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Synthesis and reactions of phthalazine derivatives: Part V—Synthesis of some more heterocyclic compounds containing 4-phenyl-phthalazin-1-yl moiety

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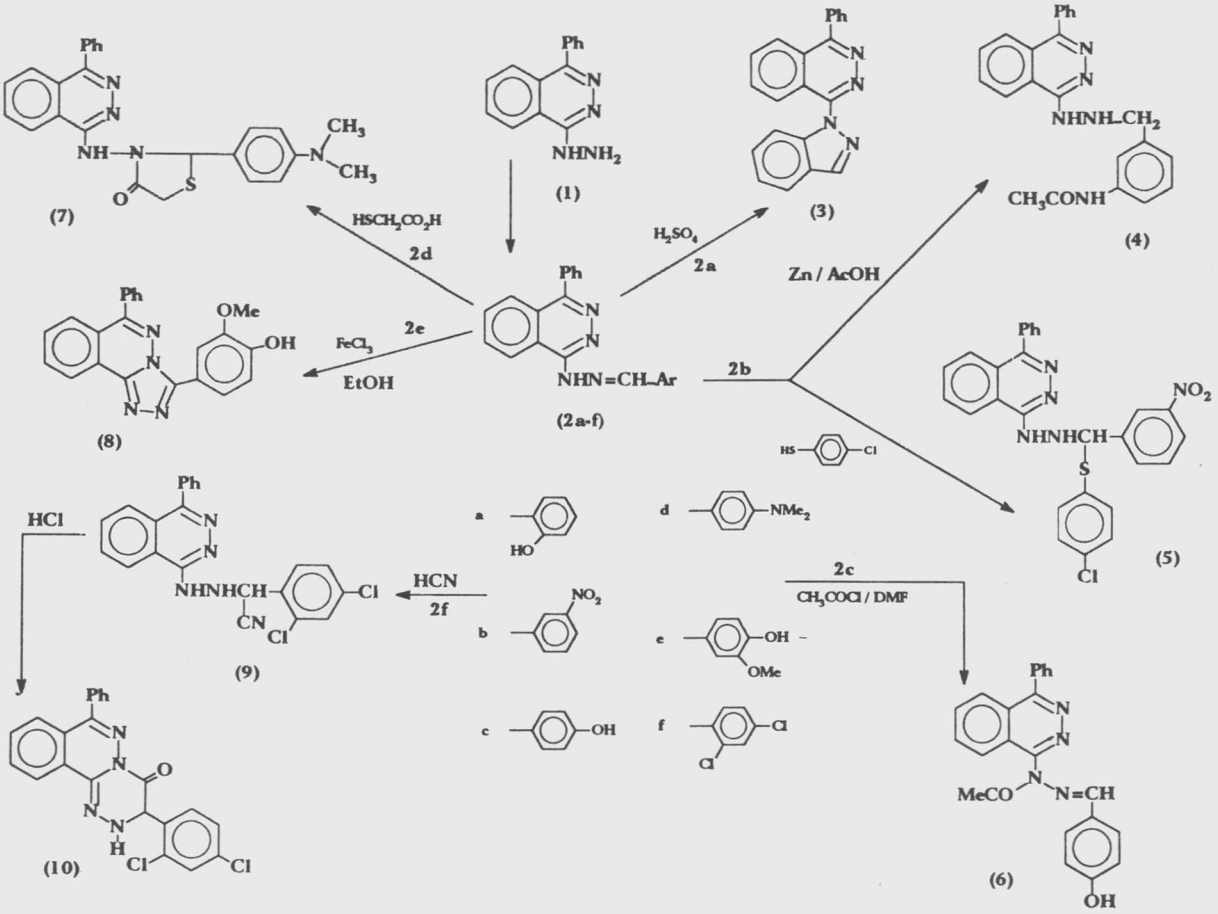
Some more heterocyclic compounds containing 4-phenylphthalazin-1-yl moiety have been synthesized by reaction of 1-hydrazino-4-phenylphthalazine with oxo- and halo- compounds followed by cyclization reactions. Their structures have been established on the basis of elemental analysis and spectral data. The mass spectra of some of the synthesized compounds have been studied to establish their fragmentation processes.

