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SYNTHESIS OF SOME NEW 4 - HYDROXY - 1,8 - NAPHTHYRIDIN - 2 - ONE DERIVATIVES

E.A. MOHAMED, R.M. ABDEL-RAHMAN, Z. EL-GENDY & M.M. İSMAİL

Dept. of Chemistry, Faculty of Education, Ain Shams University Roxy, Cairo-EGYPT.

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ABSTRACT

Some new 4-hydroxy-1, 8-naphthyridin-2-one derivatives have been synthesized and reacted with some reagents giving: pyrono, acetoxy, arylmethylidynes, nitro, sulphonic, sulphonylchloride, sulphonamide, sulphide, sulphine, oxathiine glyoxalyl chloride, formylchloride, amides, azodyes, acetamide, isonitroso, cyanomethyl and methyl derivatives. The structures of all the new compounds have been established on the basis of elemental analysis and spectroscopic data.

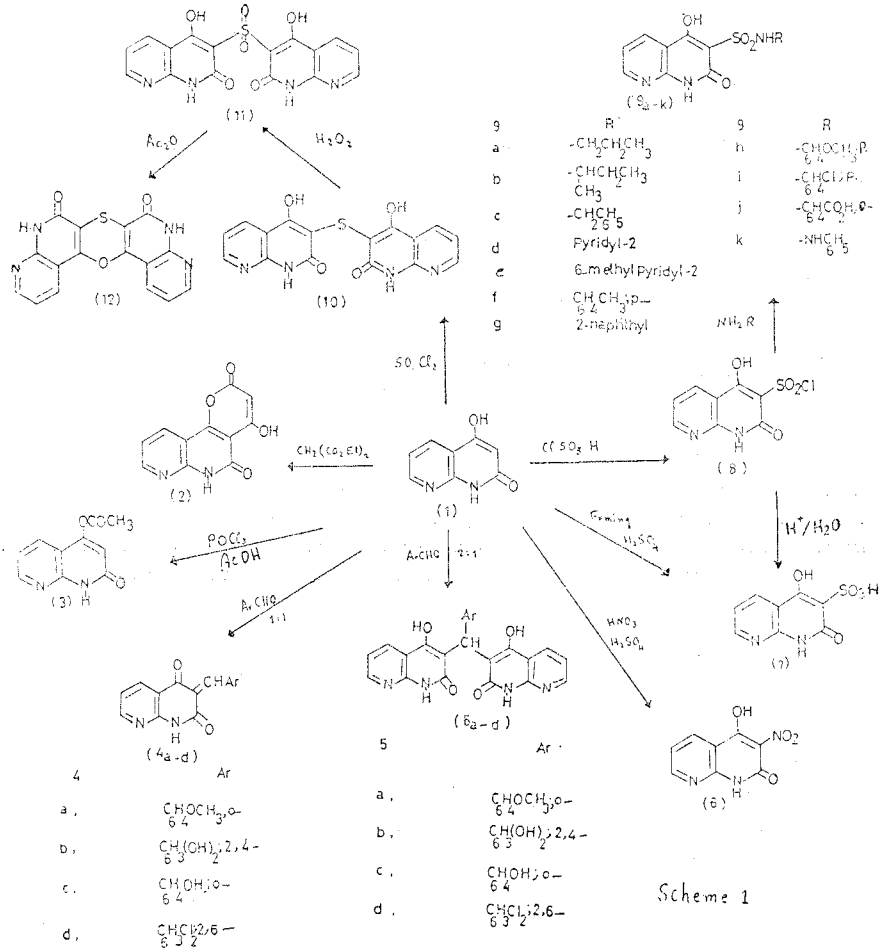
INTRODUCTION

Many 1,8-naphthyridine derivatives are useful as antibiotics, bactericides and agrochemical fungicides. Morever, they are used in controlling bacterial disorders and in treatment of allergic chronic obstructive lung diseases[1-6]. This prompted us to synthesize some more members of this class of compounds.

