# *Utility of N-2-pyridyl-3-oxobutanamide in heterocyclic synthesis: Synthesis of new dihydropyridine, fused pyridine, pyridopyridine, pyridazine and pyridopyrimidinethione derivatives*

**I. S. Abdel Hafiz [a], Safaa M Baker [a] and A. M Hussein [*b],**

**[a] Department of Chemistry, Faculty of Education Suez Canal University, Al-ArisH Egypt. [*b] Department of Chemistry, Faculty of Science, Al Azhar University, Assiut 71524, Egypt.**

*Utilidad de la N-2-piridil-3-oxobutanamida en síntesis heterocíclica: Síntesis de nuevos derivados de dihidropiridina, piridina condensada, piridopiridina, piridazina y piridopirimidinationa*
*Utilitat de la N-2-piridil-3-oxobutanamida a la síntesi heterocíclica: Síntesi de nous derivats de dihidropiridina, piridina condensada, piridopiridina, piridazina i piridopirimidinationa*

*Recibido: 8 de enero de 2009; aceptado: 31 de marzo de 2009*

## RESUMEN

Se hace reaccionar 2-aminopiridina con acetoacetato de etilo sin disolvente durante dos horas, rindiendo la *N*-2-piridil–3-oxobutanamida 1. Sin embargo, cuando se incrementa el tiempo de reacción a 5 horas, se obtiene un compuesto con la estructura 3. La condensación del producto 3 con benzaldehído rinde 4. La reacción de la piridopiridona 3 con los arilidenmalononitrilos 7a-c proporciona los derivados de 4*H*-pirano **10a-c**. En contraste con el comportamiento de los arilidenmalononitrilos 7a-c respecto a la piridopiridina 3, el benzilidenmalononitrilo 7d reacciona con el compuesto 3 para dar el producto 11. El compuesto 1 se hace reaccionar con arilidenmalononitrilos para rendir los derivados de dihidropiridina 17a-d. Se comunica también la alquilación del compuesto 1 con agentes alquilantes. Así, el compuesto 1 se condensa con DMF-DMA en dioxano a reflujo para rendir 18, pero bajo las condiciones de reacción se obtiene únicamente 21. La piridopiridona 3 reacciona con los benzoilisotiocianatos 25a,b para dar los derivados de tiourea 26a,b. La ciclación de 26a,b en dioxano seco y ácido sulfúrico concentrado proporciona los derivados de piridopirimidinationa 27a,b. Por otra parte, el acoplamiento de la piridopiridina 3 con las sales de diazonio aromáticas 28a-e rinde los correspondientes productos azo 29a-e. Al hervir el compuesto 29 en disolución acuosa de HCl, se obtienen los productos hidrazo 30. El tratamiento de la arilhidrazona 30a con malononitrilo rinde los derivados de piridazina 31.

**Palabras clave:** derivados de piridina, derivados de piridopiridina, derivados de piridazina, derivados de piridopirimidinationa.

## SUMMARY

2-Aminopyridine was fused with ethyl acetoacetate without solvent for two hours to yield the *N*-2-pyridyl–3-oxobutanamide 1. However, when the reaction time was increased to 5 hours a structure 3 was obtained. Condensation of the structure 3 with benzaldehyde gave 4. The reaction of pyridopyridone 3 with arylidenemalononitrile 7a-c afforded 4*H*-pyran derivative **10a-c**. In contrast to the behavior of arylidenemalononitrile 7a-c towards pyridopyridine 3, benzylidenemalononitrile 7d reacted with compound 3 to give a product 11. Compound 1 was allowed to react with arylidenemalononitrile to give the dihydropyridine derivative 17a-d. Alkylation of compound 1 with alkylating agents has been also reported. Thus, compound 1 was condensed with [DMF-DMA] in refluxing dioxane to yield 18, but under the reaction conditions we obtained only 21. The pyridopyridone 3 reacted with benzoylisothiocyanate 25a,b to give thiourea derivatives 26a,b Cyclization of 26a,b in dry dioxane and conc. sulphuric acid afforded pyridopyrimidinethione derivatives 27a,b. On the other hand, coupling of pyridopyridine 3 with the aromatic diazonium salt 28a-e afforded the corresponding azo products 29a-e. Boiling of compound 29 in aqueous solution of HCl afforded the hydrazo products 30. Treatment of arylhydrazone 30a with malononitrile afforded the pyridazine derivatives 31.

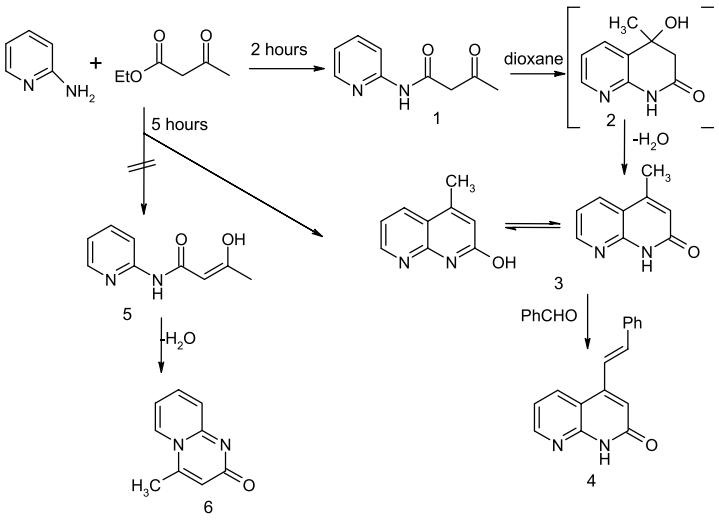
**Keywords:** pyridine derivatives, pyridopyridine derivatives, pyridazine derivatives, pyridopyrimidinethione derivatives.

