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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATIC COMPOUNDS: SYNTHESIS OF SOME NEW POLYFUNCTIONALLY SUBSTITUTED PYRIDO [3, 2-C]-PYRIDINES AND PYRIDO [2, 3-C]-PYRIDAZINES

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The phenylhydrazino derivatives of ethyl acetoacetate (**1**), acetylacetonitrile (**11**) and acetylacetone (**17**) reacted with malononitrile, malononitrile dimer (**4a**) or ethyl cyanacetate dimer (**4b**). The products were treated with benzaldehyde to yield different polyfunctionally substituted pyridopyridines and pyridopyridazines.

Key words: Pyridopyridines, Pyridopyridazines, α-arylhydrazino ketones.

Introduction

The synthesis of polyfunctionally substituted heteroaromatics has received (Sadek 1984; Elnagdi *et al* 1988; 1989a; 1990a) great attention during the last decade. The importance of such compounds is due to their use as potential biodegradable agrochemicals. Recently (Elnagdi *et al* 1990b) some pyridazine derivatives were obtained by condensing α-arylhydrazino ketones with active methylene nitriles. In this investigation, we report the synthesis of some polyfunctionally substituted pyrido [3,2-c]-pyridenes and pyrido [2,3-c]-pyridazines. Beside obtaining the compounds in good yields, the reported procedures are simpler than the earlier methods (Kato and Skamoto 1975; Terentev *et al* 1978, 1979; Jones and Rafferty 1979; Yamato and Sato 1982).

It was reported (Elnagdi 1989b; El-Kousy 1990) that fusion of ethyl-2-arylhydrazino-3-oxobutyrate (**1**) with malononitrile in the presence of ammonium acetate at 160°C produced aminopyridazinium carboxylate (**2**). Now, conducting this reaction under different condition viz. heating on a water bath, led to the formation of a completely different product to which structure (**3**) is assigned. We believe that the formation of (**3**) involved first dimerization of malononitrile to yield the dimer (**4a**), which then condensed with (**1**) to yield (**5**) and then the reaction proceeded as shown in chart 1. To support this view, (**3**) was obtained by condensing (**1**) with the dimer (**4a**) in the presence of ammonium acetate.

Compound (**3**) was also obtained through condensation of (**1**) with diethyl-3-amino-2-cyano-2-pentene-1, 5-dicarboxylate (**4b**).

When compound (**3**) was allowed to condense with benzaldehyde, a new pyridazine derivative (**10**) was formed. The formation of this product perhaps involved condensation followed by cyclization and finally aromatization (cf. chart 2). Condensation of the dimer (**4a**) with (**11**) afforded the pyridine derivative (**13**) as the only isolable product which might involve the intermediacy of (**12**) (cf. chart 3). The pyridine derivative (**13**) was subjected to two main reactions. Thus refluxing (**13**) in acetic/hydrochloric acid mixture (1:1) led to the formation of (**14**). Also condensation of (**13**) with benzaldehyde afforded the pyridopyridazine derivative (**15**). The formation of the possible cyclization product (**16**) is ruled out on the basis of IR and ^{1}H-NMR spectral data. The IR spectrum of the product revealed the presence of NH_2 group stretching at γ = 3500-3300 cm^{-1}. Furthermore, the ^{1}H-NMR showed a singlet at δ = 2.52 ppm for NH_2 (disappeared on addition of D_2O) and a singlet at δ = 6.82 ppm for the pyridazine H-4 (Table 1).

The dimer (**4a**) condensed with the phenylhydrazine derivative (**17**) with the formation of the pyridopyridazine (**20**) which is assumed to be formed via the intermediates (**18**) and (**19**) (cf. chart 4). When this pyridopyridazine (**20**) was allowed to condense with benzaldehyde, the corresponding pyridophthalazine derivative (**21**) was obtained. The forma-

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tion of the latter might involve condensation followed by ring closure and finally aromatization.

Condensation of (**17**) with dicarboxylate ester (**4b**) led to the formation of the pyridopyridine derivative (**24**). The latter might involve the intermediates (**22**) and (**23**). When (**24**) was allowed to condense with benzaldehyde, (**25**) was formed as the only isolable product.