CHEMISTRY

The starting compound 4-hydroxy-1,8-naphthyridin-2-one (1) was prepared in good yield (85 %) by fusion of 2-aminopyridine with diethyl-malonate[7]. The naphthyridinone (1) underwent cyclization by boiling with diethylmalonate gave 4-hydroxy (5′, 6′: 3, 4)- α-pyrano-1, 8-naphthyridin-2-one (2). 4-Acetoxy derivative (3) was obtained by refluxing (1) with glacial acetic acid in presence $POCl_3$ (Scheme 1).

The reaction of 4-hydroxy-1, 8-naphthyridin-2-one (1) with some aromatic aldehydes was studied at different ratios. Thus, when the reaction was carried out at the ratio 1: 1, the simple condensation pruducts (4a-d) were obtained, while if the same reaction was carried out at the ratio 2: 1 the bis compounds (5a-d) were isolated.



Scheme 1

Compound(1) was also reacted with equimolar of conc. HNO_3 in the presence of conc. H_2SO_4 at room temperature to give the 3–nitro derivative(6) (Scheme 1).

Sulphonation of 4–hydroxy–1,8–naphthyridin–2–one(1) was achieved by cold fuming H_2SO_4 to give the corresponding 3–sulphonic acid derivative(7), while, reaction of compound(1) with chlorosulphonic gave the sulphonyl chloride(8) which underwent hydrolysis yielding the sulphonic acid derivative(7). On the other hand, some sulphonamides(9a–i) have been produced by reaction of compound(8) with some

aliphatic and aromatic amines. Similarly, compound(8) reacted with phenylhydrazine to give the sulphonylhydrazide derivative (9k) (Scheme 1).

Refluxing of compound(1) with thionyl chloride gave the sulphide derivative(10). The latter compound(10) was easily oxidized by H_2O_2 in dioxane to give the sulphone(11), which underwent cyclization by heating with Ac_2O to give the oxathiine(12) (Scheme 1).

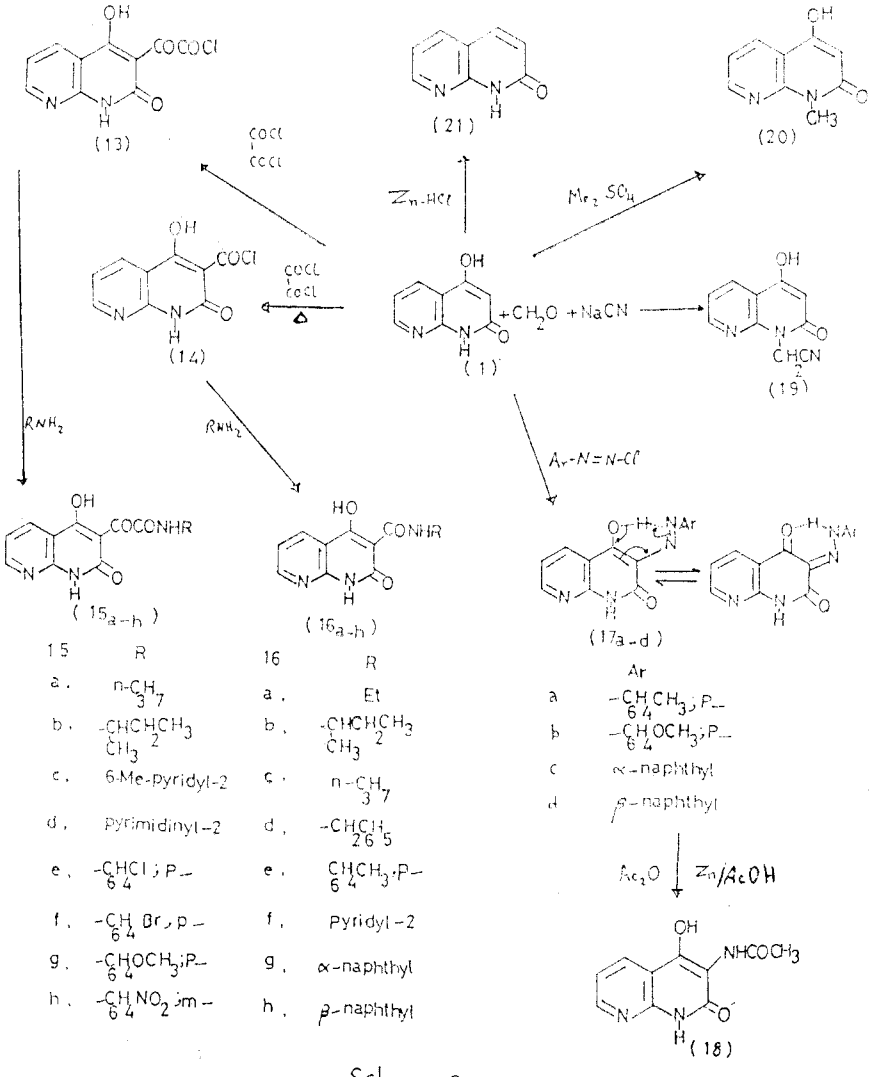
The naphthyridinone(1) was allowed to react with oxalyl chloride at different conditions and ratios. Thus, when compound(1) was reacted with oxalyl chloride at room temperature, 3–glyoxalyl chloride derivative(13) was isolated. But when it reacted with excess oxalyl chloride 3–carboxylic acid chloride(14) was produced. Each of the acid chlorides(13) and (14) reacted with some aliphatic and or aromatic amines to give α–ketoamides (15a–h) and amides (16a–h) respectively (Scheme 2).

