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NOVEL SYNTHESIS OF 1,8-ALKANOPYRIDO-[3,4-*d*]PYRIDAZINE: A NEW RING SYSTEM

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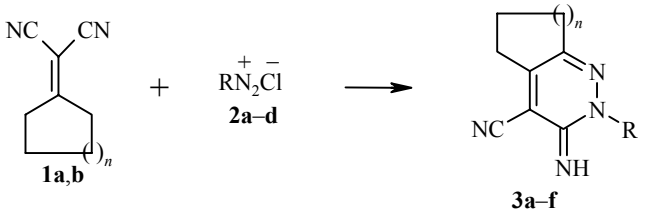
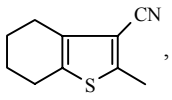
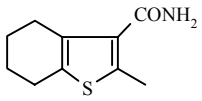
Cycloalkylidenemalononitriles couple with various diazonium salts to yield the corresponding cycloalkeno[c]pyridazines, which react with trichloroacetonitrile to give the 1,8-alkanopyrido[3,4-d]-pyridazines. The reaction of cycloalkenopyridazines with DMF dimethylacetal gives enamine derivatives, which can be converted to 1,8-alkanopyrido[3,4-d]pyridazines via treating with hydrazine hydrate or aromatic amines. Substituted cycloalkenopyridines react with diazoaminobenzene to afford the corresponding 1,8-alkanopyridopyridazines.

Keywords: 1,8-alkanopyrido[3,4-*d*]pyridazines, cycloalkenopyridazines, cycloalkenopyridines.

Activated methylene nitriles are highly reactive reagents that have found extensive application in organic synthesis [1-3]. Condensed azines comprise a very interesting class of compounds because of their biological and medicinal activities [4-6]. In the last decade we have reported several novel syntheses of azines utilizing activated nitriles as starting materials [7-9]. In conjunction with our interest, we report here on the reactivity of ylidene derivatives **1a**,**b** toward organic reagents of different types with the aim of preparing 1,8-alkanopyrido-pyridazines. Thus, ylidene derivatives **1a**,**b** readily coupled with diazonium salts **2a-d** to give a product that was established as having structure **3a-f**. The mass spectrum of **3a** showed *m/z* 281 and its IR revealed the presence of NH and cyano groups at 3320 and 2212 cm^{-1}, respectively. ^1H NMR revealed the presence of aromatic protons at δ 7.98-7.53 ppm. ^{13}C NMR indicated the presence of one cyano group at δ 116.89 ppm. Signals of other skeletal carbons appeared at the expected positions. The structures of **3b-f** were established similarly.



1 a *n* = 1, **b** *n* = 2; **2 a** R = C_6H_4Cl-*p*, **b** R = $C_6H_4NO_2$-*m*, **c** R =  , **d** R =  ; **3 a**, **b**, **e**, **f** *n* = 1, **c**, **d** *n* = 2, **a**, **d** R = $C_6H_4NO_2$-*m*, **b**, **c** R = C_6H_4Cl-*p*,