## RESUM

Es fa reaccionar 2-aminopiridina amb acetoacetat d'etil sense dissolvent durant dues hores, rendint la *N*-2-piridil–3-oxobutanamida 1. Això però, quan s'incrementa el temps de reacció a 5 hores, s'obté un compost amb l'estructura 3. La condensació del producte 3 amb benzaldehid dóna 4. La reacció de la piridopiridona 3 amb els arilidenmalononitrils 7a-c proporciona els derivats de 4*H*-pirà **10a-c**. En contrast amb el comportament dels arilidenmalononitrils 7a-c envers la piridopiridina 3, el benzilidenmalononi-

tril 7d reacciona amb el compost 3 per donar el producte 11. El compost 1 es fa reaccionar amb arilidenmalononitrils per rendir els derivats de dihidropiridina 17a-d. Es comunica també l'alquilació del compost 1 amb agents alquilants. Així, el compost 1 es condensa amb DMF-DMA en dioxà a reflux per rendir 18, però sota les condicions de reacció s'obté només 21. La piridopiridona 3 reacciona amb els benzoïlisotiocianats 25a,b per donar els derivats de tiourea 26a,b. La ciclització de 26a,b en dioxà sec i àcid sulfúric concentrat proporciona els derivats de piridopirimidinationa 27a,b. D'altra banda, l'acoblament de la piridopiridina 3 amb les sals de diazoni aromàtiques 28a-e rendeix els corresponents productes azo 29a-e. En bullir el compost 29 en dissolució aquosa d'HCl, s'obtenen els productes hidrazo 30. El tractament de l'arilhidrazona 30a amb malononitril rendeix els derivats de piridazina 31.

**Mots clau:** derivats de piridina, derivats de piridopiridina, derivats de piridazina, derivats de piridopirimidinationa.




**Scheme 1**

## INTRODUCTION

In the last few years, we have been involved in a program aimed at developing new efficient synthetic approaches for the synthesis of heterocyclic compounds of biological interest [1-3]. In previous studies, we reported the synthesis of polyfunctionally substituted pyridines and substituted pyridazines [4-6]. In continuation of this work we use here N-2-Pyridyl-3-oxobutanamide for the synthesis of polyfunctionally substituted pyridines and pyridazines.

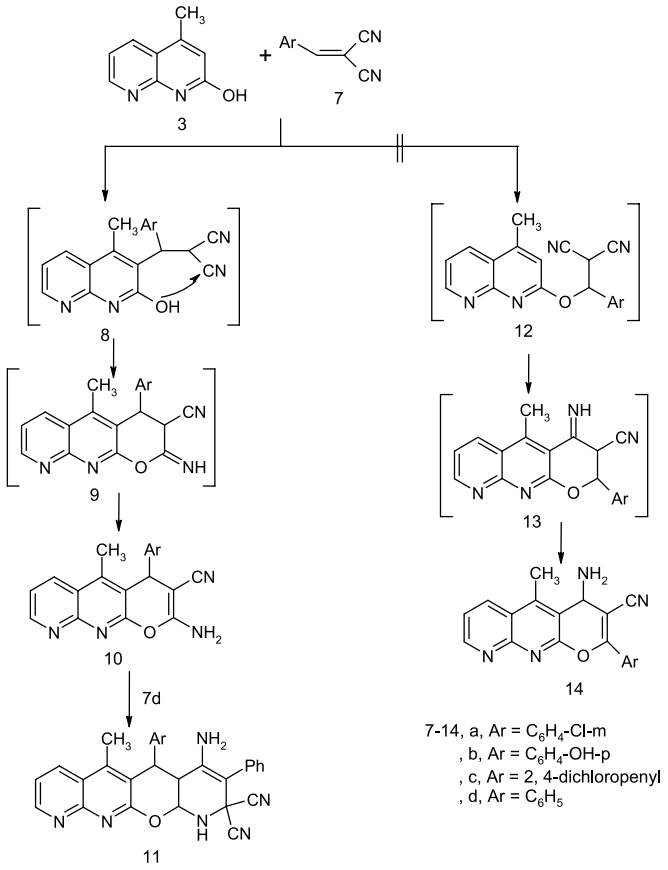
## RESULTS AND DISCUSSION

It has been found that when 2-aminopyridine was fused with ethyl acetoacetate without solvent for two hours yielded N-2-pyridyl–3-oxobutanamide 1[7]. However, when the reaction time was increased to 5 hours a product with a molecular formula $C_9H_8N_2O$ and molecular weight 160 was obtained. This was assigned structure 3 or its isomeric pyridopyrmidine 6. Structure 6 was ruled out based on the elemental analysis and the spectral data. Thus, $^1$H NMR spectrum revealed the presence of a singlet signal at δ = 3.3 ppm corresponding to the methyl group, a multiplet signal at δ = 6.9-8.3 ppm corresponding to aromatic and olefinic protons and a singlet signal at δ = 11.7 corresponding to NH group. Furthermore, this conclusion was supported by the mass spectrum. Thus, it showed a very intense molecular ion peak at *m/z* = 160. It, also, showed fragments at 131 (M - C=O), at 94 (M - $CH_3$-C=C=O) and at 78 (pyridyl radical) this data are consistent with structure 3 and not structure 6. Finally, structure 3 was confirmed via its preparation from N-2-pyridyl-3-oxobutanamide 1 according to the published procedure, using refluxing dioxane for 3 hours [mp, m.mp and TLC] were identical. Therefore, formation of compound 3 from 2-aminopyridine and ethyl acetoacetate is believed to be formed via initial condensation of 2-aminopyridine with ethyl acetoacetate to form compound 1 which cyclizes to give the non isolable intermediate 2 that loses one molecule of water to give 3. Further support of the structure 3 by its condensation with aromatic aldehydes. Thus, it was condensed with benzaldehyde in refluxing ethanol and in the presence of a catalytic amount of pipridine to give 4 as literature procedure [8,9]. Establishing the structure of compound 4 was based on its elemental analysis and spectral data. Thus, $^1$H NMR spectrum of compound 4 revealed the absence of methyl function and revealed the presence of two doublet signals at δ = 6.8 and 6.9 ppm corresponding to olifinic protons, a multiplet signal at δ = 7.2-8.2 ppm corresponding to aromatic protons and a singlet signal at δ = 11.7 ppm corresponding to NH group.