On the other hand, the naphthyridinone(1) was reacted with diazonium salts such as, p–tolyl, o–methoxyphenyl, α–naphthyl and β–naphthyl, to give the colored 3–arylazo compounds (17a–d). The IR spectra of these azodyes shows that they exist in both the tautomeric azo and the hydrazo forms 8,9 (Scheme 2).

Reductive acetylation of the azo compounds (17a–d) by acetic acid–zinc dust in the presence of acetic anhydride gave the acetamido derivative (18), while, cyanomethylation of 4–hydroxy–1,8–naphthyridin–2–one (1) using sodium cyanide and formaldehyde in the presence of sodium bisulphite gave 1–cyanomethyl derivative (19). In addition, methylation of compound(1) using dimethylsulphate in alkaline media affording N–methyl derivative(20). Finally, reduction of 4–hydroxy–1,8–naphthyridin–2–one(1) by refluxing with zinc–HCl took place at position–4– led to the formation of 1,8–naphthyridin–2–one(21) (Scheme 2).

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded an a pye Unicam SP_{3-300} spectrophotometer using KBr wafer technique The ^{1}HNMR spectra were determined on a Varian EM–360–60 MHzNMR spectrometer. In all NMR experiments the internal standard was TMS and all the chemical shifts are in ppm down field from TMS. The solvent used was DMSO–d_6 in all experiments.



15	R
a.	n-C_3H_7
b.	-$CH(CH_3)CH_3$
c.	6-Me-pyridyl-2
d.	pyrimidinyl-2
e.	-C_6H_4-Cl;P-
f.	-C_6H_4-Br;P-
g.	-$C_6H_4OCH_3$;P-
h.	-$C_6H_4NO_2$;m-

16	R
a.	Et
b.	-$CH(CH_3)CH_3$
c.	n-C_3H_7
d.	-$CH_2C_6H_5$
e.	-$C_6H_4CH_3$;P-
f.	Pyridyl-2
g.	α-naphthyl
h.	β-naphthyl

Ar	
a	-$C_6H_4CH_3$;P-
b	-$C_6H_4OCH_3$;P-
c	α-naphthyl
d	β-naphthyl

Scheme 2

4– *Hydroxy*–1,8–*naphthyridin*–2–*one* (1):

Equimolecular amounts of 2–aminopyridine and diethylmalonate were refluxed for 6 hrs. The crystalline solid formed upon cooling was separated, washed with hot ethanol and recrystallized from water affording compound 1.

