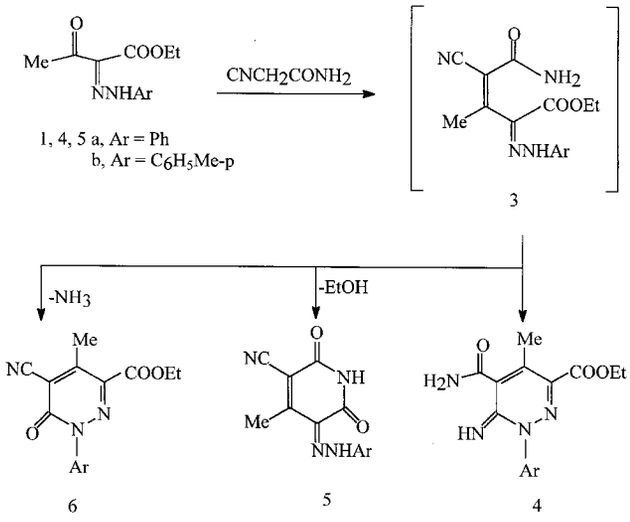
Studies on Polyfunctionalised Heteroaromatics: Synthesis of Several New Cinnoline and Pyrido[3,4-c]pyridazine Derivatives

Magda A. Barsy
Department of Chemistry, Faculty of Science, South Valley University, Aswan 81528, Egypt

One-pot reaction of ethyl 2-aryhydrazono-3-oxobutyrates with cyanoacetamide afforded pyridazine and pyridine derivatives, which were found to be excellent precursors for the synthesis of different cinnolines and pyrido[3,4-c]pyridazines, respectively.

In recent papers we have reported an efficient synthesis of fused azines and azoles with substituted pattern required for biological studies.[1-3] In continuation of our work we report here synthesis of several new cinnolines and pyridopyridazines which are difficult to be obtained by known synthetic routes.[4-7] Reaction of ethyl 2-aryhydrazono-3-oxobutyrates **1a** (Ar = Ph) with cyanoacetamide **2** in the presence of ammonium acetate at 160 °C for 10 min yielded a mixture (1:1.3) of two products, with molecular formulae $C_{15}H_{16}N_4O_3$ (M^+ = 300) and $C_{13}H_{10}N_4O_2$ (M^+ = 254), respectively. The former was identified as the pyridazine derivative **4** and the latter as the pyridine derivative **5**. Structural assignments were based on analytical and spectral data. Thus the IR spectrum of compound **4** indicated the presence of bands for ester, amide CO, and NH_2 groups. No cyano absorption band was exhibited. The ^1H NMR spectrum was also in accordance with the proposed structure. On the other hand, compound **5** is colored due to the presence of the hydrazone chromophore, which is indicated by a strong UV absorption band at 360 nm. Its IR spectrum indicates the presence of a ring CO band at 1680 cm^{-1}, as well as a cyano band at 2220 cm^{-1}. The ^1H NMR spectrum revealed only a multiplet at δ = 7.2-7.6 ppm integrating for aromatic and NH protons, a broad band at δ = 7.00 for NH protons in addition to the methyl singlet at δ = 2.52. A possible mechanism for the formation of both **4** and **5** is depicted in Scheme I; in each case a Knoevenagle condensation would yield an intermediate **3**, cyclization of which via the elimination of an ethanol molecule would afford **5**, while intramolecular cyclization addition to the nitrile function would give **4**. Similarly, when the same reaction was proceeded by refluxing in a mixture of benzene/ acetic acid (50:10 v/v), the reaction flask was provided with a device for continuous separation of water. The reaction afforded a mixture (1:1:0.5) of three products, the previous two compounds **4** and **5** in addition to the pyridazine derivative **6**. Compound **6** has been previously reported by Elnagdi et al.,[8] through an otherwise different reaction route (Scheme I). We believe that compound **6** is formed