e R =  , **f** R = 

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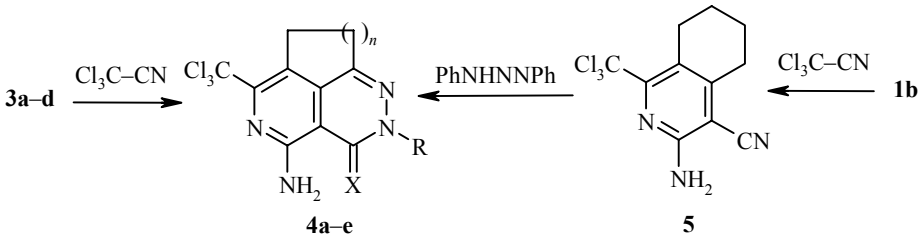
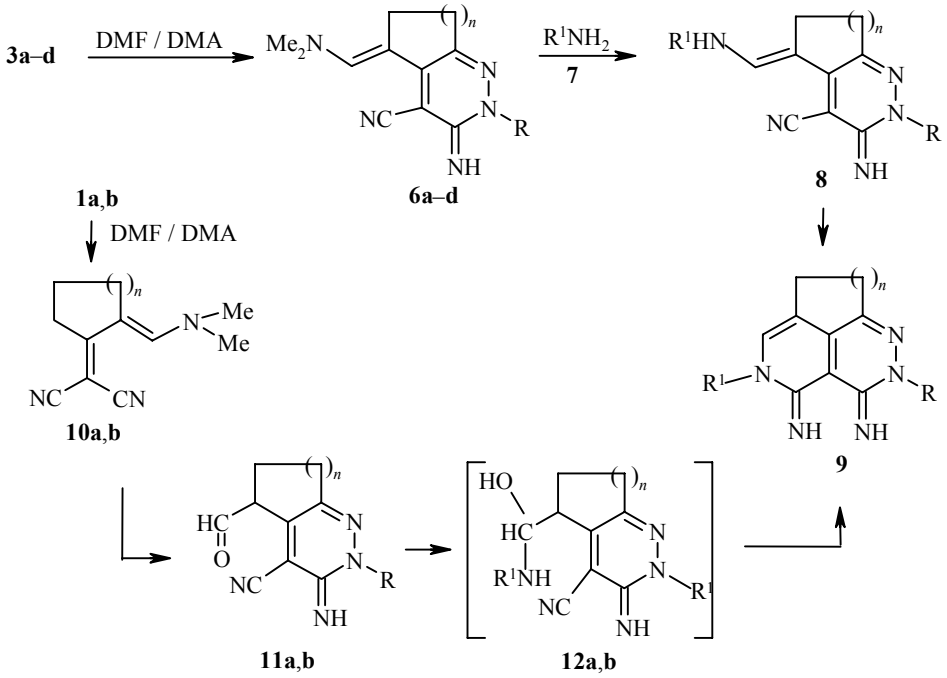


4 a,d R = $C_6H_4NO_2$-*m*, **b, c** R = C_6H_4Cl-*p*, **e** R = Ph; **a-d** X = NH, **e** X = O; **a, b** *n* = 1, **c-e** *n* = 2

Cycloalkanopyridazines **3a-d** react readily under basic condition with trichloroacetonitrile to give 1,8-alkanopyrido[3,4-*d*]pyridazine derivatives **4a-d** in good yields. The same reaction product, **4c**, could be obtained on treatment of **1b** with trichloroacetonitrile to give **5** followed by coupling with arene diazonium salt **2a** to give the final isolated product **4c** in low yield. Moreover, a good yield was obtained *via* treating pyridine derivative **5** with diazoaminobenzene in refluxing aqueous acetic acid/hydrochloric acid mixture to furnish the oxo derivative **4e**. The structures of **4a-e** were established based on their elemental analyses and spectral data.



6 a, **d** R = $C_6H_4NO_2$-*m*, **b**, **c** R = C_6H_4Cl-*p*, **a**, **b** *n* = 1, **c**, **d** *n* = 2; **7 a** $R^1 = NH_2$, **b** R^1 = Ph, **c** R^1 = 2-pyridyl;
9 a-f R = $C_6H_4NO_2$-*m*, **a**, **b** $R^1 = NH_2$, **c**, **d** R^1 = Ph, **e**, **f** R^1 = 2-pyridyl, **a**, **c**, **e** *n* = 1, **b**, **d**, **f** *n* = 2;
10 a *n* = 1, **b** *n* = 2; **11 a**,**b** R = $C_6H_4NO_2$-*m*, **a** *n* = 1, **b** *n* = 2

Furthermore, N,N-dimethylformamide dimethyl acetal (DMF/DMA) reacts with **3a-d** to give **6a-d**. Enamines **6a**,**d** react with hydrazine hydrate **7a** or aromatic amines **7b**,**c** to give *via* intermediate **8** pyridopyridazine derivatives **9a-f**. The formation of intermediates of the type **8** involves probably the loss of dimethylamine and is followed by cyclization under reaction conditions to give the final isolated product **9**. Alternatively, compounds **1a**,**b** were treated with DMF/DMA in DMF and piperidine to give the condensation products **10a**,**b**. The latter coupled with arene diazonium salt **2b** to give the aldehydes **11a,b**. Compounds **11a**,**b** reacted with hydrazine hydrate in ethanol/DMF mixture to give the final isolated products **9a**,**b** apparently through the intermediate **12**.

