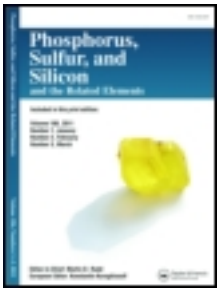

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Some Pyrido-Imidazophenazine Derivatives

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Synthesis of Some Pyrido-Imidazophenazine Derivatives

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*2,3-Diaminophenazine (**1**) was prepared[1–3]. Attempts were made to review the chemistry of phenazine[4–8], biology of phenazine derivatives and also a review on fused phenazine derivatives; for studying their pharmacological[9–15] and photoconductive properties[16,17].*

Keywords Antitumor; condensation; diketone; phenazine; photo conductivity

CONCLUSION

Potential building blocks in our program are 2,3-diaminophenazine and 2-(cyanomethyl)-imidazo[4,5-b]phenazine (**2**). we prepared a number of pyrido-imidazophenazine derivatives in order to elucidate further the effect of nitrogen atom ring substituents on the relative biological[18–20] and photo conductive properties.

RESULTS AND DISCUSSION

The structure of 2,3-diaminophenazine (**1**) was confirmed through comparison of its physical data with reported data.[1–3] The ^{1}H-NMR spectrum of (**1**) in $DMSO_4$-d_6 exhibited signals at δ 6.26 (s, 4H, $2NH_2$) which disappear by deuteration with D_2O, 6.92 (s, 2H, $H_{arm.}$), 7.53 (m, 2H, $H_{arom.}$) and 7.88 (m, 2H, $H_{arom.}$).

The condensation reaction of (**1**) with ethylcyanoacetate in n-butanol under reflux condition, compound (**2**) was obtained in high yield. The chemical structure of compound (**2**) was confirmed by elemental analysis and spectral data. The IR spectrum showed absorption bands at 3465 cm^{-1} broad due to NH group, 3120 cm^{-1} due to carbonyl hydrogen aromatic bond, 2920 cm^{-1}due to carbon aliphatic, 1623 cm^{-1} due to carbon nitrogen double and 1610–1480 cm^{-1} due to (C=N) conjugated.

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TABLE I Analytical Data of the Prepared Compounds

Comp. no.	m.p. °C	Yield/solvent of cryst.	Molecular formula (mol. Wi.)	Analysis Calculated/Found C	H	N
1	172	78	$C_{12}H_{10}N_4$	68.58	4.81	26.66
		Acetic acid	(210.16)	68.82	4.74	26.72
2	185	67	$C_{15}H_9N_5$	69.48	3.50	27.01
		Bu.	(259.27)	69.71	3.62	26.76
3	234	63	$C_{20}H_{13}N_5$	74.28	4.05	21.66
		DMF	(323.35)	74.13	4.13	21.72
4	278	71	$C_{26}H_{17}N_7$	73.05	4.01	22.94
		DMF	(427.47)	73.24	4.16	22.78
5a	256	59	$C_{19}H_{11}N_5O$	70.14	3.41	21.53
		EtOH	(325.33)	70.32	3.28	21.65
6a	269	67	$C_{27}H_{20}N_6O_3$	68.05	4.23	17.64
		DMF	(476.49)	68.24	4.15	17.82
6b	>300	73	$C_{32}H_{22}N_6O_3$	71.36	4.12	15.61
		Acetic acid	(538.56)	71.52	4.31	15.46
7	280	81	$C_{24}H_{14}N_6$	74.60	3.65	21.75
		DMF/H_2O	(386.41)	74.46	3.81	21.69
8	>300	73	$C_{30}H_{18}N_7$	75.61	3.81	20.58
		Bu.	(476.51)	75.79	3.76	20.72
9	249	64	$C_{18}H_{13}N_5O_2$	65.25	3.95	21.14
		EtOH	(331.33)	65.08	3.87	21.33
10	>300	74	$C_{24}H_{13}N_5O$	74.41	3.38	18.08
		DMF/H_2O	(387.39)	74.62	3.44	17.87

It was of interest to study the condensation reactions of (**2**) with the appropriate 1,3-diketones and their hydrazonyl derivatives (namely acetyl acetone, ethoxycarbonyl ketones and/or their hydrazonyl derivatives in acetic acid/acetic anhydride under reflux condition to afford the corresponding pyrido[1,6-a]imidazo[4,5-b]phenazine derivatives (**3**), (**4**), ($\mathbf{5}_{a,b}$) and/or ($\mathbf{6}_{a,b}$) respectively.