4'–*Hyroxy*–(5', 6': 3, 4)–*α–pyrono*–1,8–*naphthyridin*–2–*one* (2):

Action of diethyl–malonate on (1):

Conversion of 1 into 2.

A mixture of compound 1 (0.05 mole) and 20 ml diethylmalonate was heated at the boiling point of the mixture for 2 hr. Using a short air condenser, so that ethanol formed escaped freely, the precipitate was collected and recrystallized to give compound 2 (Table 1).

4– *Acetoxy*–1, 8–*naphthyridin*–2–*one* (3):

A mixture of the naphthyridone 1 (2 gm), pyridine (30 ml) and acetic anhydride (10 ml) was gradually heated up to 100°C during 3 hrs. On cooling the thickened mass was poured into ice, the product extracted with chloroform and the solid obtained after evaporation of chloroform was crystallized to give compound 3 (Table 1).

3– |(2'*methoxy;* 2', 4'–*dihydroxy;* 2'–*hydroxy or* 2', 6'–*dichloro*)–*phenyl methylidyne*| –1, 8–*naphthyridinylidene*–2.4–*dione* (4a–d):

To a suspension of 4–hydroxy–1,8 naphthyridin–2–one(1) (0.1 mole) in ethanol (10 ml), aromatic aldehyde [namely o–anisaldehyde, 2,4–dihydroxy–benzaldehyde, salicyaldehyde or 2,6–dichlorobenzaldehyde)] (0.1 mole) was added. The reaction mixture was refluxed for 4 hrs., cooled and the coloured products formed was filtered off and crystallized from the proper solvent affording campounds 4_{a-d} (Table 1).

3, 3'– |(2''–*methoxy;* 2'', 4''–*dihydroxy;* 2''–*dihydroxy;* 2''– *hydroxy or* 2'', 6''–*dichloro*) *phenyl–methylidyne*| *b is* (–4–*hydroxy*–1, 8–*naphthyridin*–2–*one*) (5a–d):

To a suspension of the naphthyridone 1 (0.1 mole) in absolute ethanol (10 ml) aromatic aldehyde (namely 0–anisaldehyde, 2,4–dihydroxy–benzaldehyde, salicyaldehyde or 2,6–dichlorobenzaldehyde) (0.2 mole) was added. The reaction mixture was refluxed for 4 hrs., cooled and the products formed was filtered off and cyrstallized from the appropriate solvent affording compounds 5a–d (Table 1)î

3– *Nitro*–1, 8–*naphthyridin*–2–*one* (6):

To a mixture of conc. nitric acid (0.1 mole), conc. sulphuric acid (0.3 mole), compound 1 (0.1 mole) was added with stirring. The reac-

Table 1. Physical Data of the Newly Synthesized Compounds: 1–21.