Scheme I



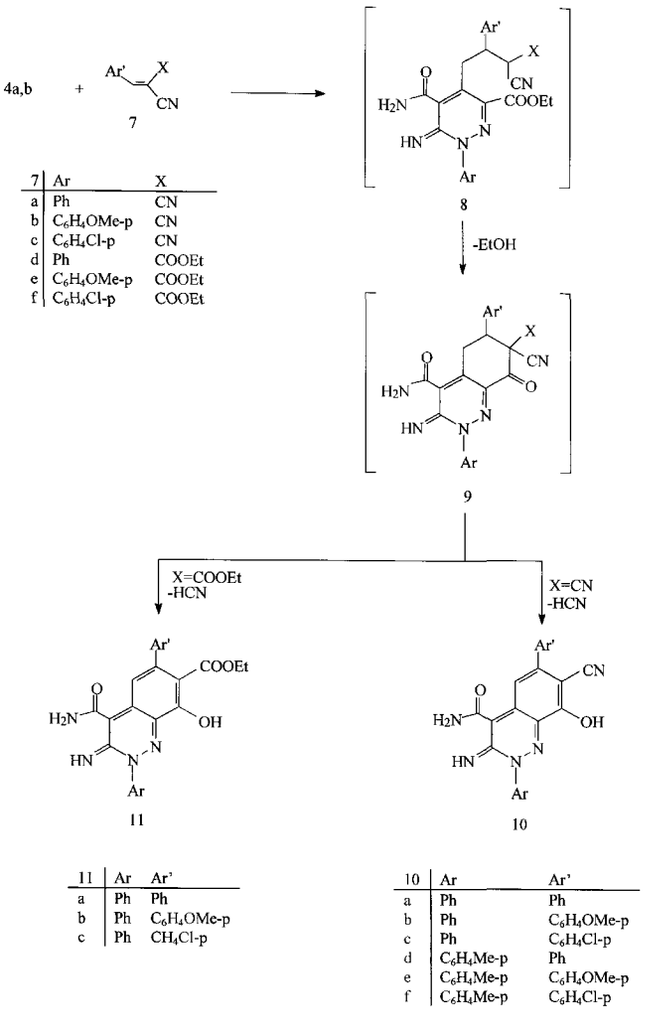
through the same intermediate **3** by elimination of ammonia. Similarly **1b** reacted with **2** to afford **4b, 5b**.

Reaction of compound **4a** with arylidenemalononitriles **7a-c** in ethanol in the presence of piperidine at reflux temperature gave cinnolines **10a-c** by elimination of ethanol and HCN .The formation of **10** is assumed to proceed via Michael-type addition of the methyl function in **4** to the activated double bond in **7,** affording the acyclic adduct **8**, which then cyclizes to give **9** via loss of ethanol and then aromatises via elimination of HCN to yield **10** (Scheme II). A similar elimination aromatization has been observed before.[2]

In contrast to the anticipated formation of the nitrile cinnolines **10a-f**, the reaction of compound **4a** with arylidene ethyl cyanoacetate **7d-f** (X = COOEt) afforded the esters **11a-c** and are assumed to proceed via the elimination of HCN from the intermediate **9**.

Compound **4a** reacted also with urea derivatives **12a,b** to yield the pyrmido[4,5-c] pyridazine derivatives **13a,b**. Attempts to cyclize **4** with formic acid, acid chlorides, aryl