TABLE 1. Physical and Analytical Data of Newly Synthesized Compounds

Com-pound	Empirical formula	Found, % / Calculated, %				mp, °C	Color	Solvent	M.Wt./ *m/z*	Yield, %
		C	H	N	S					
1	2	3	4	5	6	7	8	9	10	11
3a	$C_{14}H_{11}N_5O_2$	60.01 / 59.77	4.00 / 3.94	25.02 / 24.90		147	Brown	EtOH	281.3 (281)	78
3b	$C_{14}H_{11}ClN_4$	62.32 / 62.10	3.99 / 4.10	20.65 / 20.69		140	Yellow	EtOH	270.74	70
3c	$C_{15}H_{13}ClN_4$	63.36 / 63.26	4.50 / 4.61	19.85 / 19.67		165	Yellow	EtOH	284.77	72
3d	$C_{15}H_{13}N_5O_2$	61.00 / 60.99	4.32 / 4.44	23.73 / 23.71		123	Yellow	EtOH	295.33	76
3e	$C_{11}H_9N_5S$	54.32 / 54.29	4.00 / 3.73	28.58 / 28.78	13.43 / 13.18	200	Brown	EtOH	243.32	66
3f	$C_{17}H_{17}N_5OS$	60.53 / 60.14	5.38 / 5.05	20.53 / 20.63	9.01 / 9.44	175	Pale-brown	EtOH/DMF	339.46	65
4a	$C_{16}H_{11}Cl_3N_6O_2$	45.32 / 45.14	2.60 / 2.61	19.76 / 19.74		>250	Brown	DMF	425.68 (425)	71
4b	$C_{16}H_{11}Cl_4N_5$	46.53 / 46.29	2.59 / 2.67	16.59 / 16.87		242	Yellow	DMF	415.12 (415)	63
4c	$C_{17}H_{13}Cl_4N_5$	47.58 / 47.57	3.00 / 3.05	16.36 / 16.32		284	Brown	DMF	429.15	75
4d	$C_{17}H_{13}Cl_3N_6O_2$	46.34 / 46.43	3.01 / 2.98	19.00 / 19.11		124	Brown	DMF	439.71	73
4e	$C_{17}H_{13}ClN_4O$	51.22 / 51.59	3.53 / 3.31	14.00 / 14.16		108	Brown	DMF	395.69	70
5	$C_{11}H_{10}Cl_3N_3$	45.66 / 45.46	3.75 / 3.47	14.36 / 14.46		160	Pale-brown	EtOH	290.59	69
6a	$C_{17}H_{16}N_6O_2$	60.71 / 60.69	4.94 / 4.80	24.76 / 24.98		197	Brown	EtOH	336.39 (336)	75
6b	$C_{17}H_{16}ClN_5$	62.41 / 62.66	4.83 / 4.95	21.43 / 21.49		213	Pale-brown	EtOH	325.83	78
6c	$C_{18}H_{18}ClN_5$	63.93 / 63.60	5.41 / 5.34	20.41 / 20.61		201	Yellow	EtOH	339.86	64