Cpd. No.	Yield (%)	M.P. [°C]	Solvent	Molec. Formula*	IR (KBr); $\bar{\upsilon}Cm^{-1}$	^1H-NMR (DMSO-d_6/TMS$_{int.}$), δ (ppm)	Sulphur Analyses	
							Calcd.	Found Y.
1	85	292–4	H_2O	$C_6H_6N_2O_2$	3050, 3010 (aromatic and olefinic C–H); 2500 (br., H–bonded OH); 1680 81640 (C=O at positions–28–4;tautomeric);1500–1620(ring vib.).	9.6 (br., 1H, OH); 8.9–9.1 (br., 1H, NH); 7.3–8.2 (m, 3H, Ar); 5.2 (s, 1H, CH at position–3).	—	—
2	25	283–5	H_2O	$C_{11}H_6N_2O_4$	3280 (br., NH); 2500 (br., OH bonded, 1630 (C = O of α–pyrono); 1615 (C = O at position–2); 1080 (C–O–C pyron).		—	—
3	23	>300	DMSO	$C_{10}H_8N_2O_3$	absence of OH band; 3210 (br., NH), 2950, 2840 (C–H aliphatic), 1720 (C = O ester); 1660 (C = O at position–2); 1240 (C–O acetate).		—	—
4a	60	>300	DMP	$C_{16}H_{12}N_2O_3$	absence of OH band of position–4		—	—
4b	70	>300	H_2O	$C_{15}H_{10}N_2O_4$	1720 (C = O at position–4., besides		—	—
4c	76	264–6	DMF	$C_{15}H_{10}N_2O_3$	the other bands characteristic for			
4d	80	280–3	H_2O	$C_{15}H_8N_2O_2Cl^+_2$	the main skeleton and the side chains.			
5a	65	292–3	DMF	$C_{24}H_{18}N_4O_5$	2500 (br., OH at posotion–4), besides the other bands characteristic		—	—
5b	67	218–9	H_2O	$C_{23}H_{16}N_4O_6$				
5c	70	285–7	DMF	$C_{23}H_{16}N_4O_5$	for the main skeleton and the side			
5d	64	290–2	DMF	$C_{23}H_{14}N_4O_4Cl_2^{++}$	chains.			
6	50	268–70	H_2O	$C_8H_5N_3O_4$	1470 and 1360 (asym. and sym. streching vib. of NO_2).		—	—
7	60	>300	H_2O	$C_8H_6N_2O_5S$	3450 (OH of sulphoaic group), 1340 and 1185 (asym. and sym. strech. vib. of S = O).		13.22	12.99

8	63	250–1	DMF	$C_8H_5N_2O_4SCl$	1325 and 1185 (asym. and sym. stretch, vib. of S = O.	8.9 (br., 1H, NH); 7.3–8.1 (. 3H, Ar) and the absence of signal of H at position–3.	12.22	12.40
9a	40	295–7	DMF	$C_{11}H_{13}N_3O_4S$	1310 (asym. and sym. stretch. vib. of S = O in addition to other peaks in accordance to the rest of the molecule.		11.31	11.40
9b	42	298–300	DMF	$C_{12}H_{15}N_3O_4S$			10.77	10.70
9c	39	291–3	DMF	$C_{15}H_{13}N_3O_4S$			9.67	9.67
9d	23	>300	H_2O	$C_{13}H_{10}N_4O_4S$			10.06	10.11
9e	31	297–9	DMF	$C_{14}H_{12}N_4O_4S$			9.64	9.50
9f	26	120	EtOH	$C_{15}H_{13}N_3O_4S$		10.5 (s, H, OH) 10 (s, 1H, NH emide), 8.3 (br., 1H, NH at position–1); 7–8.1 (m, 7H, Ar) and 2.2 (s, 3H, CH_2).	9.67	9.60
9g	33	>300	pyridine	$C_{18}H_{12}N_3O_4S$			8.72	8.90
9h	30	229	EtOH	$C_{15}H_{13}N_3O_5S$			9.22	9.11
9i	40	292–4	DMF	$C_{14}H_{12}N_3O_4SCl$			9.10	9.00
9j	57	>300	H_2O	$C_{15}H_{11}N_3O_6S$			8.86	8.60
9k	46	195	H_2O	$C_{14}H_{12}N_4O_4S$			9.64	9.80
10	55	258–9	DMF	$C_{16}H_{10}N_4O_4S$	3500–2700 (a group of weak bands strech. vib. of OH, NH and CH); 1660 (C = O g oups).		9.04	9.00
11	25	>300	DMP	$C_{15}H_{10}N_4O_6S$	1340 and 1135 (asym. and sym. strech. vib. of S = O).		8.29	8.30
12	20	>300	DMF	$C_{16}H_8N_4O_3S$	1050 (C–O–C strech. vib, of cyclic ethers) and diseppearance of the OH band.		9.52	9.43
13	70	280–2	DMF	$C_{16}H_5N_2O_4Cl$	1740 (C = O strech. vib. of acid halides); 1675 (C = O of α–diketones) and 1635 (C = O at position –2).			
14	70	278–80	DMF	$C_9H_5N_2O_3Cl^{++}$	1670 (C = O of conj. acid halides)) and 1620 (C = O at position–2).			