Scheme II

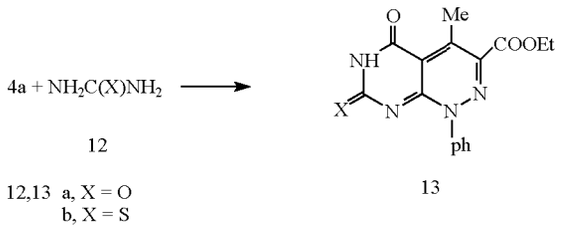


7	Ar	X
a	Ph	CN
b	C_6H_4OMe-p	CN
c	C_6H_4Cl-p	CN
d	Ph	COOEt
e	C_6H_4OMe-p	COOEt
f	C_6H_4Cl-p	COOEt

11	Ar	Ar'
a	Ph	Ph
b	Ph	C_6H_4OMe-p
c	Ph	CH_4Cl-p

10	Ar	Ar'
a	Ph	Ph
b	Ph	C_6H_4OMe-p
c	Ph	C_6H_4Cl-p
d	C_6H_4Me-p	Ph
e	C_6H_4Me-p	C_6H_4OMe-p
f	C_6H_4Me-p	C_6H_4Cl-p

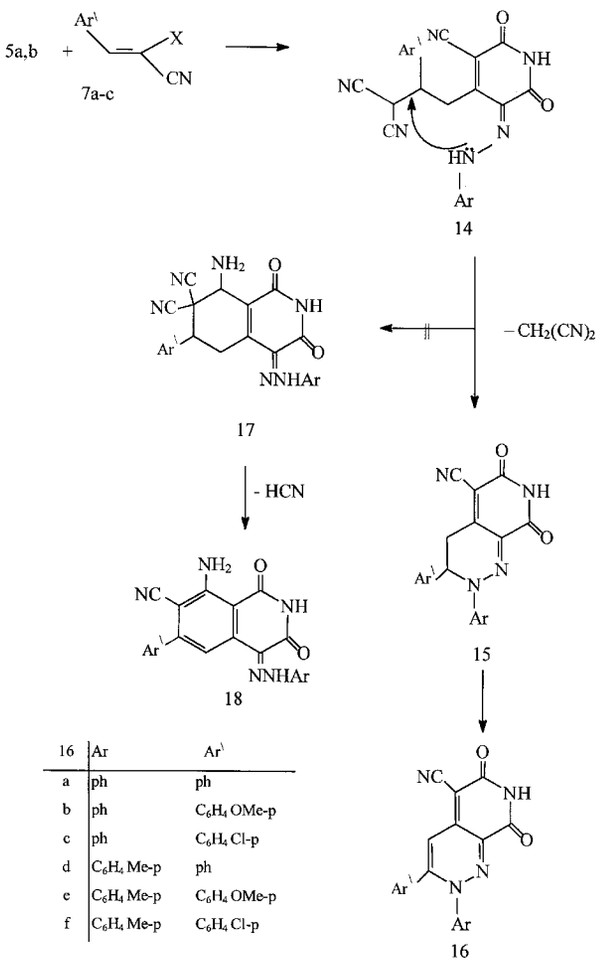
aldehyds, and phenylisocyanates to obtain further derivatives of pyrmidopyridazines were not successful. Chart 1.



12,13 a, X = O
b, X = S

Aiming at the synthesis of pyrido[3,4-c]pyridazines, compound 5 was heated with arylidenemalononitriles **7a-c** (X = CN) in ethanol (30 ml) for 6 hr. In the presence of a few drops of pipredine, a product of molecular formula $C_{20}H_{12}N_4O_2$ (M^+ = 339) was yielded. The ^1H NMR spectrum of the reaction product revealed only a multiplet at δ = 7.30-7.81 integrating for aromatic protons, in addition to the pyridazine protons at δ = 6.10 ppm. Moreover, we could detect by TLC the presence of malononitrile in the reaction mixture. Structure **16** was assigned for the reaction product. On the other hand isoquinoline **18** was ruled out based on both spectral and elemental data. The formation of **16** is assumed to proceed through the intermediacy of the Michael adduct **14** which loses malononitrile via an S_N2 displacement into dihydropyridopyridazine **15** which undergoes autooxidation under the reaction conditions affording **16**. The compound exists as a keto form based on the IR and ^1H NMR spectra (Scheme III).

Scheme III



16	Ar	Ar'
a	ph	ph
b	ph	C_6H_4OMe-p
c	ph	C_6H_4Cl-p
d	C_6H_4Me-p	ph
e	C_6H_4Me-p	C_6H_4OMe-p
f	C_6H_4Me-p	C_6H_4Cl-p

EXPERIMENTAL

Merck Silica gel (PF 25a) was used for thin layer chromatography. Melting points were determined by a Gallen-Kamb apparatus and are uncorrected. IR spectra were ob-

tained using (KBr, $\nu = cm^{-1}$) on a Shimadzu 408 and a Pye Unicam spectrophoto-meter. ^1H NMR spectra were measured in DMSO, TMS as internal standard on a Varian EM 340 40 MHz spectrometer. Mass spectra were performed on a mass spectrometer. MS 9 (AET) ET Mode. Analytical data were carried out at the Micro Analytical Centre, Cairo University, Cairo, Egypt.