The behavior of pyridopyridone 3 towards electrophilic reagents under an alkaline condition was also investigated. Thus, the reaction of pyridopyridone 3 with 3-chlorobenzylidenemalononitrile 7a afforded the compound, which can be formulated as either 4H-pyran derivative 10a or its isomeric structure 14a. Structure 14a was ruled out, while structure 10a was established as the sole reaction product based on its spectral analysis. For example, the $^1$H NMR spectrum of 10a revealed the presence of a singlet signal at δ = 3.37 pm corresponding to methyl function, a singlet function at δ = 4.45 ppm corresponding to 4H pyran, a multiplet signal at δ = 7.07-7.80 ppm corresponding to aromatic protons and a singlet signal at δ = 10.45 ppm corresponding to $NH_2$ group. Formation of compound 10 can be interpreted via intermediacy of Michael adduct 8a which cyclizes to 9a that tautomerizes into 10a. Similarly, the reaction of pyridopyridone 3 with arylidenemalononitrile 7b,c afforded the 4H pyran 10c,d. (Scheme 2).

In contrast to the behavior of arylidenemalononitrile 7a-c towards pyridopyridine 3, benzyldenemalononitrile 7d reacted with compound 3 to give a product with a molecular formula $C_{29}H_{20}N_6O$ (468). This product was assigned structure 11 on the bases of its elemental analysis and spectral data. Thus, $^1$H NMR spectrum revealed the presence of a singlet signal at δ = 3.38 ppm corresponding to methyl group, a singlet function at δ = 4.80 ppm corresponding to 4H pyran, a multiplet signal at δ = 7.31-8.02 ppm corresponding to aromatic protons and NH group and a singlet signal at δ = 8.60 ppm corresponding to amino group. The mass spectrum of compound 11 showed the molecular ion peak at m/z = 468. It also showed fragment at 313 (M-benzylidenemalononitrile).

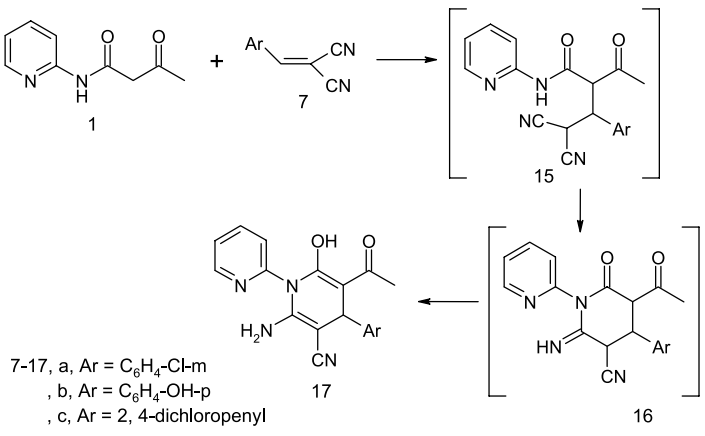
The results obtained from the behavior of 3 towards arylidenemalononitrile prompted us to investigate further behavior of N-2-pyridyl-3-oxobutanamide 1 towards ar-




**Scheme 2**

ylidenemalononitrile 7a-d. Thus, N-2-pyridyl-3-oxobutanamide 1 was allowed to react with 3-chlorobenzylidenemalononitrile to give dihydropyridine derivative 17a (Scheme 3).

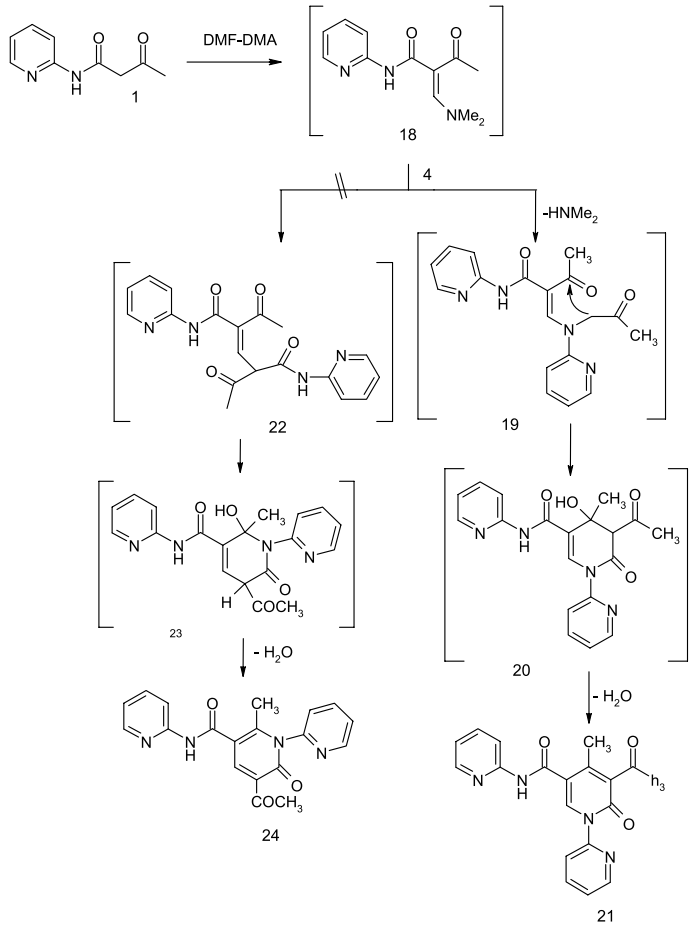
Establishing structure 17a was based on its elemental analysis and spectral data. For example, the IR spectrum of compound 17a revealed the presence of a peak at 3200 cm-1 corresponding to amino function, a peak at 2214 cm-1 corresponding to nitrile function and a peak at 1681 cm-1 corresponding to carbonyl function. 1H NMR of the same product revealed the presence of a singlet signal at δ = 1.23 ppm corresponding to methyl group, a singlet at δ = 1.66 ppm corresponding to phenolic hydroxyl, a singlet signal at δ = 3.79 ppm corresponding to




