), 145.7 (C-7), 137.7 (C-1a), 133.3 (C-5), 132.0 (C-1d), 130.1 (C-1b), 128.9 (C-1c), 124.0 (C-4a), 117.8 (C-6), 108.7 (C-3), 52.8 (CO_2CH_3).

1-Benzoyl-3-acetyl-4-hydroxy-1,8-naphthyridin-2-one (9). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), ethyl acetoacetate (**2**) (Y=$COCH_3$, R=C_2H_5) (0.58 g, 4.5 mmol) or methyl acetoacetate (**2**) (Y=$COCH_3$, R=CH_3) (0.52 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10%

hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**9**), (0.49 g, 73%) from ethyl acetoacaetate, or (0.52 g, 77%) from methyl acetoacetate.

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), ethyl acetoacetate (**2**) (Y=$COCH_3$, R=C_2H_5) (1.43 g, 11 mmol) or methyl acetoacetate (**2**) (Y=$COCH_3$, R=CH_3) (1.28 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 mL) (method C)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford product (**9**), (0.20 g, 12%) for method B, and (0.27 g, 16%) for method C, mp 211-214 °C (from methanol). Anal. Calcd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.26; H, 3.91; N, 9.08. IR (Nujol) cm^{-1}: 1700s (C=O ester, keto form), 1650m (C=O ester, enol form and CO, amide) and 1550 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 2.53 (3H, s, $COCH_3$) 7.54-7.65 (5H, m, COPh), 7.73 (1H, pseudotriplet, 6-H), 8.99 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 9.35 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H). ^{13}CNMR (DMSO-d_6) δ: 200.1 (*C*OCH_3), 164.1 (C-4), 158.9 (C-2), 155.7 (C-1′), 149.2 (C-8a), 143.6 (C-7), 136.9 (C-1a), 132.1 (C-5), 130.7 (C-1d), 129.1 (C-1b), 128.6 (C-1c), 123.8 (C-4a), 117.2 (C-6), 116.0 (C-3), 31.7 (*COC*H_3).

1,3-Dibenzoyl-4-hydroxy-1,8-naphthyridin-2-one (10). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), ethyl benzoylacetate (**2**) (Y=COPh, R=C_2H_5) (0.86 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**10**) (0.42 g, 52%).

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), ethyl benzoylacetate (**2**) (Y=COPh, R= C_2H_5) (2.11 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 mL) (method C)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**10**), (0.20 g, 10%) for method B, and (0.47 g, 23%) for method C, mp 268-270 °C (from methanol). Anal. Calcd for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.27; H, 3.78; N, 7.53. IR (Nujol) cm^{-1}: 1710s (C=O ester, keto form), 1660m (C=O ester, enol form and CO, amide) and 1560 (C=C ring streching). ^{1}HNMR (DMSO-d_6) δ: 7.40-7.94 (10H, m, protons of COPh and *N*-COPh), 7.60 (1H, pseudotriplet, 6-H), 8.79 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 9.16 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H). ^{13}CNMR (DMSO-d_6) δ: 193.5 (C-3′), 164.2 (C-4), 158.3 (C-2), 155.9 (C-1′), 149.6 (C-8a), 143.4 (C-7), 137.0 (C-3a), 136.4 (C-1a), 134.2 (C-1d, C-3d), 132.0 (C-5), 130.8 (C-1c), 129.5 (C-1b), 129.1 (C-3b), 128.4 (C-3c), 123.7 (C-4a), 117.0 (C-6), 114.2 (C-3).

1-Benzoyl-3-butanoyl-4-hydroxy-1,8-naphthyridin-2-one (11). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), ethyl butanoylacetate (**2**) (Y=COC_3H_7, R=C_2H_5) (0.71 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**11**) (0.50 g, 67%).