Earlier[1-4], we have synthesized various heterocyclic systems containing phthalazine moiety at their 2-position from 4-phenylphthalazine-2-acidhydrazide and/or from 1-chloro-4-phenylphthalazine. In continuation of this work, we have now studied the reaction of 1-hydrazino-4-phenylphthalazine **1** with some oxo- and/or halo-compounds to give some new heterocyclic systems bearing 4-phenyl-phthalazin-1-yl moiety.

Compound **1** when treated with various carbonyl compounds such as aldehydes, ketones and/or α-ketobenzoic acids in ethanol undergoes condensation. Thus, condensation of **1** with substituted aldehydes **a-f** in ethanol produced under reflux hydrazones **2a-f.** The structures of these compounds were established from their elemental analysis and spectral studies. The IR spectra of the compounds **2e** and **2f** showed bands at 3392, 1615, 1464 and 800-700 cm^{-1} due to NH, N=CH, aliphatic and aromatic groups. The ^1H NMR spectrum of **2d** displayed signals at δ 2.3, 6.8-7.0, 7.7-8.0, and 12.3 ppm attributable to $2CH_3$ groups, aromatic, benzo, CH=N and NH protons.

Compound **2a** on treatment with conc. H_2SO_4[5] by stirring for 2hr gave 1-(4-phenylphthalazin-1-yl)-4,5-benzpyrazoline **3**, while reduction of **2b** using Zn-acetic acid afforded N^1-(4-phenylphthalazin-1-yl)-N^2-(*p*-acetamidobenzyl)hydrazine **4**. In addition, fusion of **2b** with *p*-chlorothiophenol gave thioether **5**. Structure of compounds 3-5 were deduced from elemental analysis and spectral data. The IR spectrum of compound **3** showed characteristic bands at 1626 and 1582 cm^{-1} mainly due to C = N groups while compounds **4** and **5** revealed bands at 3339 and 3208 cm^{-1} due to hydrazo NH-NH group. The ^1H NMR spectrum of compound **4** displayed signals at δ 2.3 (CH_3CO), 2.6-2.7 (CH_2) and at 6.2-9.5 ppm (aromatic, benzo and NH protons).

Acylation of compound **2c** via refluxing with acetyl chloride in the presence of DMF yielded N-acetyl derivative **6**. Further, compound **2d** on refluxing with mercaptoacetic acid in the presence of dioxane produced thiazolidene-4-one derivative **7**. On the other hand, oxidative cyclization of compound **2e** on heating with $FeCl_3$-EtOH[6] led to the direct formation of s-triazolo[3,4-*a*] phthalazine derivative **8** (Scheme I). The structure of compounds **7** and **8** were established on the basis of elemental analysis and spectral data. The IR spectrum of **7** showed bands at 3392, 2918, 1657, and 1154 cm^{-1} due to NH, CH_2, C=O and C-S groups. ^1H NMR spectrum of compound **7** showed signals at δ 2.7 N($2CH_3$), 3.0 (CH_2), 4.2-4.7 (=CH), 6.8-7.0 (NH) and at 7.5-9.0 ppm for aromatic and benzo protons, while compound **8** showed signals at δ 4.0 (OCH_3), 7.7-9.7 (aromatic and benzo protons) and 9.8 ppm (OH proton). Mass spectrum of **7** displayed an intense molecular ion at m/z 441. Loss of thiazolidene-4-one moiety followed by removal of aryl radical, in addition of 1-amino-4-phenylphthalazine moiety (m/z 221, 100%).