**Scheme 3**

4H pyridine and a multiplet signal at δ = 7.24-8.35 ppm corresponding to aromatic protons and amino group. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a molecular ion peak at 363. It also showed fragments at 323 (M-C-C=O) and 281(M-pyridine). Formation of 17a from reaction of N-2-pyridyl-3-oxobutanamide 1 and 3-chlorobenzylidenemalononitrile is believed to be formed via intermediacy of Michael adduct 15 which cyclizes to give 16 that tautomerizes readily to give the dihydropyridine 17a. Similarly, N-2-pyridyl-3-oxobutanamide 1 was allowed to react with arylidenemalononitrile derivatives 7b-d to give the dihydropyridine derivatives 17b-d (Scheme 3).

Ready oxidation of dihydroazines into azines has been reported earlier under mild conditions [10]. Thus, alkylation of compound 1 with alkylating agents has been also reported. Thus, N-2-pyridyl-3-oxobutanamide 1 was condensed with N,N-dimethylformamide-dimethylacetal [DMF-DMA] in refluxing dioxane to yield the product which may be formulated as 2-dimethylaminomethylene-3-oxo-N-2-pyridyl-butyramide 18. But under the reaction condition we obtained only a product with a molecular mass m/z = 349 ($M^{+1}$) corresponding to a molecular formula $C_{19}H_{16}N_4O_3$ this was considered to be 21 or its isomeric structure 24. Structure 21 was actually the only reaction product based on the spectral data and its chemical behavior. Thus, 1H NMR spectrum revealed the presence of a singlet signal at δ = 2.12 ppm corresponding to methoxy group, a singlet signal at δ = 3.34 ppm corresponding to methyl group, a

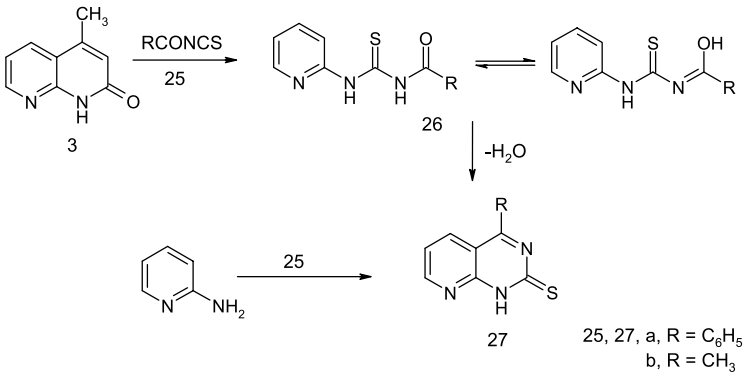


**Scheme 4**

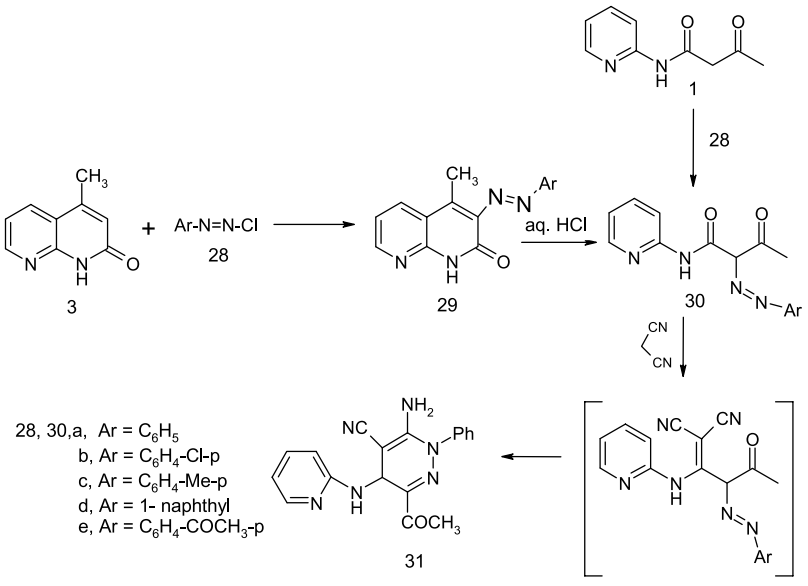
multiplet signal at δ = 7.13-8.71 ppm corresponding to aromatic protons and amino group and a singlet signal at δ = 11.11 ppm corresponding to NH group. Formation of compound 21 is assumed to be proceed via initial condensation of N-2-pyridyl-3-oxobutanamide 1 with one molecule of DMF-DMA to yield the unstable enaminone 18, which in turn, reacts with another molecule of 1 to give intermediate 19 via losing dimethyl amine molecule. This molecule cyclized into structure 20, then, loses $H_2O$ to yield the pyridone 21. Alternatively, initial condensation of N-2-pyridyl-3-oxobutanamide 1 to enaminone 18 lead to condensation at the methylene group ($CH_2$) in 1. But the latter compound might than cyclized and loss $H_2O$ to give 24 (Scheme 4).

The behavior of pyridopyridone 3 towards isothiocyanate reagents was also investigated. Thus, when pyridopyridone 3 reacted with benzoylisothiocyanate 25a, which, in turn prepared from benzoylchloride and ammonium thiocyanate in refluxing acetone, afforded a product with a molecular formula $C_{13}H_{11}N_3OS$ (257), this was considered to be the acyclic thiourea derivative 26a based on its elemental and spectral analysis. Compound 26a could be prepared also in an excellent yield from treatment of 2-aminopyridine with benzoylisothiocynate 25a in the same reaction condition. Thus, formation of 26a from the reaction of pyridopyridone 3 and benzoylisothiocynate is believed to be formed via initial ring opening in pyridopyridone 3 and subsequent loss of crotonaldehyde molecule. Similarly acylisothiocyanate 25b reacted with pyridopyridone 3 to give the acyclic thiourea derivative 26b (Scheme 5). Cyclization of thiourea derivatives 26a,b in dry dioxane and conc. sulphuric acid afforded pyridopyrimidinethione derivatives 27a,b (Scheme 5).

