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Synthesis and Reactions of Some Pyridazine Derivatives

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Abstract□3,4-Diphenyl-5-cyanopyridazin-6-one **3** was prepared from the reaction of cyanoacetamide **2** with benzilhydrazone in dry pyridine. A series of its derivatives was prepared. Tolyl and benzene sulphonyl derivatives **6a** and **6b** are also prepared. 3,4-Diphenyl-5-cyanopyridazin-6-thione **5** was obtained from **3** by the action of P_2S_5 while 3,4-diphenyl-5-cyano-6-chloropyridazine **4** was obtained from **3** by the action of $POCl_3$. The reaction of **4** with hydrazine hydrate directly afforded the pyrazolopyridazine derivative **7**. Compound **4** also reacted with phenylhydrazine, aniline, thiophenol and anthranilic acid to yield pyridazine derivatives **8, 9, 10** and **11**, respectively. On treatment of compound **11** with acetic anhydride it cyclised to afford pyridazino pyrimidine derivatives **12.**

Keywors□Pyriazines.

The considerable biological and medicinal activities of pyridazine derivatives in the past time stimulated considerable research in this field.[1, 2] As a part of a program[3, 4] directed for synthesis of some pyridazine derivatives as anticancer agents[5], bactericides[6] and fungicides[7], I report here a novel synthesis of some pyridazine derivatives and their substitution reactions. Thus, it has been found that benzilhydrazone **1** reacted with cyanoacetamide **2** to yield 3,4-diphenyl-5-cyanopyridazine-6-one **3**. Structure of **3** was confirmed by elemental analysis, IR and ^{1}H NMR spectra (Table I and II). Treatment of **3** with P_2S_5 in pyridine afforded 3,4-diphenyl-5-cyanopyridazine-6-thione **5**, which was found to be identical with authentic sample prepared by another route[8]. Thus, treatment of **3** with benzene sulphonyl chloride and with p-toluene-sulphonyl chloride in basic medium afforded **6a** and **b**, respectively. The structure of **5** and **6a, b** was confirmed by elemental analyses, IR and ^{1}H NMR spectral data (Table I and II). 3,4-Diphenyl-5-cyano-6-chloropyriazine **4** was obtained by the action of phosphorous oxychloride[9] on **3** in dioxane. The structure of **4** was confirmed by elemental analyses and spectral data (Table I and II). IR spectrum of **4** displayed no absorption in the carbonyl region. The reactivity of chlorine atom in position 6 of **4** is proved *via* its substitution reactions with phenylhydrazine, aniline and thiophenol to yield the corresponding 6-substituted pyridazine derivatives **8, 9** and **10**, respectively. The IR spectra of **8, 9** and **10** displayed the corresponding characteristic bands. The ^{1}H NMR spectra of **8, 9** and **10** were in a good agreement with the