15a	60	293–5	DMF	$C_{13}H_{13}N_3O_4$	3270–3000 (a group of weak bands (NH amides, NH–naphthyridione, C–H aromatic); 2600 (br. band: H–bonded OH) and 1710–1620 (a group of strong bands (C = O amide, α–C = O and C = O at posotoon–2).	10.4 (s, 1H, OH); 9.9 (s, 1H NH aride); 8.9 (br., 1H, NH naphthyridinone; 6.8–8 (m, 7H, Ar) and 2.1 (s, 3H, CH_2).		
15b	59	>300	H_2O	$C_{14}H_{15}N_3O_4$				
15c	43	240–1	H_2O	$C_{16}H_{12}N_4O_4$				
15d	70	235–6	H_2O	$C_{14}H_9N_5O_4$				
15e	68	<300	H_2O	$C_{16}H_{10}N_3O_4Cl^+$				
15f	60	270–2	H_2O	$C_{16}H_{10}N_3O_4Br^{++}$				
15g	45	242–3	H_2O	$C_{17}H_{13}N_3O_5$				
15h	64	285–7	H_2O	$C_{16}H_{10}N_4O_6$				
16a	30	292–4	DMF	$C_{11}H_{11}N_3O_3$	3275–3010 (a group of weak bands (NH–amide, NH naphthyridinone, C–H aromatic); 2600 (br. and, H–bonded OH); 1670 and 1620 (C = O amide and C = O at position–2).	10.3 (s, 1H, OH); 9.7 (s, 1H, NH amide); 8.8 (br., 1H, NH naphthyridinone); 6.8–8 (m, 7H, Ar.) and 1.9 (s, 3H, CH_2).		
16b	40	285–6	DMF	$C_{13}H_{15}N_3O_3$				
16c	45	296–8	DMF	$C_{12}H_{13}N_3O_3$				
16d	35	288–90	DMF	$C_{16}H_{13}N_3O_3$				
16e	60	297–8	benzene	$C_{16}H_{13}N_3O_3$				
16f	44	298–9	H_2O	$C_{14}H_{10}N_4O_3$				
16g	56	158–9	DMF	$C_{19}H_{13}N_3O_3$				
16h	40	170–1	EtOH	$C_{19}H_{15}N_3O_3$				
17a	57	220–1	H_2O	$C_{15}H_{12}N_4O_2$	1680, 1640 and 1610 agroup of strong bands (C = O at positions–2 84– and C = N; respectively).			
17b	59	290–2	H_2O	$C_{15}H_{12}N_4O_3$				
17c	60	287–9	DMF	$C_{18}H_{12}N_4O_2$				
17d	63	280–2	DMF	$C_{18}H_{12}N_4O_2$				
18	20	195–6	EtOH	$C_{10}H_9N_3O_3$	3400 and 3200 (br. NH naphthyridinone and acetamide); 1680 and 1640 (C = O of acetamide and that at position–2).			
19	45	288–90	H_2O	$C_{10}H_7N_3O_2$	absence of the NH peak; 2245 (C= N): 2980, 2860 (weak, C–H aliphtic).	absence of the H–signal of NH; 8.1–7 (m, 3H, Ar.); 4.9 (s, 1H, CH at position–3 a and 3.25 (s, 2H, CH_2CN).		
20	25	226–8	H_2O	$C_9H_8N_2O_2$	absence of the NH peak; 2930, 2860 (weak, C–H alliphatic).	8.35 (s, 1H, NH), 8.4–6.9 (m, 3H, Ar) and 5 (br., 2H, olefinic at positions–3)–4).		
21	22	155	H_2O	$C_8H_6N_2O$	absence of OH peak.			