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam SP-110 spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM-390-90 MHz

Table 1

Spectral data of the new compounds

Comp.	IR, γ cm^{-1} (KBr)					^{1}H-NMR, δ ppm
	CO	CN	NH	NH_2	OH	
3	1680	2120	3250	--	3620	1.36 (s, 3H, CH_3); 7.6-7.7 (m, 5H, Ar-H); 8.2 (s, 2H, NH); 9.2 (s, 1H, OH, disappeared by D_2O).
8	1690	2220	3200	--	--	6.3 (d, J=11.2 Hz, 2H, CH=CH); 7.35-7.62 (m, 10H, Ar-H); 8.4 (s, 2H, NH).
10	1690	2220	3200	--	--	6.8 (s, 1H, CH); 7.2-7.8 (m, 10H, Ar-H); 8.2 (s, 2H, NH).
13	--	2220	3200	3400	--	1.35 (s, 3H, CH_3); 2.5(s, 2H, NH_2); 7.35-7.65 (sm, 5H, Ar-H); 8.6 (s, 1H, NH).
14	1660	2220	3240	3400	--	1.2(s, 3H, CH_3); 2.4 (s, 2H, NH_2); 7.3-7.6 (m, 5H, Ar-H); 7.9 (s, 2H, NH).
15	--	2100	--	3400	--	2.52 (s, 2H, NH_2); 6.82 (s, 1H, pyridazine-H); 7.35-7.55 (m, 10H, Ar-H).
20	1680	2220	3105	3400	--	1.36, 2.21 (2s, 6H, $2CH_3$); 2.35 (s, 2H, NH_2); 7.32-7.38 (m, 5H, Ar-H); 8.22 (s, 1H, NH).
21	--	2220	3150	3450	--	2.35 (s, 2H, NH_2); 7.00-7.8 (m, 10H, Ar-H) 8.12 (s, 1H, NH).
24	1685	2220	3100	--	--	1.00, 1.25 (2s, 6H, $2CH_3$); 7.20-7.82 (m, 5H, Ar-H); 8.40 (m, 2H, 2NH).

Table 2

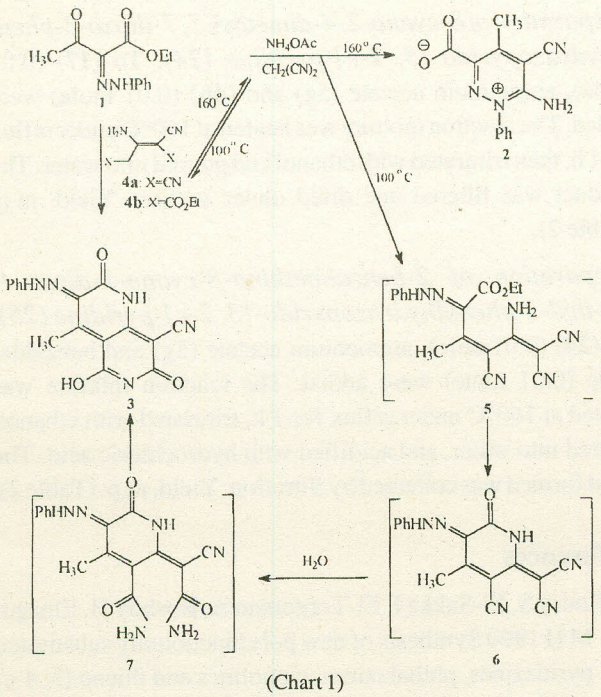
Microanalytical data of the new compounds

Comp.	Yield (%)	*M.P. (°C)	M. F.	Calc (%)			Found (%)		
				C	H	N	C	H	N
3	80,64	240*	$C_{16}H_{11}N_5O_3$	59.81	3.45	21.80	59.8	3.3	21.9
8	94	210**	$C_{23}H_{15}N_5O_3$	67.48	3.69	17.11	67.6	3.6	17.2
10	80	220**	$C_{23}H_{13}N_5O_3$	67.81	3.17	17.19	68.0	3.2	17.2
13	94	290*	$C_{16}H_{11}N_7$	63.78	3.68	32.54	63.6	3.6	32.6
14	95	160*	$C_{16}H_{12}N_6O_2$	60.00	3.78	26.24	59.8	3.8	26.3
15	95	101*	$C_{23}H_{13}N_7$	71.31	3.38	25.31	71.2	3.3	25.3
20	90	240*	$C_{17}H_{14}N_6O$	64.14	4.43	26.40	64.0	4.3	26.3
21	90	190**	$C_{24}H_{16}N_6O$	71.28	4.00	20.78	71.1	4.0	20.8
24	74	120*	$C_{17}H_{13}N_5O_2$	63.94	4.10	21.93	64.0	4.2	22.0
25	85	115**	$C_{24}H_{17}N_5O_2$	70.75	4.21	17.19	70.6	4.4	17.0