On the other hand, coupling of pyridopyridine 3 with the aromatic diazonium salt 28a [11, 12] afforded the corresponding azo products 29a. Establishing structure 29a was based on its spectral data. For example, the mass spectrum of compound 29a showed a molecular ion peak at m/z = 264 ($M^+$) corresponding to the molecular formula $C_{15}H_{12}N_4O$. Also, $^1H$ NMR of compound 29a revealed the presence of a singlet signal at δ = 2.3 ppm corresponding to methyl function, a multiplet signal at δ = 6.9-8.5 ppm corresponding to aromatic protons and a singlet signal at δ = 13.13, 14.45 ppm corresponding to NH and OH groups. Similarly, coupling of pyridopyridine 3 with aromatic diazonium salt 28b-e afforded the azo products 29b-e (Scheme 6). Boiling of compounds 29 in aqueous solution of HCl afforded the hydrazo products 30. Spectral data are in favor with the proposed hydrazo structure. For example the IR spectrum of 30d showed absorption bands at 3100, 3058 $cm^{-1}$ corresponding to NH, and absorption bands at




**Scheme 5**




**Scheme 6**

1662 and 1635 cm-1 corresponding to amidicarbonyl and acetylcarbonyl respectively. $^1$H NMR revealed to the presence of a singlet signal at δ = 2.60 ppm corresponding to methyl group, a multiplet signal at δ = 7.04-8.42 ppm corresponding to aromatic protons and a singlet signal at δ = 11.90 ppm corresponding to NH group. Moreover, the mass spectrum of 30d showed the molecular ion peak at m/z = 332 ($M^{+1}$). Treatment of arylhydrazone 30a with malononitrile in absence of solvent and in presence of a little amount of ammonium acetate afforded the pyridazine derivatives 31 as demonstrated in (Scheme 6). Establishing structure 31 was based on its elemental analysis and the spectral data.

## EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, $cm^{-1}$). The $^1$H NMR spectra were recorded in DMSO-d6 and CDCl3 at 200, 400 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analysis was carried out by the Micro analytical Research Center, Faculty of Science, Cairo University.

**Preparation of N-2-pyridyl–3-oxobutanamide (1):**
A mixture of 2-aminopyridine (9.4 g, 0.1mol) and ethyl acetoacetate (13 g, 0.1mol) was allowed to fuse at 130°C for 2 hrs. The reaction mixture was allowed to cool and treated with petroleum ether (40-60). The solid product, so formed, was collected by filtration and crystallized from ethanol. It was obtained as colorless crystals (60 %); mp 99-100 OC; $\nu_{max}$/ $cm^{-1}$(KBr) 3243 (NH), 1721, 1667 (C=O); Found: C, 60.62; H, 5.70; N, 15.80; Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.61; N, 15.73%.

**Preparation o f 1,2-Dihydro-4-methyl[1,8]naphthyridine-2-one(3):**
A mixture of 2-aminopyridine (9.4 g, 0.1 mol) and ethylacetoacetate (13 g, 0.1 mol) was allowed to fuse at 130°C for 5 hrs.The reaction mixture was allowed to cool and treated with petroleum ether(40-60), the solid product, so formed, was collected by filtration and crystallized from ethanol. It was obtained as colorless crystals (50%); mp 162-164°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3150 (NH), 1651 (C=O); δH (DMSO-$d_6$) 3.3 (s, 3H, $CH_3$), 6.9-8.3 (m, 4H, aromatic H), 11.7 (s, 1H, NH); m/z =160 (M). Found: C, 67.40; H, 5.10; N, 17.42; Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50%.

**Preparation of 4-(2-styryl)naphthryidin-2-one (4):**
A mixture of pyridopyridone 3 (1.6 g; 0.01 mol) and benzaldehyde (1.06 g; 0.01 mol) in ethanol (30ml) was treated with a catalytic amount of piperidine (1 ml). The reaction mixture was refluxed for 2 hrs and left to cool. The solid product was collected by filtration and crystallized from ethanol. It was obtained as colorless crystals (50%); mp 166-168°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3444 (NH), 2923 (CH-aliph), 1651 (C=O); δH ($CDCl_3$) 6.8 (d, 1H, alkenyl proton), 6.9 (d, $^1$H, alkenyl proton), 7.2-8.2 (m, 9H, aromatic-H), 11.7 (s, $^1$H, NH); m/z 248 (M); Found: C, 77.50; H, 4.80; N, 11.35; Calcd for $C_{16}H_{12}N_2O$: C, 77.41; H 4.83; N, 11.29 %.

**Preparation of fused pyran derivatives (10a-c and 11):**
General procedure: A mixture of pyridopyridone derivative 3 (1.60 g; 0.01 mol) and arylidenemalononitrile s (0.01 mol) in ethanol (30 ml) was treated with few drops of piperidine and heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl, The solid product was collected by filtration and crystallized from the proper solvent

**2-Amino-4-(3-chlorophenyl)-5-methyl-4H-1-oxa-9,10-diaza-anthracene-3-carbonitrile (10a):**
It was obtained as pale yellow crystals from ethanol (62 %); mp 268-270°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3307 ($NH_2$), 3080 (CH-arom), 2966 (CH-aliph), 2203 (CN); δH (DMSO-$d_6$) 3.06 (s, 3H, $CH_3$), 4.4 (s, 1H, 4H pyran), 7.07-7.80 (m, 7H, aromatic H), 10.45 (s, 2H, $NH_2$); m/z = 348 (M); Found: C, 65.50; H, 3.58; N, 16.20; Calcd for $C_{19}H_{13}N_4OCl$: C 65.42; H, 3.7; N, 16.06 %.