Reaction of arylhydrazones 1a,b with cyanoacetamide 2

General procedure:

Method A

A mixture of equimolar amounts of **1a** (2.3 g, 0.01 mol)

Table 1. Physical and Analytical Data of New Compounds

Comp.	Yield (%)	M.p. (°C)	Solvent of recrystallization	Molecular formula	MS (70 ev) (*m/z*)	Analysis found /calcd.				
						C	H	N	S	Cl
4a	40	241-3	Acetone	$C_{15}H_{16}N_4O_3$ (300.31)	300	59.98 59.83	5.37 5.20	18.85 18.62		
4b	39	250-1	Acetone	$C_{16}H_{18}N_4O_3$ (314.33)	314	61.13 61.00	5.77 5.50	17.82 17.61		
5a	35	315	DMF	$C_{13}H_{10}N_4O_2$ (254.24)	254	61.41 61.31	3.96 3.72	22.03 22.15		
5b	35	268	DMF	$C_{14}H_{12}N_4O_2$ (268.33)	268	62.66 62.71	4.50 4.63	20.88 20.62		
10a	82	270-2	DMF-H_2O	$C_{22}H_{14}N_5O_2$ (380.37)	380	69.46 69.61	3.70 3.71	18.41 18.00		
10b	80	240	DMF-H_2O	$C_{23}H_{16}N_5O_3$ (410.4)	410	67.30 67.15	3.93 3.80	17.06 17.29		
10c	83	250	Dioxane	$C_{22}H_{13}N_5O_2Cl$ (418.81)	415	63.69 63.72	3.15 3.00	16.88 16.63	-	8.54 8.61
10d	81	> 300	DMF	$C_{23}H_{16}N_5O_2$ (394.4)	394	70.03 69.85	4.08 3.95	17.75 17.28		
10e	80	> 300	DMF	$C_{24}H_{18}N_5O_3$ (424.42)	424	67.91 67.77	4.24 4.15	16.50 16.32		
10f	85	260-1	Dioxane	$C_{22}H_{15}N_5O_2Cl$ (416.83)	416	63.38 63.11	3.82 3.51	16.80 16.78	-	8.50 8.41
11a	80	295	DMF	$C_{24}H_{19}N_4O_4$ (427.42)	427	67.43 67.22	4.48 4.15	13.10 12.95		
11b	80	297-8	DMF	$C_{25}H_{21}N_4O_5$ (457.45)	457	65.63 65.05	4.62 4.33	12.24 11.98		
11c	81	260-1	Ethanol	$C_{24}H_{18}N_4O_4$ 426.41)	426	67.59 67.05	4.25 4.03	13.13 12.97		
13a	69	> 300	Dioxane	$C_{16}H_{14}N_4O_4$ (326.3)	326	58.89 58.67	4.32 4.36	17.17 16.93		
13b	70	> 300	Dioxane	$C_{16}H_{14}N_4O_3S$ (392.36)	392	48.47 48.77	3.59 3.81	14.28 14.00	8.17 8.33	
16a	70	> 300	DMF	$C_{20}H_{12}N_4O_2$ (340.33)	339	70.75 70.70	3.55 3.41	16.46 16.61		
16b	71	> 300	DMF	$C_{21}H_{14}N_4O_3$ (370.35)	369	68.10 68.00	3.80 3.60	15.12 15.45		
16c	75	> 300	DMF	$C_{20}H_{11}N_4O_2Cl$ (37.77)	374	69.09 69.23	2.95 2.81	19.95 19.63	-	9.45 9.31
16d	71	> 300	DMF	$C_{21}H_{14}N_4O_2$ (354.35)	353	71.87 72.01	3.98 3.81	15.81 15.62		
16e	73	> 300	DMF	$C_{22}H_{16}N_4O_3$ (384.38)	383	68.73 68.60	4.14 4.34	14.57 14.50		
16f	70	> 300	DMF	$C_{21}H_{13}N_4O_2Cl$ (388.79)	388	64.86 64.67	3.36 3.14	14.41 14.21	-	9.11 8.88

and\or **1b** (2.4 g, 0.01 mol); cyanoacetamide (0.84 g, 0.01, mol) and anhydrous ammonium acetate (0.77 g, 0.01 mol) was heated in an oil bath at 160 °C for 10 min. The resulting mixture, was cooled and then treated with ethanol; the solid product so formed was collected by filtration and subjected to thin plate chromatography using toluene-ethylacetate (2:1 V/V) as eluent. Analytical samples were further purified by recrystallization from appropriate solvents. The results are listed in Tables 1, 2.