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
6d	$C_{18}H_{18}N_6O_2$	61.39 61.69	5.01 5.18	23.74 23.98		189	Yellow	EtOH	350.42	66
9a	$C_{15}H_{13}N_7O_2$	55.69 55.71	4.31 4.06	30.63 30.32		157	Yellow	DMF	323.35 (323)	79
9b	$C_{16}H_{15}N_7O_2$	57.01 56.95	4.53 4.49	29.01 29.06		168	Yellow	DMF	337.38	72
9c	$C_{21}H_{16}N_6O_2$	65.71 65.60	4.36 4.20	22.01 21.86		>250	Brown	DMF	384.43	74
9d	$C_{22}H_{18}N_6O_2$	66.31 66.31	4.81 4.56	21.38 21.09		165	Brown	EtOH	398.46	76
9e	$C_{20}H_{15}N_7O_2$	62.31 62.32	4.01 3.93	25.53 25.44		134	Brown	EtOH	385.42	71
9f	$C_{21}H_{17}N_7O_2$	63.31 63.13	4.39 4.29	24.63 24.55		176	Brown	EtOH	399.45	73
11a	$C_{15}H_{11}N_5O_3$	58.24 58.24	3.52 3.59	22.46 22.64		144	Red	Acetone	309.31 (309)	69
11b	$C_{16}H_{13}N_5O_3$	59.38 59.42	3.84 4.06	21.77 21.66		158	Red	Acetone	323.34	72
14b	$C_{16}H_{13}N_3OS$	65.00 65.25	4.34 4.44	14.01 14.22	11.00 10.85	173	Brown	EtOH	295.39	64
16a	$C_{21}H_{15}N_5O_3S$	60.51 60.41	3.45 3.62	16.98 16.77	7.83 7.68	188	Deep-yellow	DMF	417.48 (417)	70
16b	$C_{21}H_{16}N_4OS$	67.60 67.71	4.05 4.33	14.91 15.04	8.31 8.60	218	Brown	DMF	372.48	71
16c	$C_{22}H_{15}N_5O_4S$	59.37 59.30	3.13 3.40	16.01 15.72	7.28 7.19	243	Yellow	DMF	445.49	74
16d	$C_{22}H_{16}N_4O_2S$	66.01 65.97	3.98 4.03	14.02 13.99	8.34 8.00	>250	Brown	DMF	400.49	73
16e	$C_{22}H_{17}N_5O_3S$	61.60 61.23	3.61 3.97	16.43 16.23	7.34 7.43	206	Deep-yellow	DMF	431.51	74
16f	$C_{22}H_{18}N_4OS$	68.21 68.36	4.57 4.70	14.23 14.49	8.56 8.29	233	Brown	DMF	386.51	73
16g	$C_{23}H_{17}N_5O_4S$	60.45 60.11	3.51 3.73	15.50 15.24	7.90 7.97	195	Yellow	DMF	459.52	72
16h	$C_{23}H_{18}N_4O_2S$	66.89 66.63	4.00 4.38	13.80 13.51	7.32 7.73	212	Brown	DMF	414.52	70