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), ethyl butanoylacetate (**2**) (Y=COC_3H_7, R= C_2H_5) (1.74 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 mL) (method C)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**11**), (0.20 g, 11%) for method B, and (0.76 g, 41%) for method C, mp 158-160 °C (from methanol). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.88; H, 4.78; N, 8.30. IR (Nujol) cm^{-1}: 1710s (C=O ester, keto form), 1670m (C=O ester, enol form and CO, amide) and 1560 (C=C ring streching). ^{1}HNMR (DMSO-d_6) δ: 0.79 [3H, t, J = 2, $(CH_2)_2CH_3$], 1.50 (2H, m, $CH_2CH_2CH_3$), 2.71 (2H, t, J = 7, $CH_2CH_2CH_3$), 7.51-7.56 (5H, m, COPh), 7.59 (1H, pseudotriplet, 6-H), 8.75 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H), 9.19 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H). ^{13}CNMR (DMSO-d_6) δ: 202.5 (COC_3H_7), 164.1 (C-4), 158.1 (C-2), 155.4 (C-1′), 149.1 (C-8a), 142.5 (C-7), 136.7 (C-1a), 132.0 (C-5), 130.8 (C-1d), 129.1 (C-1b), 128.5 (C-1c), 123.7 (C-4a), 117.1 (C-6), 116.1 (C-3), 45.4 ($CH_2CH_2CH_3$), 16.6 ($CH_2CH_2CH_3$), 13.4 [$(CH_2)_2CH_3$].

1-Benzoyl-3-hexanoyl-4-hydroxy-1,8-naphthyridin-2-one (12). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), ethyl hexanoyl acetate (**2**) (Y=COC_5H_{11}, R=C_2H_5) (0.84 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**12**) (0.36 g, 46%), mp 107-110°C (from methanol). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.22; H, 5.51; N, 7.67. IR (Nujol) cm^{-1}: 1730s (C=O ester, keto form), 1660m (C=O ester, enol form and CO, amide) and 1550 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 0.84 [3H, t, J = 7, $(CH_2)_4CH_3$], 1.22 [4H, m, $(CH_2)_2(CH_2)_2CH_3$], 1.58 [2H, m, $CH_2CH_2(CH_2)_2CH_3$], 2.78 [2H, t, J = 7, $CH_2(CH_2)_3CH_3$], 7.56-7.66 (5H, m, COPh), 7.72 (1H, pseudotriplet, 6-H), 8.98 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 7, 5-H) and 9.33 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 7, 7-H). ^{13}CNMR ($(CD_3)_2CO$) δ: 202.7 (COC_5H_{11}), 164.1 (C-4), 159.3 (C-2), 156.6 (C-1′), 150.9 (C-8a), 145.4 (C-7), 137.9 (C-1a), 133.2 (C-5), 131.6 (C-1d), 129.9 (C-1b), 129.6 (C-1c), 123.8 (C-4a), 117.8 (C-3), 117.6 (C-6), 44.5 [$CH_2(CH_2)_3CH_3$], 31.8 [$CH_2CH_2(CH_2)_2CH_3$], 23.8 [$(CH_2)_2CH_2CH_2CH_3$], 23.0 [$(CH_2)_3CH_2CH_3$], 14.1 [$(CH_2)_4CH_3$].

Ethyl [(2-acetylamino-3-pyridyl)hydroxymethylidene]benzoylacetate (3a). *Following method A.*-The reaction mixture [compound (**1a**) (0.36 g, 2.2 mmol), ethyl benzoylacetate (**2**) (Y=COPh, R=C_2H_5) (0.86 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 30 min after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**3a**) .

The product (**3a**) was cyclized rapidly to **3** (within 4 h in chloroform or in few seconds on 10% hydrochloric acid) so the reaction described must be controlled with chromatographic methods, as thin layer chromatography, in order to have a pure product (0.20 g, 30%). ^{1}HNMR ($CDCl_3$) δ: 7.40-7.94 (10H, m, protons of COPh and *N*-COPh), 6.95 (1H, dd, $J_{6,5}$ = 3, $J_{6,7}$ = 7 6-H), 8.42 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 8.57 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H), 15.9 (1H, broad, OH).

Methyl [(2-benzoylamino-3-pyridyl)hydroxymethylidene]cyanoacetate (13). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), methyl cyanoacetate (**2**) (Y=CN, R=CH_3) (0.44 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**13**) (0.51 g, 72%).