Method B

A mixture of equimolar amounts of **1a** or **1b** (0.01 mol) and cyanoacetamide (0.84 g, 0.01 mol) in acetic acid/benzene mixture (50:10 v/v) was heated for 3 hours under reflux using a device of continuous separation of water after 3h. The solid product crystallized out of the hot solution was filtered off; and identified as compounds **4a,b**. The filtrate was evaporated

Table 2. ^{1}H NMR and IR Spectra of New Compounds

Comp.	^{1}H NMR (DMSO-d_6) δ (H_z)	IR (KBr) ν (cm^{-1})
4a	1.32 (t,3H,CH_3), 2.48 (s,3H,CH_3), 4.26 (q,2H, CH_2), 6.71 (b,1H,NH), 7.20-7.51 (m,5H,arom), 7.77 (bs, 2H, NH_2).	3439-3300 (NH_2), 3200 (NH), 1730 (CO), 1680 (CO).
4b	1.34 (t,3H,CH_3), 2.50 (s,3H,CH_3), 3.00 (s,3H, CH_3), 4.29 (q,2H,CH_2), 6.85 (br,1H,NH), 7.31-7.62 (m,5H,arom), 7.92 (br,2H,NH_2).	3470-3380 (NH_2), 3250 (NH), 1725 (CO), 1675 (CO).
5a	2.52 (s,3H,CH_3), 7.00 (br,1H,NH), 7.31-7.60 (m,5H,arom, and NH).	3188, 3011 (NH), 2229 (CN), 1685 (CO).
5b	2.61(s,3H,CH_3), 2.75 (s,3H,CH_3), 7.11 (br,1H, NH), 7.44-7.82 (m,5H,arom. and NH).	3156, 3130 (NH), 2225 (CN), 1680 (CO).
10a	3.91 (s,1H,cinnoline H-5), 7.49-7.96 (m,11H,arom. And NH),7.81 (br, 2H, NH_2).	3448-3380 (NH_2), 3280 (NH), 2200 (CN), 1680 (CO), 1640 (ring CO).
10b	3.60(s,3H,OCH_3), 6.87(s,1H,cinnoline H-5), 7.13-7.26(m,1H,arom. and NH),7.86(br, 2H, NH_2).	3428-3390(NH_2), 3250(NH), 2225(CN), 1960 (CO), 1640(ring CO).
10c	6.93 (s,1H,cinnoline H-5), 7.31-7.61 (m,10H, arom. and NH), 7.9 (br,2H,NH_2).	3480-3380 (NH_2), 3250 (NH), 2210 (CN), 1695 (CO), 1650 (ring CO).
10d	2.33(s,3H,CH_3),6.45(s,1H,cinnoline H-5), 7.49-8.11(m,10H,arom. and NH),8.31(br,2H,NH_2).	3450-3300 (NH_2), 3200(NH), 2222(CN), 1685(CO), 1650(ring CO).
10e	2.44 (s,3H,CH_3), 3.50 (S,3H,OCH_3), 6.93 (s,1H, cinnoline H-5), 7.53-7.72 (m,9H,arom. and NH), 8.22 (br,2H,NH_2).	3440-3380 (NH_2), 3250 (NH), 2200 (CN), 1690 (CO), 1650 (ring CO).
10f	2.31 (s,3H,CH_3), 6.88 (s,1H,cinnoline H-5), 7.33-7.60 (m,9H,arom. and NH), 7.92 (br,2H,NH_2).	3450-3360 (NH_2), 3250 (NH), 2223 (CN), 1685 (CO), 1650 (ring CO).
11a	1.41 (t,3H,CH_3), 4.31 (q,2H,CH_2), 6.75 (s,1H, cinnoline H-5), 7.43-7.56 (m,11H,arom. and NH), 8.11 (br,2H,NH_2).	3460-3320 (NH_2), 3200 (NH), 1730 (CO), 1670 (CO), 1636 (ring CO).
11b	1.33 (t,3H,CH_3), 3.50 (s,3H,OCH_3), 4.27 (q,2H, CH_2), 6.72 (s,1H,cinnoline H-5), 7.51-7.77 (m, 10H,arom. And NH), 7.92 (br,2H, NH_2).	3440-3300 (NH_2), 3195 (NH), 1725 (CO), 1665 (CO), 1636 (ring CO).
11c	1.32 (t,3H,CH_3), 4.11 (q,2H,CH_2), 6.85 (s,1H, cinnoline H-5), 7.50-7.81 (m,10H,arom. and NH), 8.11 (br,2H,NH_2).	3400-3320 (NH_2), 3250 (NH), 1710 (CO), 1670 (CO), 1640 (ring CO).
13a	1.46 (t,3H,CH_3), 2.51 (s,3H,CH_3), 4.11 (q,2H, CH_2), 7.44-7.65 (m,5H,arom.), 11.51 (s,1H,NH).	2926 (NH), 1720 (CO), 1701,1660 (ring CO).
13b	1.44 (t,3H,CH_3), 2.50 (s,3H,CH_3), 4.15 (q,2H, CH_2), 7.51-7.70 (m,5H,arom.), 11.61 (s,1H,NH).	2955 (NH), 1710 (CO), 1685,1645 (ring CO), 1528 (CS=NH), 1230 (C=S).
16a	6.10 (s,1H, pyridazine), 7.30-7.81 (m,11H,arom. and NH).	3020 (NH), 2220 (CN), 1667,1625 (CO).
16b	3.41 (s,3H,OCH_3), 6.12 (s,1H,pyridazine), 7.44 -7.72 (m,10H,arom. and NH).	3072 (NH), 2200 (CN), 1670, 1632 (CO).
16c	6.11 (s,1H,pyridazine), 7.45-7.69 (m,10H, arom. and NH).	3284 (NH), 2225 (CN), 1665, 1620 (CO).
16d	1.50 (s,3H,CH_3), 6.09 (s,1H,pyridazine), 7.43-7.62 (m,10H, arom. and NH).	3264 (NH), 2222 (CN), 1659, 1636 (CO).
16e	1.49 (s,3H,CH_3), 3.41 (s,3H,OCH_3), 6.11 (s,1H, pyridazine), 7.51-7.80 (m,9H,arom. and NH).	3152 (NH), 2220 (CN), 1668, 1620 (CO).
16f	1.44 (s,3H,CH_3), 6.11 (s,1H,pyridazine), 7.51-7.72 (m,9H,arom. and NH).	3160 (NH), 2223 (CN), 1664, 1632 (CO).