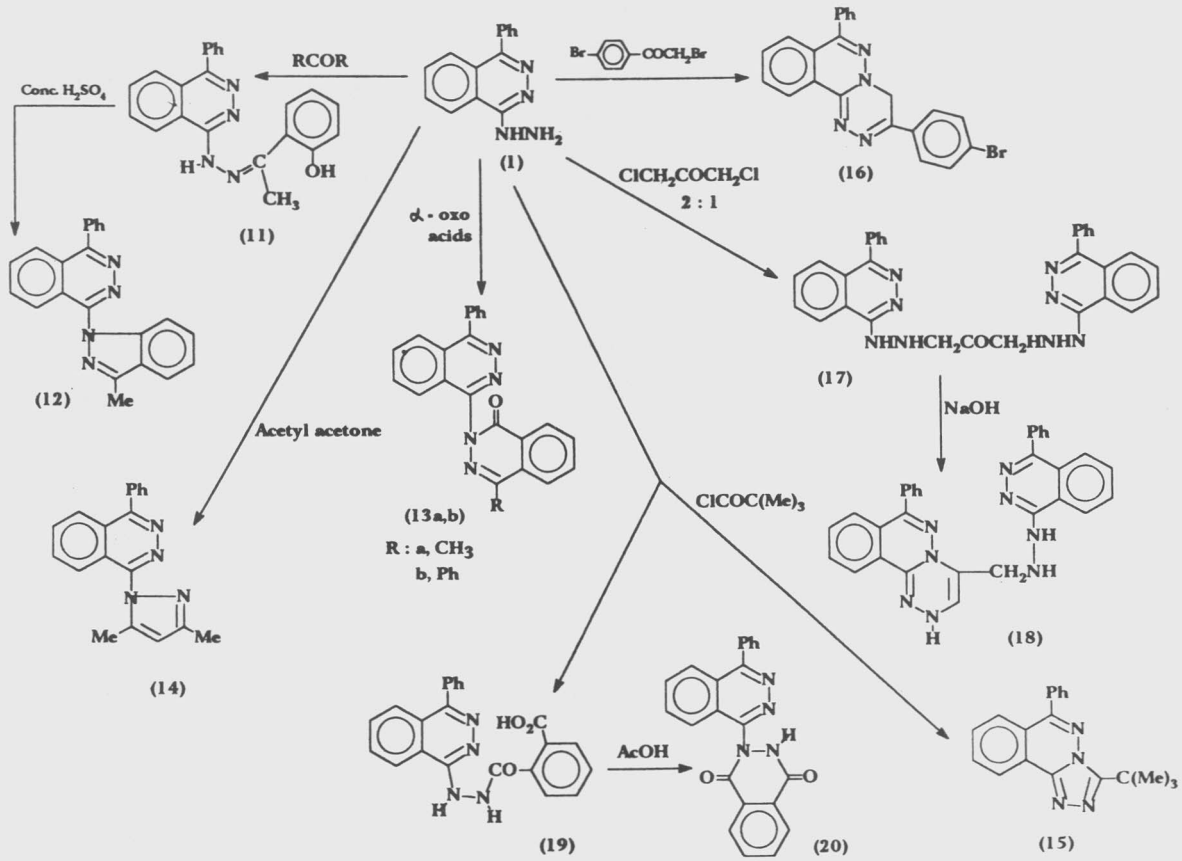


Scheme I

The reaction of hydrazones with some nucleophilic nitrogen compounds clearly indicated that the course of this reaction is governed by the reactivity of the neighbouring groups in the hydrazones and the type of medium used. Thus, addition of HCN to compound **2f** in ethanol-acetic acid gave the adduct product **9** which on hydrolysis with conc. HCl produced 2,3-dihydro-3-(2, 4-dichlorophenyl)-7-phenyl[1,2, 4]triazino[3,4-*a*]phthalazin-4-one **10** (Scheme I). The structure of compounds **9** and **10** were confirmed from their elemental analysis and spectral studies. The IR spectrum of **9** revealed the presence of bands at 3392 (NH, NH), and 2372 cm^{-1} (CN) while that of **10** showed the absence of absorption band due to CN group. Mass spectrum of 10 recorded the base peak at m/z 77 obtained by loss of phenyl moiety.