* All compounds gave satisfactory CH, N and halogen analyses

tion mixture was poured into ice cold water, the solid formed was filtered off and cyrstallized to give the 3-nitro derivative 6 (Table 1).

4- *Hydroxy*-1, 8-*naphthyridin*-2-*one*-3-*sulphonic acid* (7):

To cold fuming sulphuric acid (35 ml), 4-hydroxy-1,8-naphthyridin-2-ane (1) (3 gm) was added in portions and the reaction mixture was poured into 100 gm of crushed ice. The solid formed was collected and crystallized to give the titled compound 7 (Table 1).

4- *Hydroxy*-1, 8-*naphthyridin*-2-*one*-3-*sulphonylchloride* (8):

A finely powdered 4-hydroxy-1,8-naphthyridine-2-one(1) (10 gm), was added portionwise with shaking to chlorosulphonic acid (40 ml) at a period of 30 minutes. The reaction mixture was poured into ice, the solid deposited was filtered off, washed with ice cold water, dried and crystallized to produce compound 8 (Table 1).

Conversion of 8 *into* 7:

Hydrolysis of 4-*hydroxy*-1,8-*naphthyridine*-2-*one*-3-*sulphonylchloride* (8):

A suspension of 8 (0.5 gm) in 10 ml H_2O was refluxed for 2 hours, left to cool, filtered off and crystallized from water to give compound 7 m.p. and mixed m.p. and spectra.

Sulphonamide and Sulphonylhydrazide derivarives 9a-k:

To a solution of 8 (0.02 mole) in dry pyridine (10 ml) the appropriate amine namely (n-propylamine, sec. butylamine, benzylamine, 2-aminopyridine, 6-methyl-2-aminopyridine, p-toludine, B-naphthylamine, p-anisidine, 4-chloroaniline and o-aminobenzoic acid) (0.03 mole) was added. The reaction mixture was refluxed for 2 hrs., the crystalline solid formed upon cooling was filtered off and recrystallized from the suitable solvent affording compound 9_{a-j} (Table 1).

Similar technique had been applied for the reaction of 8 with phenylhydrazine to give the sulphonylhydrazide 9_k (Table 1).

Bis (4-*hydroxy*-1, 8-*naphthyridin*-2-*one*-3-*yl*) *sulphide* (10):

To a solution of 1 (2 gm) in dioxane (10 ml), thionylchloride (20 ml) was added and the clear solution obtained was refluxed for 2 hrs.

The reaction mixture was cooled, poured into ince cold water and the solid formed was filtered off, washed with water and crystallized affording compound 10 (Table 1).

Bis (4–hydroxy–1, 8–naphthyridin–2–one–3–yl) sulphone (11):

To a suspension of 10 (0.5 gm) in dioxane (10 ml) hydrogenperoxide (5 ml; 30 %) was added. The mixture was refluxed for 2 hrs., cooled and diluted with water. The solid precipitated was filtered off and crystallized to give the titled compound 11 (Table 1).

1'', 4''–*Oxathiine* (2'', 3''–C, 5'', 6''–C')–*di*–(1, 8–*naphthyridine*–2–*one*) (12):

A mixture of compound 10 (0.5 gm) and acetic anhydride (3ml) was refluxed for 3 hrs. The reaction mixture was cooled and diluted with water. The precipitate formed was filtered off, washed with water, dried and crystallized to give compound 12 (Table 1).

4– *Hydroxy*–1, 8–*naphthyridin*–2–*one*–3–*glyoxalylchloride* (1):

Compound 1 (0.1 mole) was mixed well with oxalylchloride (0.11 mole) at room temperature and the pasty mass formed was separated. Crystallization of the obtained crude product afforded the titled compound 13 (Table 1).