under vacuum and subjected to TLC as above to give compounds **5, 6**.

Synthesis of Ethyl-4-amino-3-imino-2,3-dihydro-8-hydroxy-2,6-diarylcinnoline-3-carbonitrile (10a-f)
General procedure:

A mixture of **4a** (3.0 g, 0.01 mol) or **4b** (3.1 g, 0.01 mol), arylidenemalononitrile (0.01 mol) in ethanol (30 ml), and catalytic amounts of piperidine were heated under reflux for 4-6 h. The solvent was reduced under vacuum and the solid product so formed on cooling was collected by filtration and crystallized from an appropriate solvent. (Tables 1, 2)

Synthesis of Ethyl-4-amino-3-imino-2,3-dihydro-8-hydroxy-2,6-diarylcinnoline-3-carboxylate (11a-c)
General procedure:

A mixture of **4a** (3.0 g, 0.01 mol) or **4b** (3.1 g, 0.01 mol), arylidenethyl cyanoacetate (0.01 mol) in ethanol (30 ml), and catalytic amounts of piperidine were heated under reflux for 4-6 h. The solvent was reduced under vacuum and the solid product so formed on cooling was collected by filtration and crystallized from an appropriate solvent. (Tables 1, 2)

Synthesis of pyrimidopyridazine derivatives 13a,b
General procedure:

A solution of **4a** (3.0 g, 0.01 mol) in absolute ethanol (30 ml) was treated with urea (0.06 g, 0.01 mol) or thiourea (0.07 g, 0.01 mol) in the presence of 20 ml concentrated hydrochloric acid. The reaction mixture was heated under reflux for 25 h (TLC control); the solid product so formed on hot was collected by filtration and crystallized from the proper solvent.

Synthesis of pyrido[3,4-c]pyridazines
General procedure:

A mixture containing **5a** (2.5 g, 0.1 mol) or **5b** (2.6 g, 0.1 mol) and arylidenemalononitrile **7a-c** (0.1 mol) and a few drops of piperidine was heated in ethanol under reflux for 4h. The reaction solution was evaporated till dryness and the residue was treated with methanol. The solid product so formed was collected by filtration and crystallised from the proper solvent. (Tables 1, 2)

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Key Words
Cinnolines; Pyrido[3,4-c]pyridazines.

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