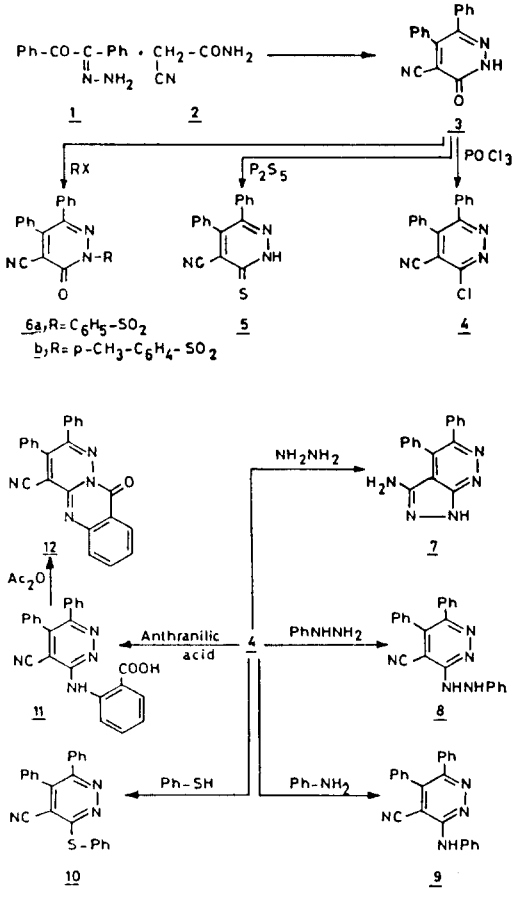

Table 1. Elemental analyses of pyridazine derivatives 3-12

Compound	Solvent of Crystallization	Colour	M.p. (°C)	Yield (%)	Mol. Formula	Analysis, Calcd./Found				
						C	H	N	S	Cl
3	Ethanol	Colourless	260-1	70	$C_{17}H_{11}N_3O$	74.71	4.06	15.38		
						74.20	4.00	15.4		
4	Ethanol	Colourless	201	63	$C_{17}H_{10}N_3Cl$	69.99	3.46	14.40	–	12.15
						69.56	4.00	13.90	–	12.20
5	Acetic acid	Brown	290-2	55	$C_{17}H_{11}N_3S$	70.58	3.83	14.53	11.08	–
						71.00	4.01	14.6	11.10	–
6a	Petr. ether	Yellow	131	60	$C_{23}H_{15}N_3SO_3$	66.82	3.66	10.17	7.76	–
						66.61	3.50	10.30	7.80	–
6b	Ethanol	Brown	142	60	$C_{24}H_{17}N_3SO_3$	67.44	4.02	9.83	7.50	–
						67.50	4.00	9.63	7.40	–
7	Ethanol	Yellow	273-4	65	$C_{18}H_{13}N_5$	72.22	4.38	23.40	–	–
						72.50	4.33	23.10	–	–
8	Ethanol	Brown	230-1	70	$C_{23}H_{17}N_5$	76.01	4.72	19.27	–	–
						76.00	4.73	19.32	–	–
9	Ethanol	Brown	222	65	$C_{23}H_{16}N_4$	79.29	4.63	16.08	–	–
						79.30	4.51	16.18	–	–
10	Petr. ether	Yellow	220	70	$C_{23}H_{15}N_3S$	75.60	4.14	11.50	8.77	–
						75.41	4.13	11.70	8.66	–
11	Dioxane	Brown	>300	65	$C_{24}H_{16}N_4O_2$	73.46	4.11	14.28	–	–
						73.50	4.00	14.20	–	–
12	Ethyl acetate	Brown	271.3	55	$C_{24}H_{14}N_4O$	76.99	3.77	14.97	–	–
						76.81	3.8	15.00	–	–

proposed structure (Table I and II). In contrast to the behaviour of phenylhydrazine, hydrazine hydrate reacted with **4** under the same experimental condition to afford pyrazolopyridazine derivatives **7**. The assignment of structure **7** to the reaction product was based on analytical and spectral data. Thus, the IR spectrum of **7** displayed no bands for CN group, and its ^1H NMR spectrum showed the corresponding cahracteristic signals (Table I and II). Compound **4** reacted with anthranilic acid in boiling glacial acetic acid to give **11**. The IR and ^1H NMR spectra of **11** showed OH, CO. and CN absorption bands. Cyclisation of **11** using acetic anhydride afforded **12**. The structure of compounds **11** and **12** was confirmed by elemental analyses, IR and ^1H NMR spectral data (Table I and II).

EXPERIMENTAL

M.P., uncorrected; IR spectra (KBr), Pye Unicam SP-1100 spectrophotometer; ^1H NMR spectra, Varian EM-360 60 MHz spectrometer in DMSO, TMS int. stand. Chemical shifts (δ ppm); Elementary analyses, microanalytical Centre, Cairo University.

Reaction of 3 with $POCl_3$

A mixture of **3** (0.01 mole), $POCl_3$ (30 m*l*) and dioxane (50 m*l*) was heated under reflux for 3 hr. The solution was cooled and poured onto ice water. The solid obtained was crystallised from ethanol to give **4**.