Chemical and spectroscopic evidences for the synthesized compounds are presented (c.f. Tables I and II).

For example compound (**6a**) was established on the basis of its elemental analysis and spectral data. Thus, the IR spectrum of (**6a**) showed absorption band at 3470 cm^{-1} broad due to free (OH) group, 1910 cm^{-1} due to —N=N—, 1760 cm^{-1} due to carbonyl ester group, 1623 cm^{-1} due to carbon nitrogen double bond and 1158, 1193due to (C—O—C) group.

The ^{1}H-NMR spectrum of (**6a**) in DMSO-d_6 exhibited bands at 1.3 (t, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.1–4.2 (m, 2H, O-$\underline{CH_2}CH_3$), 7.2 (br., 1H, OH), 7.4 (m, 5H, $H_{arom.}$), 7.9 (m, 2H, $H_{arom.}$) and 9.1 (s, 2H, $H_{arom.}$).

TABLE II Spectral Data for Selected Compounds

Comp. no.	IR (ν_{max}/cm^{-1})	^{1}H-NMR (δ/ppm)
1	3400–3320 (NH_2), 3098 C—H (arom.), 1610–1480 (C═C) conj., 162 (C═N)	6.26 (s, 4H, $2NH_2$), disappear by deuteration with D_2O, 6.92 (s, 2H, $H_{rom.}$), 7.53 (m, 2H, arom.) and 7.88 (m, 2H, arom.)
2	3465 (NH) cyclic, 3120 (C—H) arom., 2920 (—CH) aliph., 1610–1480 (C═N) conj., 1623 (C═N)	4.6 (s, 2H, CH_2-), 7.9 (m, 2H, arom.), 8.42 (m, 2H, arom.), 9.1 (s, 2H, arom.) and 12.9 (br.(s), 1H, NH).
4	3120 (CH) arom., 2930 (CH) aliph., 2210 (C≡N), 1890 (N═N—), 1624 (C═N), 1616–1510 (C═C) conj.	2.6 (s, 6H, $2CH_3$), 7.4 (m, 5H, arom.), 7.86 (m, 2H, arom.); 8.38 (m, 2H, arom.) and 9.12 (s, 2H, arom.)
5b	3480 (OH), 2220 (C≡N), 1620 (C═N)	6.9 (s, 1H, arom.), 7.2 (br., 1H, OH); 7.4 (m, 5H, arom.); 7.8 (m, 2H, arom.); 8.3 (m, 2H, arom.) and 9.08 (s, 2H, arom.)
6a	3470 (OH), 1910 (N═N—), 1760 (C═O) ester, 1623 (C═N), 1158, 1193 (C—O—C)	1.3 (t, 3H, CH_3), 4.1–4.2 (m, 2H, o-CH_2CH_3); 2.6 (s, 3H, CH_3); 7.2 (br., 1H, OH); 7.4 (m, 5H, arom.); 7.9 (m, 2H, arom.); 8.4 (m, 2H, arom.) and 9.1 (s, 2H, arom.)
7	3300–3180 (NH_2), 3100 (CH) arom., 2210 (C≡N), 1620 (C═N)	6.3 (s, 2H, NH_2); 7.2 (s, 1H arom.); 7.4 (m, 5H, arom.); 7.84 (m, 2H, arom.), 8.37 (m, 2H, arom), 9.12 (s, 2H, arom.)
8	3390–3280 (NH_2), 3098 (CH) arom., 2210 (C≡N), 1910 (N═N—), 1624 (C═N), 1610–1485 (C═C) conj.	6.3 (s, 2H, NH_2), 7.3 (m, 10H, arom.), 7.87 (m, 2H, arom.); 8.43 (m, 2H, arom.) and 9.12 (s, 2H, arom.)
9	3100 (CH) arom., 2910 (CH) aliph., 2210 (C≡N), 1760 (C═O) ester, 1624 (C═N), 1160, 1195 (C—O—C)	1.4 (t, 3H, CH_3); 4.2–4.3 (m, 2H, OCH_2CH_3); 4.7 (s, 2H, CH_2CN), 7.83 (m, 2H, arom.), 8.39 (m, 2H, arom.) and 9.08 (s, 2H, arom.)
10	3098 (CH) arom., 2220 (C≡N), 1720 (C═O), 1623 (C═N)	3.6 (s, 2H, CH_2); 7.4 (m, 5H, arom.); 7.84 (m, 2H, arom.); 8.41 (m, 2H, arom.); and 9.12 (s, 2H, arom.)