TABLE 2. Spectral Data of Newly Synthesized Compounds

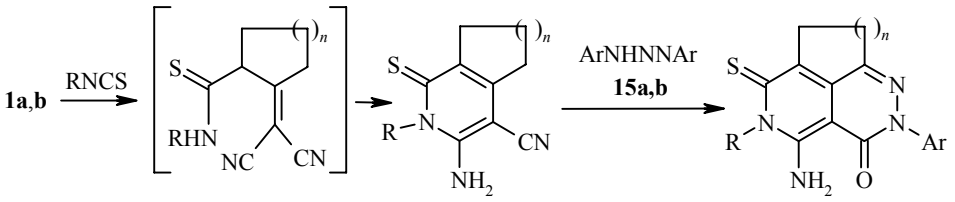
Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
1	2	3
3a*	3320 (NH), 2212 (CN)	7.98-7.53 (m, 4H, Ar); 6.25 (br, 1H, NH); 1.82-1.45 (m, 6H, $3CH_2$)
3b	3324 (NH), 2209 (CN)	7.89-7.33 (m, 4H, Ar); 6.05 (br, 1H, NH); 1.81-1.45 (m, 6H, $3CH_2$)
3c	3320 (NH), 2212 (CN)	7.78-7.21 (m, 4H, Ar); 6.30 (br, 1H, NH); 2.82-1.17 (m, 8H, $4CH_2$)
3d	3330 (NH), 2210 (CN)	7.97-7.43 (m, 4H, Ar); 6.20 (br, 1H, NH); 2.84-1.18 (m, 8H, $4CH_2$)
3e	3239 (NH), 2211 (CN)	10.98 (br, 1H, NH); 7.99-7.46 (m, 2H, thiazolyl-H); 1.85-1.07 (m, 6H, $3CH_2$)
3f	3406, 3329, 3225 (NH_2 & NH), 2224 (CN), 1660 (CO)	7.48, 6.45 (br, 3H, NH & NH_2); 2.66-1.55 (m, 14H, $7CH_2$)
4a	3401, 3358, 3325 (NH_2 & NH)	7.87-7.42 (m, 4H, Ar); 8.50, 6.25 (br, 3H, NH & NH_2); 1.72-1.45 (m, 4H, $2CH_2$)
4b	3411, 3345, 3320 (NH_2 & NH)	7.98-7.32 (m, 4H, Ar); 8.40, 6.25 (br, 3H, NH & NH_2); 1.71-1.50 (m, 4H, $2CH_2$)
4c	3434, 3373, 3331 (NH_2 & NH)	7.76-7.01 (m, 4H, Ar); 8.40, 6.24 (br, 3H, NH & NH_2); 1.85-1.06 (m, 6H, $3CH_2$)
4d	3422, 3331, 3321 (NH_2, & NH	7.88-7.24 (m, 4H, Ar); 8.42, 6.31 (br, 3H, NH & NH_2); 1.82-1.06 (m, 6H, $3CH_2$)
4e	3418, 3321 (NH_2), 1659 (CO)	7.57-7.10 (m, 5H, Ar); 8.40 (br, 2H, NH_2); 1.80-1.07 (m, 6H, $3CH_2$)
5	3422, 3328 (NH_2), 2213 (CN)	8.05 (br, 2H, NH_2); 1.85-105 (m, 8H, $4CH_2$)
6a	3323 (NH), 2210 (CN)	7.93-7.15 (m, 4H, Ar); 6.98 (s, 1H, CH); 5.89 (br, 1H, NH); 2.45 (s, 6H, 2Me); 1.71-1.51 (m, 4H, $2CH_2$)
6b	3329 (NH), 2211 (CN)	7.67-7.15 (m, 4H, Ar); 6.98 (s, 1H, CH); 5.87 (br, 1H, NH); 2.45 (s, 6H, 2Me); 1.70-1.51 (m, 4H, $2CH_2$)
6c	3331 (NH), 2212 (CN)	7.87-7.15 (m, 4H, Ar); 6.98 (s, 1H, CH); 5.89 (br, 1H, NH); 2.45 (s, 6H, 2Me); 1.83-1.08 (m, 6H, $3CH_2$)
6d	3331(NH), 2212(CN)	7.98-7.13 (m, 4H, Ar); 6.97 (s, 1H, CH); 5.79 (br, 1H, NH); 2.46 (s, 6H, 2Me); 1.85-1.07 (m, 6H, $3CH_2$)
9a*[2]	3412, 3334; 3226; 3215 (NH_2, 2NH)	10.32 (br, 2H, NH_2); 8.03 (s, 1H, pyridine-H); 7.89-7.10 (m, 4H, Ar); 6.95, 5.79 (br, 2H, 2NH); 1.85-1.07 (m, 4H, $2CH_2$)
9b	3411, 3333; 3229; 3220 (NH_2, 2NH)	10.02 (br, 2H, NH_2); 8.13 (s, 1H, pyridine-H); 7.79-7.10 (m, 4H, Ar); 6.85, 5.77 (br, 2H, 2NH); 2.78-1.11 (m, 6H, $3CH_2$)
9c	3331, 3219 (2NH)	8.69 (s, 1H, pyridine-H); 7.89-7.01 (m, 9H, Ar); 6.85, 5.59 (br, 2H, 2NH); 1.85-1.07 (m, 4H, $2CH_2$)
9d	3331, 3219 (2NH)	8.57 (s, 1H, pyridine-H); 7.91-7.11 (m, 9H, Ar); 6.85, 5.77 (br, 2H, 2NH); 2.79-1.23 (m, 6H, $3CH_2$)
9e	3345, 3219 (2NH)	8.78 (s, 1H, pyridine-H); 7.84-7.21 (m, 8H, pyridine & Ar); 6.75, 5.59 (br, 2H, 2NH); 1.85-1.17 (m, 4H, $2CH_2$)
9f	3365, 3223 (2NH)	8.35 (s, 1H, pyridine-H); 7.91-7.12 (m, 8H, pyridine & Ar); 6.65, 6.09 (br, 2H, 2NH); 2.80-1.11 (m, 6H, $3CH_2$)
11a	3323 (NH), 2212 (CN), 1728 (CO)	10.45 (s, 1H, CHO); 7.98-7.23 (m, 4H, Ar); 6.23 (br, 1H, NH); 2.84-1.53 (m, 5H, 1CH & $2CH_2$)
11b	3333 (NH), 2210 (CN), 1727 (CO)	10.50 (s, 1H, CHO); 7.97-7.20 (m, 4H, Ar); 6.05 (br, 1H, NH); 2.86-1.43 (m, 7H, 1CH & $3CH_2$)
14b	3342, 3328 (NH_2), 2210 (CN), 1661 (CO)	7.54-7.01 (m, 5H, Ar); 6.52 (br, 2H, NH_2); 1.85-1.17 (m, 6H, $3CH_2$)
16a	3343, 3332 (NH_2), 1658 (CO)	7.82-7.23 (m, 9H, Ar); 6.51 (br, 2H, NH_2); 1.85-1.06 (m, 4H, $2CH_2$)