Reaction of 3 with benzene sulphonyl chloride and p-toluene sulphonyl chloride

A mixture of **3** (0.01 mole), arylsulphonyl halide (0.01 mole) and anhydrous potassium carbonate was refluxed for 5 hr in dry acetone (40 m*l*). The N-substituted derivatives **6a** and **b** were crystallized from the proper solvent.

Reaction of 4 with aniline, phenylhydrazine, hydrazine, thiophenol and anthranilic acid

Table II. IR and ^1H NMR data of compounds 3-12

Comp.	IR (KBr), cm^{-1}	^1H NMR (δ ppm)
3	3400, 3300, 3120 (NH); 2220 (CN) and 1690 (ring C = O)	8.8 (s, 1H, NH); 7.62, 7.9 (m, 8H, aromatic protons)
4	2220 (CN)	
5	3400, 3300, 3100 (NH); 2220 (CN)	8.7 (s, 1H, NH); 7.63, 7.90 (m, 8H aromatic protons)
6a	2220 (CN), 1690 (ring C=O), 1390 1195 (N-SO_2)	
6b	2100 (CN), 1690 (ring C=O), 1380, 1195 (N-SO_2)	1,75 (s, 3H, aromatic CH_3) 6.9-7.80 (m, 13 Arom. protons)
7	3350, 3250, 3180 (NH_2 and NH)	8.8 (s, 1H, NH), 7.61-7.91 (m, 10, aromatic protons) 10.1 (s, 2H, NH_2)
8	3400, 3300, 3120 (NH); 2220 (CN)	
9	3500, 3250, 3120 (NH); 2220 (CN)	7.60-7.92 (m, 15H, aromatic protons) 9.58 (s, 1H, NH)
10	2220 (CN)	
11	3150 (broad), NH, OH, 2220 (CN), 1650 (CO)	7.63-7.97 (m, 14-H aromatic protons); 8.64 (s, 1H, NH) 11.93 (s, 1H, COOH)
12	2220 (CN), 1680 (CO)	7.78, 8.20 (m, 14H, aromatic protons)

A mixture of **4** (0.01 mole) and aniline, phenylhydrazine, hydrazine, thiophenol or anthranilic acid (0.01 mole) in glacial acetic acid (60 m*l*) was refluxed for 5 hr. The reaction mixture was poured onto water after cooling. The solid separated was collected and crystallized from the proper solvent.

Cyclization of 11

A solution of **11** (1.5 gm) in acetic anhydride (20 m*l*) was refluxed for 3 hr. The solid separated while boiling was collected and crystallized from ethyl acetate to give **12**.

LITERATURE CITED

1. Robins, R.K., Townsend, L.B., Cassidy, F.G., Geroter, J.P., Lewis, A.F. and Millar, R.L.: *J. Heterocycl. Chem.*, **3**, 10 (1963).
2. Koyama, G. and Umezawa, H.: *J. Antibiotic*, **18**, 175 (1965).
3. Khalifa, F.A., Riad, B.Y. and Hafez, F.H.: *Heterocycles*, **20**, 1021 (1983).
4. Riad, B.Y., Khalifa, F.A., Abdel Galil, F.M. and Elnagdi, M.H.: *Heterocycles*, **19**, 1637 (1982).
5. Ito (Tanabe Seiyaku Co. Ltd.), **70**, 30, 101 (1970); *Chem. Abstr.*, **74**, 22827 (1971).
6. Prshin, G.N., Sherbakova, L.I., Zykova, I.N. and Sokolova, V.N.: *Farmakal. Tokisikol*, **35**, 466 (1971); *Chem. Abstr.*, **77**, 1355802 (1972).
7. Matolcsy, G.: *World Rev., Pesteontr.*, **10**, 50 (1971); *Chem. Abstr.*, **76**, 820315 (1972).
8. Khalifa, F.A.: *Sulfur Lett.*, 1989, in press.
9. Sakurai, A., Motomura, Y. and Midori, H.: *J. Org. Chem.*, **37**, 1523 (1972).