Reaction of compound (**2**) with cyanoacetophenone, hydrazonyl-acetophenone and/or ethyl chloroformate in acetic acid/acetic anhydride under reflux condition give the corresponding pyrido[1,6-a]imidazo[4,5-b]phenazine derivatives (**7**), (**8**) and/or (**9**) respectively.

Condensation reactions of (**2**) with different ketones such as acetone and/or acetophenone in ethanol/piperidine under reflux condition, yield the corresponding pyridoimidazophenazine derivatives (**5a**), and/or (**10**) respectively. Finally compounds (**3**) and/or (**7**) can be coupled with diazonium salts such as phenyldiazonium chloride in ethanol/sod. acetate to afford the corresponding compounds (**4**) and/or (**8**) respectively.

Compound (**7**) was established on the basis of its elemental analysis and spectral data. Thus, the IR spectrum of (**7**) showed absorption bands at 3300–3180 cm^{-1} due to (NH_2), 3100 cm^{-1} due to carbon hydrogen aromatic bond, 2210 cm^{-1} due to cyano group and 1820 cm^{-1} due to carbon nitrogen double bond.

Also compound (**10**), was established on the basis of its elemental analysis and spectral data. Thus the ^{1}H-NMR spectrum of (**10**) in DMSO-d_6 exhibited bands at 3.6 (s, 2H, CH_2), 7.4 (m, 5H, $H_{arom.}$), 7.84 (m, 2H, $H_{arom.}$), 8.41 (m, 2H, $H_{arom.}$) and 9.12 (s, 2H, $H_{arom.}$).

EXPERIMENTAL

Melting points uncorrected determined on a Gallen Kamp melting point apparatus. I.R. spectra were recorded in KBr using a Shimadu spectra 200–91506 spectrophotometer. ^{1}H NMR in DMSO as a solvent on a varian 90MHz using TMS as the internal reference. Elemental analyses were carried out in the Microanalytical unit, Cairo University, Giza, Egypt.

1) Preparation of 2,3-Diaminophenazine (1)

Finally powdered o-phenylenediamine (54.0 g, 0.5 mol) was dissolved in conc. hydrochloric acid (83.3 ml) and distilled water (2.5 L).A filtered solution of ferric chloride (400 g) in (750 ml) water was added slowly and the mixture was stirred mechanically.

After standing overnight at room temperature the red-brown coloured crystalline product was filtered off, washed with cold dilute 0.3N hydrochloric acid until free from ferric ions, then dissolved in hot water (2.5 L), 2,3-diaminophenazine was precipitated by the addition of a concentrated solution of potassium hydroxide. The product was filtered off, washed with water and dried at 100–110°C. The strongly alkaline filterate was heated and acidified (pH 4.5) with glacial acetic acid. After cooling, 2-amino-3-hydroxyphenazine was collected, washed with water and dried at 100–110°C. The crude products used without further purification.

2) Reaction of Compound (1) with Ethyl Cyanoacetate

A mixture of 2,3-diaminophenazine (**1**) (0.21 g, 1.0 mmol) and ethylcyanoacetate (0.11 g, 1.0 mmol) in n-butanol (30ml) was heated

under reflux for 8hours. After cooling the formed precipitate was filtered off, dried and recrystallized from the proper solvent to obtain 2-(cyanomethyl)-imidazo[4,5-b]phenazine (**2**).

3) Reaction of Compound (2) with Different 1,3-Diketones and Their Hydrazonyl Derivatives

A mixture of compound (**2**) (0.26 g, 1.0 mmol) and different 1,3-diketones and their hydrazonyl derivatives (namely, acetyl acetone, ethoxycarbonyl ketones and/or their hydrazonyl derivatives (1.0 mmol) in 20 ml) acetic acid and (5 ml) acetic anhydride was refluxed for 3–5hours. The product obtained was filtered off and recrystallized from a suitable solvent to give the corresponding pyrido[1,6-a]imidazo[4,5-b]phenazine derivatives (**3**), (**5a**,**b**), (**4**) and/or (**6a**,**b**) respectively.