TABLE 2 (continued)

1	2	3
16b	3342, 3329 (NH_2), 1559 (CO)	7.72-7.23 (m, 10H, Ar); 6.53 (br, 2H, NH_2); 1.85-1.07 (m, 4H, $2CH_2$)
16c	3343, 3329 (NH_2), 1651, 1659 (2CO)	7.91-7.21 (m, 9H, Ar); 6.54 (br, 2H, NH_2); 1.85-1.07 (m, 4H, $2CH_2$)
16d	3343, 3328 (NH_2), 1655, 1661 (2CO)	7.85-7.31 (m, 10H, Ar); 6.53 (br, 2H, NH_2); 1.85-1.10 (m, 4H, $2CH_2$)
16e	3348, 3335 (NH_2), 1663 (CO)	7.93-7.22 (m, 9H, Ar); 6.52 (br, 2H, NH_2); 2.85-1.37 (m, 6H, $3CH_2$)
16f	3342, 3329 (NH_2), 1659 (CO)	7.83-7.32 (m, 10H, Ar); 6.52 (br, 2H, NH_2); 2.85-1.36 (m, 6H, $3CH_2$)
16g	3342, 3328 (NH_2), 1663, 1659 (2CO)	7.93-7.22 (m, 9H, Ar); 6.50 (br, 2H, NH_2); 2.85-1.35 (m, 6H, $3CH_2$)
16h	3331, 3328 (NH_2), 1660, 1658 (2CO)	7.73-7.22 (m, 10H, Ar); 6.51 (br, 2H, NH_2); 2.85-1.37 (m, 6H, $3CH_2$)

* ^{13}C NMR spectrum, δ, ppm: 165.16 (C-3); 157.12 (C-7a); 140.06, 139.12, 137.01, 135.11, 134.21, 129.61, 127.11, 124.10 (arom. carbons); 116.89 (CN); 28.66, 27.45, 25.98 ($3CH_2$).

*^{2} ^{13}C NMR spectrum, δ, ppm: 159.13, 158.78, 158.33, 157.02, 153.21, 149.12, 148.25, 147.68, 143.21, 138.21, 137.25, 135.01, 132.35 (arom. carbons); 26.35, 27.60 ($2CH_2$).



13 **14a–d** **16a–h**

14 a, **c** R = Ph, **b**, **d** R = COPh, **a**, **b** *n* = 1, **c**, **d** *n* = 2; **15 a** Ar = Ph, **b** Ar = $C_6H_4NO_2$-*m*;
16 a,**c**,**e**,**g** Ar = $C_6H_4NO_2$-*m*, **b**,**d**,**f**,**h** Ar = Ph, **a**,**b**,**e**,**f** R = Ph, **c**,**d**,**g**,**h** R = COPh, **a-d** *n* = 1, **e-h** *n* = 2

The target ring system, 1,8-alkanopyrido[3,4-*d*]pyridazine, could be obtained *via* treating **1a**,**b** with phenylisothiocyanate or benzoylisothiocyanate to give **14a-d** through the presumed intermediate **13**. Compounds **14a-d** reacted with diazoaminobenzenes **15a**,**b** in aqueous acetic acid/hydrochloric acid mixture to afford the final isolated products **16a-h**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr with an IR spectrophotometer Shimadzu 408. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian EM-390 MHz spectrometer (390 MHz) using TMS as internal reference and chemical shifts are expressed as ppm. Mass-spectra were measured on a Shimadzu GCMS-QP 1000 Ex mass-spectrometer. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt. Compounds **14a**,**c**,**d** were prepared as described previously [10, 11]. Characteristics of newly synthesized compounds are presented in Tables 1 and 2.