**2-Amino-4-(4-hydroxyphenyl)-5-methyl-4H-1-oxa-9,10-diaza-anthracene-3-carbonitrile (10b):**
It was obtained as orange crystals (35%); mp 230-232°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3336 (OH), 3220 ($NH_2$), 2202 (CN); Found: C, 69.30; H, 4.15; N, 16.77; Calcd for $C_{19}H_{14}N_4O_2$: C, 69.09; H 4.24; N, 16.96 %.

**2-Amino-4-(2,4-dichlorophenyl)-5-methyl-4H-1-oxa-8,10-diaza-anthracene-3-carbonitrile (10c):**
It was obtained as yellow crystals from ethanol (25%); mp 263-265°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3433, 3321 ($NH_2$), 3070 (CH-arom), 2218 (CN); m/z = 383 ($M^{-1}$); Found: C, 59.60; H, 3.19; N, 14.70 Calcd for $C_{19}H_{12}N4OCl_2$: C, 59.68; H 3.14; N, 14.65 %.

**7-Amino-5-methyl-6,8-diphenyl-6,10-dihydro-11-oxa-1,10,12-triaza-naphthacene-9,9-dicarbonitrile (11):**
It was obtained as pale yellow crystals from ethanol (51 %); mp >300°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3468 ($NH_2$), 3321 (NH), 3029 (CH-arom), 2927 (CH-aliph), 2206 (CN); δH (DMSO-$d_6$) 3.29 (s, 3H, $CH_3$), 4.9 (s, 1H, 4 H pyran), 7.11-8.11 (m, 15H, aromatic H and $NH_2$), 8.6 (s, 1H, NH), m/z = 468 (M); Found: C, 74.30; H, 4.15; N, 17.82; Calcd for $C_{29}H_{20}N_6O$: C, 74.35; H, 4.27; N, 17.94%.

**Preparation of 4H-pyridine derivatives 17a-d**
General procedure: A mixture of N-2-pyridyl-3-oxobutanamide 1 (1.78 g; 0.01 mol) and arylidenemalononitrile s (0.01 mol) in ethanol (30 ml) was treated with few drops of piperidine and heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl, The solid product was collected by filtration and crystallized from the proper solvent.

**5-Acyl-2-amino-4-(3-chlorophenyl)-6-hydroxy-4H-[1,2] bipyridinyl-3-carbonitrile (17a) :**
It was obtained as canarian yellow crystals from ethanol (64 %); mp 310-311°C; $\nu_{max}$ /$cm^{-1}$ (KBr) 3200 ($NH_2$), 3090 (CH-arom), 2927 (CH-aliph), 2214 (CN), 1681 (C=O); δH ($CDCl_3$) 1.23 (s, 3H, $CH_3$), 1.66 (s, 1H, OH), 3.79 (s, 1 H, 4 H pyridine), 7.24-8.35 (m, 10H, aromatic H and NH2); m/z = 363 ($M^{-3}$); Found: C, 62.30; H, 4.15; N, 15.12; Calcd for $C_{19}H_{15}N_4O_2Cl$:s C, 62.21; H, 4.09; N, 15.27 %.

**5-Acyl-2-amino-6-hydroxy-4-(4-hydroxyphenyl)-4H-[1,2]bipyridinyl-3-carbonitrile (17b):**
It was obtained as orange crystals from ethanol (68.5 %); mp 180-182°C; m/z = 348 (M); Found: C, 65.33; H, 4.55; N, 16.02; Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.59; N 16.09 %.

**5-Acyl-2-amino-4-(2,4-dichlorophenyl)-6-hydroxy-4H-[1,2]bipyridinyl-3-carbonitrile (17c):**
It was obtained as pale yellow crystals from ethanol (68.4 %); mp 160-162°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3271 ($NH_2$), 2214 (CN), 1650 (C=O); δH ($CDCl_3$) 1.46 (s, 1H, OH), 1.8 (s, 3H, $CH_3$), 4.35 (s, 1 H, 4 H pyridine), 6.98-7.31 (m, 9H, aromatic H and $NH_2$), m/z = 398 ($M^{-3}$); Found: C, 56.80; H, 3.45; N, 13.82; Calcd for $C_{19}H_{14}N_4O_2Cl_2$: C, 56.85; H, 3.49; N, 13.96 %.

**5-Acyl-2-amino-6-hydroxy-4-phenyl-4H-[1,2]bipyridinyl-3-carbonitrile (17d):**
It was obtained as pale yellow crystals from ethanol (72.4 %); mp 140-142°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3259, 3215 ($NH_2$), 3101 (CH-arom), 2960 (CH-aliph), 2194 (CN), 1706 (C=O); m/z = 333 ($M^{+1}$); Found: C, 68.54; H, 4.75; N, 16.82; Calcd for $C_{19}H_{16}N_4O_2$: C, 68.67; H, 4.81; N, 16.86 %.

**Preparation of 5-Acyl-4-methyl-6-oxo-6H-[1,2]bipyridinyl-3-carboxylic acid pyridin-2-ylamide (21):**
To a solution of N-2-pyridyl-3-oxobutanamide (1) (1.78 g; 0.01 mol) in dry dioxane, dimethylformamide-dimethylacetal (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then cooled. The precipitate was filtered off, washed with ether and crystallized from ethanol. It was obtained as pale yellow crystals (50 %) mp 245-247°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3241 (NH), 3022 (CH-arom), 2920 (CH-aliph), 1774, 1672, 1655(3 C=O); δH (DMSO-$d_6$) δ = 2.12 (s, 3H, $CH_3$), 3.34 (s, 3H, $CH_3$), 7.13-8.71 (m, 9H, aromatic H), 11.11(s, 1H, NH); m/z = 349 ($M^{+1}$); Found: C, 65.88; H, 4.33; N, 16.15 Calcd for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.59; N, 16.09 %.

**Preparation of thiourea derivative (26a,b):**
Procedure (A): To a solution of pyridopyridone 3 (1.6 g; 0.01 mol) in dry acetone (50 ml), benzoyl or acyl isothiocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.
Procedure (B): To a solution of 2-aminopyridine (0.94 g; 0.01 mol) in dry acetone (50 ml), benzoyl or acyl isothiocyanate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.