Reactions of 1-hydrazino-4-phenylphthalazine **1** with various ketonic reagents were also investigated. It underwent condensation by refluxing with *o*-hydroxyacetophenone in ethanol containing a few drops of acetic acid to give hydrazone **11** which on stirring with conc. H_2SO_4 underwent cyclisation by lose one mole of water leading to the formation of 1-(4-phenylphthalazin-1-yl)-3-methyl-4,5-benzpyrazoline **12** (Scheme II). The ^1H NMR spectrum of **11** showed signals at δ 2.3, 7.0-9.0, 12.0 and 13.2 ppm which attributable to CH_3, aromatic, OH and NH protons. The main fragmentation processes involves rupture of phthalazinyl radical (m/z 205, 100%) in order to give further support to the structure of compound **12**.

Moreover, reaction of compound 1 with O-acetyl/benzoyl benzoic acid in gl. acetic acid led[7] directly to the formation of 3-(4-phenylphthalazin-1-yl)-1-methylphthalazin-4-one **13a** and/or 3-(4-phenylphthalazin-1-yl)-1-phenylphthalazin-4-one **13b** respectively (Scheme II). The mass spectrum of **13a** recorded the base peak at (m/z 160, 100%) obtained by loss of 4-phenylphthalazinyl radical (m/z 205), in addition, IR spectrum of **13a** showed



Scheme II

characteristic bands at 1673 cm^{-1} due to cyclic carbonyl groups. Further, on refluxing compound **1** with acetylacetone in ethanol afforded the corresponding 1,3,5-trisubstituted pyrazole **14**. The structure of **14** was established from elemental analysis and spectral data. The IR spectrum of **14** showed bands at 2967, 1610, 1570 cm^{-1} due to aliphatic and C=N groups, while its ^1H NMR spectrum showed signals at δ 2.25, 6.56 and 7.0-9.0 ppm due to $2CH_3$, CH= of pyrazole and aromatic protons.

Acylo condensation[8] of **1** by boiling with pivolayl chloride in the presence of DMF furnished 3-trimethyl-6-phenyl-5-triazolo[5,4-*a*]phthalazine **15** while its alkylation using *p*-bromophenacyl bromide in ethanol-NaOH via nucleophilic interaction produced 4-dihydro-3-(*p*-bromophenyl)-7-phenyl-1,2,4-triazino[3,4-*a*]phthalazine **16** (Scheme II). The IR spectra of compounds **15** and **16** showed the absorption bands due to aromatic, aliphatic and C=N groups at 3057, 2967 and 1616 cm^{-1}.

Also, treatment of compound **1** with 1,3-dichloroacetone (2:1 by moles) in DMF yielded 1,3-dihydrazinoacetone **17**. Basic cyclization of **17** via refluxing with 2N aq. NaOH solution[9] gave 3H-4-substituted-methyl-7-phenyl-1, 2, 4-triazino-[3,4-*a*]phthalazine **18**. The IR spectrum of **17** showed broad band at 3500-2800 cm^{-1} due to NHNH, aromatic and aliphatic groups, in addition, at 1650 cm^{-1} due to C=O group. The ^1H NMR spectrum of **18** revealed a signals at δ 2.7-3.0 and 7.2-8.8 ppm due to CH_2 and CH=C, aromatic and NH protons.

Compound **1** was also reacted with phthalic anhydride in presence of ethanol to afford N^1-(phenyl)-N^2-(aroyl)hydrazine **19** which underwent cyclization by losing one mole of water to give 2-(4-phenylphthalazin-1-yl)phthalazin-1, 4(3H)dione **20** (Scheme II).

Experimental Section

Melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin Elmer 293 FT spectrophotometer (ν_{max} in cm^{-1}), UV absorption spectra (in DMF) on a LASTACQU. MRD (300-400) test spectrophotometer (λ_{max} in nm), ^1H NMR spectra on a EM NMR spectrometer 200 MH_z PMR using DMSO and/or acetone as a solvent and TMS as internal reference (chemical shift's in δ ppm) and mass spectra using GCMS qp 1000 ey scheimadzn instrument (70 ev).

Preparation of the hydrazones 2a-f. A mixture of 1 (0.01 mole) and the appropriate aldehydes (0.01 mole) in abs. ethanol (50 mL) was refluxed for 1 hr, cooled and the solid thus obtained was filtered and recrystallized from a proper solvent to give **2a-f**.