Preparation of Cycloalkeno[*c*]pyridazine Derivatives 3a-f. A solution of the diazonium salts (prepared from 0.01 mol of aromatic or heteroaromatic amine with the appropriate quantities of sodium nitrite and hydrochloric acid) was added to cycloalkylidenemalononitrile **1a** or **1b** (0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.50 g). The reaction mixture was stirred at room temperature 2 h. The solid product formed was collected by filtration and recrystallized from ethanol.

Preparation of 1,8-Alkanopyrido[3,4-*d*]pyridazines 4a-e. A (compounds **4a-d**). To a solution of compound **3a-d** (0.01 mol) in DMF, trichloroacetonitrile (0.01 mol) and a few drops of piperidine were added. The reaction mixture was refluxed for 1 h. The reaction product was treated with ice-cold water and the solid product formed was filtered off and recrystallized from DMF.

B (compound **4e**). A mixture of **5** (0.01 mol), diazoaminobenzene (0.01 mol), acetic acid (15 ml), hydrochloric acid (15 ml), and a few drops of water was refluxed for 3 h and then allowed to cool. The reaction product was neutralized using sodium bicarbonate solution. The solid product so formed was collected by filtration, washed with ice-cold water several times, dried, and recrystallized from DMF.

Preparation of Tetrahidroisoquinoline 5. A solution of ylidene derivative **1b** (0.01 mol) in DMF (20 ml), trichloroacetonitrile (0.01 mol), and a few drops of piperidine was refluxed for 2 h. The reaction mixture was evaporated under vacuum and the solid product formed was collected by filtration and recrystallized from ethanol.

Preparation of N,N-Dimethylaminomethylidenecycloalkeno[*c*]pyridazines 6a-d. A solution of pyridazines **3a-d** (0.01 mol) in DMF (25 ml) was treated with DMF/DMA (0.01 mol) and a few drops of piperidine. The reaction mixture was refluxed for 2 h, then treated with cold water. The reaction product was collected by filtration and recrystallized from ethanol.

Preparation of N-Substituted Pyrido[3,4-*d*]pyridazines 9a-f. A. To a solution of **6a-d** (0.01 mol) in DMF (25 ml), hydrazine hydrate (aniline or 2-aminopyridine) (0.01 mol) was added. The reaction mixture was refluxed for 2 h. Ice-cold water was added and the solid product so formed was collected by filtration and recrystallized from proper solvent.

B. To a solution of **11a** or **11b** (0.01 mol) in DMF (25 ml), hydrazine hydrate (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h. Ice-cold water added and the solid product so formed was collected by filtration and recrystallized from the proper solvent.

Synthesis of Cycloalkenepyridazinealdehydes 11a,b. A solution of diazonium salt (prepared as described in the preparation of **3a-d**) was added dropwise with intensive stirring for 2 h to a solution of **10a** or **10b** (0.01 mol) in DMF and a solution of NaOH (0.1 g dissolved in 10 ml of water). The solid product so formed was collected by filtration and recrystallized from acetone.

Preparation of Hydroisoquinoline 14b. To a solution of 1a (0.01 mol) in ethanol (25 ml) benzoyl isothiocyanate (0.01 mol) and a few drops of piperidine were added. The reaction mixture was refluxed for 3 h. The solid product formed upon treating the reaction mixture with ice-cold water was collected by filtration and recrystallized from ethanol.

Preparation of Thioxopyridopyridazinones 16a-h. A mixture of **14a-d** (0.01 mol), diazoaminobenzene (0.01 mol), acetic acid (15 ml), hydrochloric acid (15 ml), and a few drops of water was refluxed for 3 h and then allowed to cool. The reaction product was neutralized with sodium bicarbonate solution. The solid product so formed was collected by filtration, washed with ice-cold water several times, dried, and recrystallized from DMF.

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