4) Reaction of Compound (2) with Different Nitriles and/or Ethyl Chloroformate

A mixture of compound (**2**) (0.26g, 1.0mmol) and different nitriles and/or ethyl chloroformate (namely, cyanoacetophenone, hydrazonylcyanoacetophenone and/or ethyl chloroformate (1.0 mmol) in acetic acid (30 ml) and (5 ml) acetic anhydride was refluxed for 4 hours. The product obtained was filtered off and recrystallized from a suitable solvent to afford the corresponding pyrido[1,6-a]imidazo[4,5-b]phenazine derivatives (**7**), (**8**) and/or N-substituted-2-(cyanomethyl)imidzo[4,5-b]phenazine derivative (**9**).

5) Reaction of N-Substtuted-2-(cyanomethyl)imidazo[4,5-b] phenazine (9) with Different Ketones

A mixture of compound (**9**) (0.33g, 1.0mmol) and different ketones such as acetone and/or acetophenone (1.0 mmol) in ethanol (20 ml) containing piperidine (0.5 ml). The reflux mixture was refluxed for 3hours. Product was collected by filtration, crystallized from the proper solvent to obtain the corresponding pyrido[1,6-a]imidazo[4,5-b]phenazine derivatives (**5a**) and /or (**10**) respectively.

6) Coupling Reactions with Diazonium Salts

To a solution of compound (**3**) and/or (**7**) (1.0 mmol) in ethanol (20 ml), sodium acetate (0.25 g, 3.0 mmol) followed by diazonium salts as phenyl diazonium chloride was added over a (**30**) minutes