Synthesis of 4,5-benzpyrazoline derivative 3. A suspension of **2a** (0.5 g) in conc. H_2SO_4 (5 mL) was stirred for 2hr and then poured onto ice-NaOH solution. The solid obtained was washed with water and crystallized from ethanol to give **3**.

Reduction of 2b : Formation of compound 4. A mixture of **2b** (0.5 g), Zn dust (0.5 g) in gl. acetic acid-ethanol mixture (1:1, 10 mL) was heated under reflux for 2hr, filtered on hot and concentrated, cooled and poured onto HCl-ice mixture. The separated product was filtered, washed with hot water and crystallized to give **4**.

Fusion of 2b with p-chlorothiophenol: Formation of thioether 5. A mixture of **2b** (0.01 mole) and p-chlorothiophenol (0.01 mole) was heated at 150-60° on a sand-bath for 1hr. The solid obtained was triturated with pet. ether to give **5**.

Acylation of 2c: Formation of N-acetyl derivative 6. Compound **2c** (0.01 mole) in DMF (10 mL) and acetyl chloride (0.02 mole) was refluxed for 8hr. The reaction mixture was cooled and poured onto ice. The precipitated solid was filtered and crystallized to give **6**.

Addition of mercaptoacetic acid to compound 2d : Formation of 7. Equimolar mixture of **2d** and mercaptoacetic acid in dioxane (50 mL) was refluxed for 12hr, concentrated by remove the excess solvent and neutralized with aq. Na_2CO_3. The resultant solid was recrystallized to give **7**.

Oxidative cyclization of 2e : Synthesis of s-triazolophthalazine 8. To a solution of **2e** (1 g) in EtOH (50 mL) was added $FeCl_3$ dropwise (10 mL) and the reaction mixture was refluxed for 2hr and filtered. The filtrate was poured onto ice and the separated product was filtered, washed with cold water and crystallized to give **8**.

Addition of HCN to 2f: Formation of adduct product 9. To a solution of **2f** (0.01 mole) in ethanol-gl. acetic acid mixture (1:1, 20 mL), was added HCN (0.01 mole) (NaCN in 10 mL H_2O), and the reaction mixture refluxed for 2hr. The solid obtained upon dilution was filtered and crystallized to give **9**.

Acidic hydrolysis of 9: Formation of 1,2,4-triazino[3,4-a]phthalazin-4-one derivative 10. A mixture of **9** (1 g) and HCl (20%, 20 mL) was refluxed for 4hr, cooled and the resultant solid filtered and crystallized to give **10**.

Preparation of hydrazone 11. A mixture of **1** (0.01 mole) and *o*-hydroxyacetophenone (0.01 mole) in ethanol (50 mL) containing a few drops of acetic acid, was refluxed for 1hr and then cooled. The separated solid was filtered and crystallized to give **11**.

Synthesis of 1,3-disubstituted-4,5-benzopyrazoline 12. A suspension of **11** (0.5 g) in conc. H_2SO_4 (5 mL) was stirred for 2hr, then poured onto ice-NaOH solution. The solid obtained was washed with cold water and crystallized to give **12**.

Synthesis of 1,3-disubstituted phthalazin-4-one 13a,b. A mixture of 1 (0.01 mole) and *o*-acetylbenzoic or *o*-benzoylbenzoic (0.01 mole) in gl. acetic acid (50 mL) and fused sodium acetate (5 g) was refluxed for 6hr, cooled and poured onto ice. The solid obtained was filtered and crystallized to give **13a** and/or **13b**.

1,3,5-trisubstituted-pyrazoline 14. A mixture of **1** (0.01 mole) and acetylacetone (0.01 mole) in abs. ethanol was refluxed for 2hr, cooled and concentrated to remove the excess solvent. The resultant solid was filtered and crystallized to give **14**.

Acylation of 1 using pivollyl chloride: Formation of s-triazolo phthalazine 15. An equimolar mixture of **1** and pivollyl chloride in DMF (20 mL) was refluxed for 1hr, cooled and then poured onto ice. The precipitated solid was filtered off and recrystallized to give **15**.