Following method B or C.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), methyl cyanoacetate (**2**) (Y=CN, R=CH_3) (1.09 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL) (method B) or in anhydrous THF (20 ml) (method C)] was stirred for 2 h after which it was evaporated and acidified with 10% hydrochloric acid to give an oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**13**), (0.21 g, 12%) for method B, and (0.62 g, 35%) for method C, mp 135-139 °C (from methanol). Anal. Calcd for $C_{17}H_{13}N_3O_4 \cdot 1/3H_2O$: C, 62.01; H, 3.95; N, 12.76. Found: C, 62.40; H, 4.11; N, 12.77. IR (Nujol) cm^{-1}: 3500 (OH stretching), 2200s (CN), 1720s (C=O ester, keto form), 1670m (C=O ester, enol form and CO, amide) and 1570 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 3.88 (3H, s, CO_2CH_3), 7.44-8.10 (6H, m, COPh and 6-H), 8.23 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 8.62 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H).

Ethyl [(2-benzoylamino-3-pyridyl)hydroxymethylidene]cyanoacetate (14). *Following method A.*-The reaction mixture [compound (**1b**) (0.49 g, 2.2 mmol), ethyl cyanoacetate (**2**) (Y=CN, R=C_2H_5) (0.51 g, 4.5 mmol) and potassium *tert*-butoxide (0.5 g, 4.5 mmol) in *tert*-butyl alcohol (25 mL)] was stirred for 2 h after which it was acidified with 10% hydrochloric acid to give a precipitate. This was filtered off and washed with cold water to afford the product (**14**) (0.50 g, 68%).

Following method B.- The reaction mixture [compound (**1b**) (1.23 g, 5.5 mmol), ethyl cyanoacetate (**2**) (Y=CN, R=C_2H_5) (1.24 g, 11 mmol) and sodium hydride (0.5 g, 11 mmol) in anhydrous benzene (20 mL)] was stirred for 2 h after which it was evaporated and acidified with 10% hydrochloric acid to give an

oily residue. Petroleum ether was added and the precipitate was filtered off and washed with cold water to afford the product (**14**) (0.18 g, 10%) with no further purification, mp 135-139 °C. Anal. Calcd for $C_{18}H_{13}N_3O_4 \cdot 1/3H_2O$: C, 62.97; H, 4.37; N, 12.24. Found: C, 62.89; H, 4.39; N, 12.26. IR (Nujol) cm^{-1}: 3550 (OH streching), 2210s (CN), 1720s (C=O ester, keto form), 1670m (C=O ester, enol form and CO, amide) and 1560 (C=C ring streching). ^{1}HNMR ($(CD_3)_2CO$) δ: 1.31 (3H, t, J = 7, CH_2CH_3), 4.35 (2H, q, J = 7, CH_2CH_3), 7.43-8.10 (6H, m, COPh and 6-H), 8.22 (1H, dd, $J_{5,7}$ = 1, $J_{5,6}$ = 7, 5-H) and 8.63 (1H, dd, $J_{7,5}$ = 1, $J_{7,6}$ = 7, 7-H).

3-Cyano-4-hydroxy-1,8-naphthyridin-2-one (15).

The *C*-acylation compound [2.0 mmol, (**13**) (0.65 g) or (**14**) (0.67 g)]was added in a solution of sodium ethoxide in absolute ethanol [prepared from sodium (0.09 g, 4.0 mmol) in absolute ethanol (10 mL)] and was stirred under reflux for 5 h. The mixture was then evaporated *in vacuo* to give the product salt. Water was added until the salt is dissolved and acidified with 10% hydrochloric acid. The product was extracted with chloroform. The extract was dried with sodium sulfate and evaporated *in vacuo* to give the solid product (**15**) (0.3 g, 80%). ^{1}HNMR (DMSO-d_6) δ: 7.25 (1H, dd, $J_{6,5}$ = 5, $J_{6,7}$ = 8, 6-H), 8.35 (1H, dd, $J_{5,7}$ = 2, $J_{5,6}$ = 8, 5-H), 8,56 (1H, dd, $J_{7,5}$ = 2, $J_{7,6}$ = 8, 7-H). ^{13}CNMR (DMSO-d_6) δ: 170.5 (C-4), 162.2 (C-2), 153.0 (C-7), 150.5 (C-8a), 133.9 (C-5), 118.3 (C-6), 116.0 (C-4a), 111.3 (C-3), 85.9 (-CN).

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