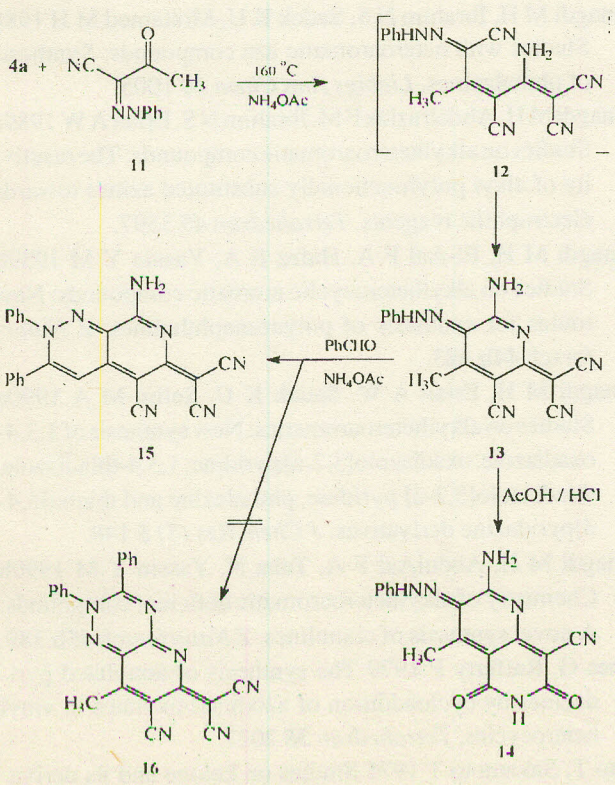
*Solvent of Crystallisation, * Ethanol, ** Dioxane.*

spectrometer using TMS as internal standard and chemical shifts are expressed as δ ppm. The microanalyses were carried out by the Microanalytical Unit at Cairo University.

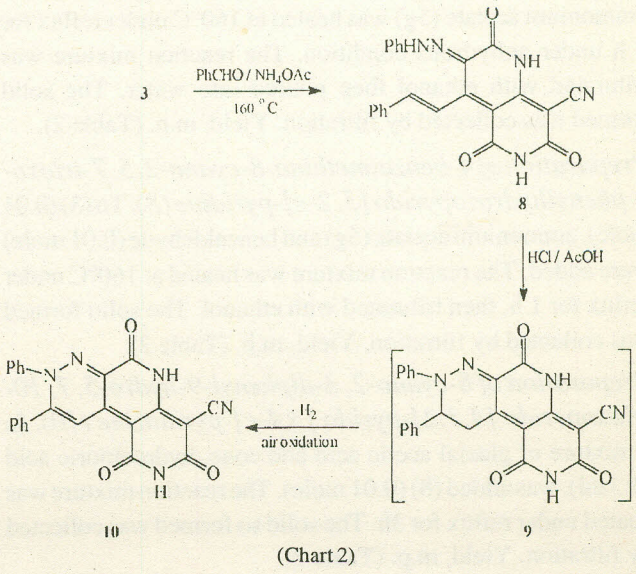
Preparation of 8-cyano-5-hydroxy-4-methyl-2, 7-dioxo-3-phenylhydrazopyrido [3, 2-c]pyridine (3). Method A: To (**1**) (0.01 mole) ammonium acetate (5g) and malononitrile (0.02 mole) or malononitrile dimer (**4a**) (0.01 mole) were added. The reaction mixture was heated under reflux at 100°C



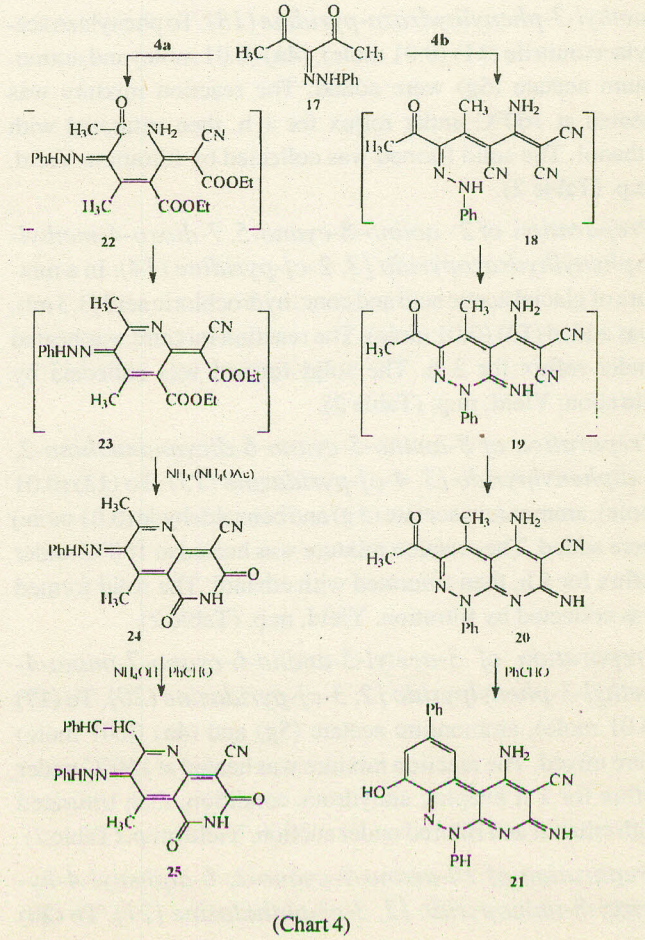
(Chart 1)