**N-Pyridin-2-yl-N-phenylthiourea (26a):**
It was obtained as yellow crystals from ethanol (64.4 %); mp 180-182°C; $\nu_{max}$ /cm$^{-1}$ (KBr) I3274, 3152 (2NH), 1678 (C=O); δH (DMSO-d6) 6. 8-8.2 (m, 9H, aromatic H), 11.2 (s, 1 H, NH), 12.4 (s, 1 H, NH); m/z = 257 (M); Found: C, 60.65; H, 4.33; N, 16.13; Calcd for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34 %.

**N-Pyridin-2-yl-N-acylthiourea (26b):**
It was obtained as yellow crystals from ethanol (60 %); mp 258-260°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3250, 3200 (NH), 1693 (C=O); δH (DMSO-$d_6$) 2.39 (s, 3H, $CH_3$), 6.7-8.8 (m, 4H, aromatic H), 11.3 (s, 1 H, NH), 13.6 (s, 1 H, NH); m/z = 195 (M); Found: C, 49.15; H, 4.55; N, 21.43; Calcd for $C_8H_9N_3OS$: C, 49.23; H, 4.61; N, 21.53 %.

**Preparation of pyridopyrimidinethione derivative (27a,b):**
General procedure: To a solution of thiourea derivatives 26a,b (0.01 mol) in dry dioxane (50 ml), conc. sulphuric acid (0.01 mol) was added. The reaction mixture was heated under reflux for 2 hrs, and then poured onto cold water. The solid product was collected by filtration and crystallized from the proper solvent.

**4-Phenyl-1H-pyrido[2,3-d]pyrimidine-2-thione (27a).**
It was obtained as pale yellow crystals from ethanol (55.4 %); mp > 300°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3100 (NH); m/z = 239 (M); Found: C, 65.20; H, 3.65; N, 17.53; Calcd for $C_{13}H_9N_3S$: C, 65.27; H, 3.76; N, 17.57 %.

**4-Methyl-1H-pyrido[2,3-d]pyrimidine-2-thione (27b):**
It was obtained as pale yellow crystals from ethanol (63.8%); mp > 300°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3371 (NH); δH (DMSO-$d_6$) 2.13 (s, 3 H, $CH_3$), 7.21-7.36 (m, 3H, aromatic H), 10.45 (s, 1H, NH); Found: C, 65.20; H, 3.65; N, 17.53; Calcd for $C_8H_7N_3S$: C, 65.27; H, 3.76; N, 17.57 %.

**Preparation of compounds (29a-e) and (30a-e):**
General procedure: A cold solution of diazonium salt (prepared by adding a solution of sodium nitrite, 1.5 g into 10 ml $H_2O$, is added to the cold solution of the corresponding amine hydrochloride, 0.1 mol in 10 ml concentrated HCl, The mixture is stirred in an ice bath). The resulting solution of diazonium salt was then added to cold solution of either N-2-pyridyl-3-oxobutanamide (1) or pyridopyridinethione 3 (0.01 mole) in ethanol (30 ml) containing 2 g sodium acetate at 0°C for 1 hr. The resulting solid was collected by filtration, washed with water and crystallized from the proper solvent.

**4-Methyl-3-phenylazo-1H-[1,8]naphthyridin-2-one (29a):**
It was obtained as yellow crystals from ethanol (87%); mp 195-197°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3200 (NH), 1639 (CO); δH ($CDCl_3$) 2.32 (s, 3H, $CH_3$), 6.97-8.50 (m, 8H, aromatic H), 13.13 (s, 1H, NH), 14.45(s, 1H, OH); m/z = 264 (M); Found: C, 68.19; H 4.61; N, 21.27; Calcd for $C_{15}H_{12}N_4O$: C, 68.18; H, 4.54; N, 21.21 %.

**3-(4-Chlorophenylazo)-4-methyl-1H-[1,8]naphthyridin-2-one (29b):**
It was obtained as yellow crystals from ethanol (85 %); mp 201-203 °C; δH ($CDCl_3$) 2.30 (s, 3H, $CH_3$), 7.03-8.49 (m, 7H, aromatic H), 13.13 (s, 1H, NH), 14.47(s, 1H, OH); m/z = 298 (M); Found: C, 60.45; H, 3.75; N, 18.83; Calcd for $C_{15}H_{11}N_4OCl$: C, 60.40; H, 3.69; N, 18.79 %.

**4-Methyl-3-p-tolylazo-1H-[1,8]naphthyridin-2-one (29c):**
It was obtained as yellow crystals from ethanol (96 %); mp 182-184°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3290 (NH), 1635 (CO); δH ($CDCl_3$) 2.31 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 6.96-8.22 (m, 7H, aromatic H), 13.20 (s, 1H, NH), 14.45(s, 1H, OH) ; m/z = 278 (M); Found: C, 69.10; H, 5.00; N, 20.16; Calcd for $C_{16}H_{14}N_4O$: C, 69.06; H, 5.03; N, 20.14%.

**4-Methyl-3-(naphthalene-1-ylazo)-1H- [1,8]naphthyridin-2-one (29d):**
It was obtained as deep yellow crystals from ethanol (80%); mp 223-225°C; Found: C, 72.50; H, 4.50; N, 17.66; Calcd for $C_{19}H_{14}N_4O$: C, 72.61; H, 4.45; N, 17.83 %.

**3-(4-Acetylphenylazo)-4-methyl-1H-[1,8]naphthyridin-2-one (29e):**
It was obtained as deep yellow crystals from ethanol (94 %); mp 234-6°C; $\nu_{max}$ /cm$^{-1}$ (KBr) 3200 (NH), 1666 (CO); δH ($CDCl_3$) 2.31 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 6.97-8.50 (m, 7H, aromatic H), 13.09 (s, 1H, NH), 14.52(s, 1H, OH); m/z =

305($M^{-1}$); Found: C, 66.63; H, 4.51; N, 18.28; $C_{16}H_{14}N_4O_2$: C, 66.66; H, 4.57; N, 18.30%.