4– *Hydroxy*–1, 8–*naphthyridin*–2–*one*–3–*carboxylic acid chloride* (14:

A mixture of 1 (0.1 mole), and oxalylchloride (0.5 mole), was refluxed for 5 hrs., the product was collected and crystallized to give crystals of compound 14 (Table 1).

3– *Glyoxalylamide derivatives* 15_{a_h}:

A solution of 1 (0.02 mole), appropriate amine namely (n–propylamine, sec. butylamine, 2–amino–6–methylpyridine, 2–aminopyrimidine, 4–chloroaniline, 4–bromoaniline, p–anisidine and / or m–nitroaniline) (0.02 mole) in dry pyridine (10 ml) was refluxed for 3 hours. The solid deposited was filtered off dnd crystallized from the propcr solvent to afford compounds 15_{a_h} (Table 1).

3– *Formamide derivatives* 16_{a_h}:

A solution of 14 (0.02 mole) in dry pyridine (10 ml) was treated with the appropriate amine namely (ethylamine, sec. butylamine,

n–propylamine, benzylamine, p–toluidine, 2–aminopyridine, α–naphtylamine and / or β–naphthylamine) (0.02 ml) and refluxed for 4 hours. The products formed after cooling was filtered off and crystallized from the proper solvents to give the amides 16_{a-h} (Table 1).

3– *Arylazo–4–hydroxy–*1, 8–*naphthyridin–2–one* (17_{a-d}):

A solution of 1 (13 gm) in absolute ethanol(15 ml) and sodium hydroxide solution (1.2 gm. in 18 ml, water) was coupled with the equivalent amount of the diazoniumchloride derived from (p–toluidine, o–methoxyaniline, α–and / or β–naphthylamine) [amine (0.8 gm), conc. HCl (1,8 ml), water (1.8 ml)and sodium nitrite (0.6 gm)] at 0°C. The colored dyes were filtered off and crystallized from the suitable solvent to give the corresfonding azodyes 17_{a-d} (Table 1).

3– *(N'–acetamido(–4–hydroxy–*1, 8–*naphthyridin–2–one* (18):

A mixture of each of 17_{a-d} (0.5 gm), acetic acid (10 ml), acetic anhydride (5 ml) and activated zinc dust (0.5 gm) was refluxed for 2 hrs., the reaction mixture was filtered off while still hot and left to cool. Yellow crystalline product was collected, and recrystallized to give compound 18 (Table 1).

1–*Cyanomethyl–4–hydroxy–*1, 8–*naphthyridin–2–one* (19):

Formaldehyde (0.4 mole), was added to a solution of sodium bisulphite (0.24 mole) in 20 ml water, the temperature of the mixture was retained at 35°C. To this mixture compound 1 (0.1 mole) was added portionwise with stirring at a period of 1 hour, the reaction mixture is then stirred for further 2 hours. Sodium cyanide (0.24 mole) was then added, the formed precipitate was filtered off and crystallized to give the titled compound 19 (Table 1).

4– *Hydroxy–*1–*methyl–*1,8–*naphthyridin–2–one* (20):

A mixture of 1 (2.5 gm), aqueous solution of sodium hydroxide (50 ml; 20 %) and dimethylsuphate (20 ml) was heated for 2 hours at 100°C. The reaction mixture was treated periodicaly with dimethylsulphate (2 ml) at intervals of 15 minutes. The cooled reaction mixture was neutralized by dilute acetic acid, the solid formed was filtered of and crystallized to give compound 20 (Table 1).

1,8-*Naphthyridin-2-one* (21):

To a mixture of 1 (0.25 mole), zinc dust (0.62 gm) and glacial acetic acid (200 ml), conc. hydrochloric acid (90 ml) was added dropwise, while the temperature was maintained at 75–80°C. The reaction mixture was then poured into water, extracted by chloroform, evaporation of the organic layer gave compound 21 (Table 1).

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