(Chart 3)



(Chart 2)



(Chart 4)

for 1 h under anhydrous condition. After cooling the reaction mixture was triturated with ethanol then poured into water. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Method B: A mixture of (**1**) (0.01 mole), (**4b**) (0.01 mole) and ammonium acetate (5g) was heated at 160°C under reflux for 3 h under anhydrous condition. The reaction mixture was triturated with ethanol then poured into water. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 4-benzalmethino-8-cyano-2, 5, 7-trioxo-3-phenylhydrazopyrido [3, 2-c]-pyridine (8). To (**3**) (0.01 mole), ammonium acetate (5g) and benzaldehyde (0.01 mole) were added. The reaction mixture was heated at 160°C under reflux for 1 h, then triturated with ethanol. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 8-cyano-2, 3-diphenyl-9-hydro-5, 7, 10-trioxopyrido [4,3:2]-pyrido [3,4-c]-pyridazine (10). In a mixture of glacial acetic acid and conc. hydrochloric acid (3:3 ml), was added (**8**) (0.01 mole). The reaction mixture was heated under reflux for 3h. The solid so formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 2-amino-5-cyano-6-dicyanomethino-4-methyl-3-phenylhydrazo-pyridine (13). To phenylazo acetylacetonitrile (**11**) (0.01 mole), (**4a**) (0.01 mole) and ammonium acetate (5g) were added. The reaction mixture was heated at 160°C under reflux for 1 h, then triturated with ethanol. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 2-amino-8-cyano-5, 7-dioxo-4-methyl-3-phenylhydrazopyrido [3, 2-c]-pyridine (14). In a mixture of glacial acetic acid and conc. hydrochloric acid (3:3 ml), was added (**13**) (0.01 mole). The reaction mixture was heated under reflux for 3 h. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 8-amino-5-cyano-6-dicyanomethino-2, 3-diphenylpyrido [3, 4-c]-pyridazine (15). To (**13**) (0.01 mole), ammonium acetate (5 g) and benzaldehyde (0.01 mole) were added. The reaction mixture was heated at 100°C under reflux for 1 h, then triturated with ethanol. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 3-acetyl-5-amino-6-cyano-7-imino-4-methyl-1-phenylpyrido [2, 3-c]-pyridazine (20). To (**17**) (0.01 mole), ammonium acetate (5g) and (**4a**) (0.01 mole) were mixed. The reaction mixture was heated at 160°C under reflux for 1 h keeping anhydrous condition, then triturated with ethanol and filtered under suction. Yield, m.p. (Table 2).

Preparation of 10-amino-9-cyano-2, 6-diphenyl-4-hydroxy-8-iminopyrido [2, 3-c]-phthalazine (21). To (**20**) (0.01 mole), ammonium acetate (5g) and benzaldehyde (0.01 mole) were added. The reaction mixture was heated at 160°C under reflux, then triturated with ethanol and poured into water, then acidified with hydrochloric acid. The solid formed was collected by filtration. Yield, m.p. (Table 2).

Preparation of 8-cyano-2, 4-dimethyl-5, 7-dioxo-3-phenylhydrazopyrido [3, 2-c]-pyridine (24). To (**17**) (0.01 mole), ammonium acetate (5g) and (**4b**) (0.01 mole) were added. The reaction mixture was heated at 160°C under reflux for 1 h, then triturated with ethanol and poured into water. The product was filtered and dried under suction. Yield, m.p. (Table 2).

Preparation of 2-benzalmethino-8-cyano-5-dioxo-4-me-thyl-3-phenylhydrazopyrido-[3, 2-c]-pyridine (25). To (**24**) (0.01mole), ammonium acetate (5g) and benzaldehyde (0.01 mole) were added. The reaction mixture was heated at 160°C under reflux for 1 h, triturated with ethanol, poured into water, and acidified with hydrochloric acid. The solid formed was collected by filtration. Yield, m.p. (Table 2).

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