**Another procedure for preparation of aryl hydrazo derivative (30a-e):**
A suspension of Arylazo pyridopyridinethione 29a-e in dil. hydrochloric acid solution was refluxed for 2 hrs. The reaction mixture was left to cool and neutralized with ammonia solution until complete precipitation. The solid product so formed was collected by filtration and crystallized by the proper solvent.

**3-Oxo-2-(phenylhydrazono)-N-pyridin-2-yl-butyramide (30a):**
It was obtained as yellow crystals from ethanol (90.8 %); mp 178-179°C; $\nu_{max}$ /$cm^{-1}$(KBr) 3395, 3159 (NH), 1663, 1636 (C=O); δH ($CDCl_3$) 2.60 (s, 3H, $CH_3$), 7.04-8.41 (m, 9H, aromatic H), 11.85 (s, 1H, NH), 14.61 (s, 1H, NH); m/z = 282 (M); Found: C, 63.89; H, 4.65; N, 19.80; Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 4.60; N, 19.85%.

**2-[(4-Chlorophenyl)-hydrazono]-3-oxo-N-pyridin-2-yl-butyramide (30b):**
It was obtained as reddish brown crystals from ethanol (77.4 %); mp 188-190°C; Found: C, 56.79; H, 4.05; N, 17.55; Calcd for $C_{15}H_{13}N_4O_2Cl$: C, 56.87; H, 4.10; N, 17.69%.

**2-[(4-Tolyl)-hydrazono]-3-oxo-N-pyridin-2-yl-butyramide (30c):**
It was obtained as yellow crystals from ethanol (98%); mp 180-182°C; $\nu_{max}$ /$cm^{-1}$(KBr) 3422, 3128 (2NH), 1658, 1718 (CO); δH ($CDCl_3$) 2.33 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 6.99-8.36 (m, 8H, aromatic H), 11.83 (s, 1H, NH), 14.58 (s, 1H, NH); m/z = 296 (M); Found: C, 64.89; H, 5.36; N, 18.90; Calcd for $C_{16}H_{16}N_4O_2$: C, 64.86; H, 5.40; N, 18.91%.

**2-[(Naphthalen-1-ylhydazono)]-3-oxo-N-pyridin-2-yl-butyramide(30d):**
It was obtained as reddish brown crystals from ethanol (83.3%); mp 210-212°C; $\nu_{max}$ /$cm^{-1}$(KBr) 3100, 3058 (NH), 1662, 1635 (CO); δH ($CDCl_3$) 2.60 (s, 3H, $CH_3$), 7.04-8.42(m, 11H, Ar-H), 11.90 (s,1H,NH), 15.49 (s, 1H, NH); m/z=331 ($M^{-1}$); Found: C, 68.60; H, 4.76; N, 16.90; Calcd for $C_{19}H_{16}N_4O_2$: C, 68.67; H, 4.81; N, 16.86%.

**2-[(4-Acyl-phenyl)-hydrazono]-3-oxo-N-pyridin-2-yl-butyramide (30e):**
It was obtained as brown crystals from ethanol (73.7 %); mp 223-225°C; Found: C, 62.85; H, 4.86; N, 17.30; $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.93; N, 17.28%.

**3-Acetyl-6-imino-1-phenyl-4-phenylamino-1,4-dihydro-pyridazine-5-carbonitrile (31):**
A mixture of aryl hydrazo 30a (2.82 g; 0.01 mol), malononitrile (0.66 g; 0.01 mol) and ammonium acetate (0.5 g) was fused for 30 minutes at 140°C. The reaction mixture was left to stand, and then triturated with ethanol. The solid product so formed was collected by filtration and crystallized from ethanol to give (31). It was obtained as gold crystals from ethanol (55%); mp 180°C; $\nu_{max}$ /$cm^{-1}$(KBr) 3168 (NH), 2200 (CN), 1663 (CO); δH (DMSO-$d_6$) 2.47 (s, 1H, aliph-H), 3.32 (s, 3H, $CH_3$), 7.19-8.36 (m, 9H, aromatic H), 11.67 (s,1H,NH); m/z = 330 (M); Found: C, 65.49; H, 4.30; N, 25.50; Calcd for $C_{18}H_{14}N_6O$: C, 65.45; H, 4.24; N, 25.45%.

## REFERENCES


1. A. R. Katritzky, S. Zhang, A. M. Hussein and Y. Fang .J .Org. Chem, 66, 5606(2001).
2. I. S. Abdel Hafiz, A. M. Hussein and V. F. Mahmoud, Z. Naturforsch, 54b, 923 (1999).
3. A. M. Hussein, A. A. Harb and I. A. Mousa, J. Heterocyclic Chem, 45, 1 (2008)
4. A. M. Hussein, Heteroatom chemistry, 8, 1(1997).
5. A. M. Hussein, Afinidad Lv1, 484,377, (1999)
6. F. Bigi, B. Frullanti, R. Maggi, G. Sartori and E. Zambonin, J. Org. Chem., 64, 1004-1006 (1999).
7. M. H. Elnagdi and A. W. Erian, Bull. Chem.Sec.Jpm, 63,854 (1990).
8. A. S. S. Rathod, B. N. Berad, S. D. Patil and A. G. Doshi, Orient. J. Chem., 16 (2), 315-318 (2000).
9. K. G. Ojha, J. Neera and T. Heer, Journal of the Indian Chemical Society, 79 (2), 191-192 (2002).
10. H.G.Garg; S.S.Joshi; J.Ind.Chem.Soc. 37, 626(1960).
11. A. D. Mitchell; D. C. Nonhebel; Tetrahedron Lett. 3859 (1995).
12. A. H. H. El ghandour; A. M. Hussein; M. H. Elnagdi; A. A. Harb and S. A. Metwally; J. Prarit. Chem, 334, 723 (1992).