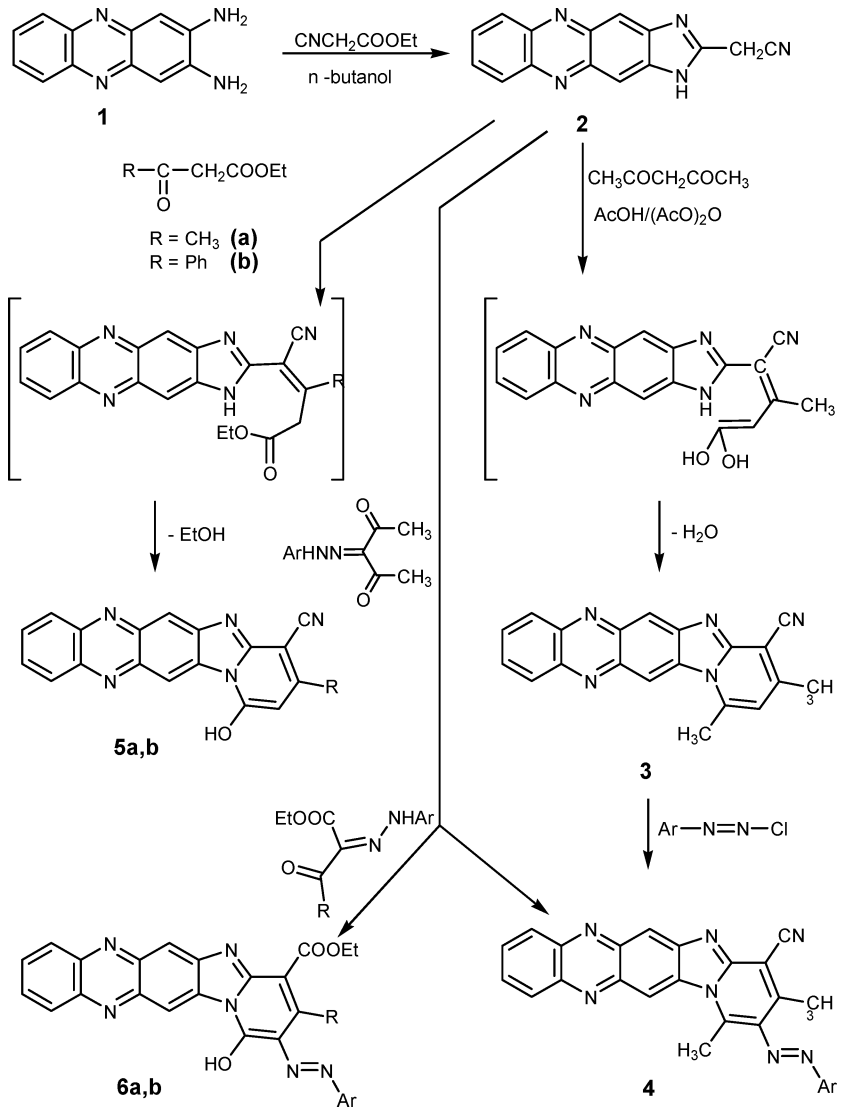

CHART 1

period while stirring for an hour. The reaction mixture was left over night in a refrigerator at 4°C. The solid product was filtered off and recrystallized from the proper solvent to afford the corresponding pyrido[1,6-a]imidazophenazine derivatives (**4**) and/or (**8**) respectively.

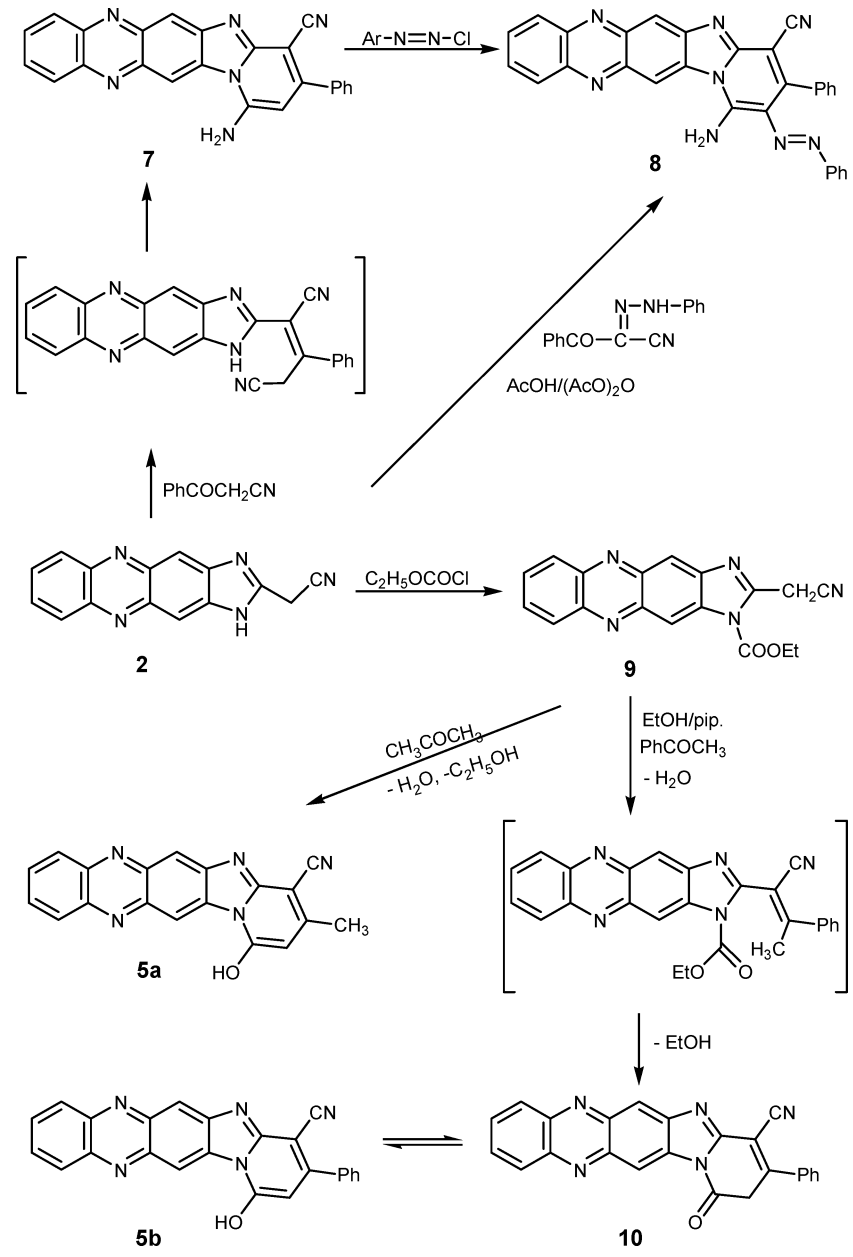

CHART 2

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