Synthesis of 3,7-disubstituted-1,2,4-triazino-

[3,4-a]phthalazine 16. A mixture of **1** (0.01mole) and *p*-bromophenacyl bromide (0.01 mole) in ethanol (50 mL) was refluxed for 30 min, then added NaOH solution (5%, 25 mL) and it was further refluxed for 2hr, cooled and poured onto ice-HCl mixture. The resultant solid was filtered and recrystallized to give **16**.

Synthesis of 1,3-dihydrazinoacetone 17. To a solution of **1** (0.02 mole) in DMF (100 mL) was added 1,3-dichloroacetone (0.01 mole) and refluxed for 1hr, cooled and poured onto ice. The solid obtained was filtered and crystallized to give **17**.

Synthesis of 3*H*-4-substituted methyl-7-phenyl-1,2,4-triazino[3, 4-*a*]phthalazine 18. A mixture of **17** (1 g) and aq. NaOH (2N, 20 mL) was refluxed for 4 hr, cooled and poured onto ice-HCl mixture. The solid obtained was filtered and recrystallized to give **18**.

Reaction of compound 1 with phthalic anhydride: Formation of 19. A mixture of **1** (0.01 mole) and phthalic anhydride (0.01 mole) in aq. ethanol (100 mL) was heated under reflux for 2 hr, cooled and poured onto ice. The solid obtained was filtered and recrystallized to give **19**.

Synthesis of 2-(4-phenylphthalazin-1-yl)phthalazin-1,4-(3*H*)dione 20. A mixture of compound **19** (0.5 g) gl. acetic acid (20 mL) and fused sodium acetate (0.5 g) was refluxed for 4 hr, cooled, diluted with cold water and the resultant solid obtained was filtered and recrystallized to give **20**.

Characteristic data of all the above compounds are given in Table I.

Table I—Characteristic data of the various prepared compounds

Compd* No	Crystallized from	m.p. (°C)	Mol. formula*	Mol. weight
1	EtOH	135-37	$C_{14}H_{12}N_4$	236
2a	EtOH	278-80	$C_{21}H_{16}N_4O$	340
2b	EtOH	165-67	$C_{21}H_{15}N_5O_2$	369
2c	EtOH	263-64	$C_{21}H_{16}N_4O$	340
2d	EtOH	160-61	$C_{23}H_{21}N_5$	367
2e	EtOH	105-06	$C_{22}H_{18}N_4O_2$	368
2f	EtOH	185-87	$C_{21}H_{14}N_4Cl_2$	390
3	Dil. EtOH	248-50	$C_{21}H_{14}N_4$	320
4	Dil. DMF	140-41	$C_{23}H_{21}N_5O$	383
5	Benzene	240-41	$C_{27}H_{20}N_5O_2SCl$	513.5
6	Dil. DMF	275-77	$C_{23}H_{18}N_4O_2$	382
7	Pet. ether	175-77	$C_{25}H_{23}N_5SO$	441
8	EtOH	230-31	$C_{22}H_{16}N_4O_2$	368
9	Dil. DMF	175-76	$C_{22}H_{15}N_5Cl_2$	419
10	AcOH	225-26	$C_{22}H_{14}N_4OCl_2$	420
11	EtOH	90-92	$C_{22}H_{18}N_4O$	354
12	AcOH	275-76	$C_{22}H_{16}N_4$	336
13a	EtOH	185-87	$C_{23}H_{16}N_4O$	364
13b	EtOH	168-70	$C_{28}H_{18}N_4O$	426
14	Et. Benzene	155-56	$C_{19}H_{16}N_4$	300
15	EtOH	175-76	$C_{19}H_{18}N_4$	302
16	Dil. DMF	120-21	$C_{22}H_{15}N_4Br$	415
17	Dil. EtOH	185-86	$C_{31}H_{26}N_8O$	526
18	Dil. DMF	240-42	$C_{31}H_{24}N_8$	508
19	EtOH	204-05	$C_{22}H_{16}N_4O_3$	384
20	EtOH	284-85	$C_{22}H_{14}N_4O_2$	366

*C, H, N, S, Cl and Br analyses within ± 0.5 % theoretical values

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