Synthesis of Novel Phthalazines Containing Heterocyclic Moieties

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Abstract: The phthalazine (1) was allowed to react with 2-aminoethanol, allyl bromide, benzoyl chloride, 2-chloroethanol, phosphorous pentasulfide, ethyl cyanoacetate, phenyl isothiocyanate, piperazine and ethyl piperazine-1-carboxylate to give (2), (18), (17), (12), (9), (15), (19), (7) and (8). The compound (2) was allowed to react with phenyl isothiocyanate, acetic anhydride and piperonaldehyde giving (3), (5) and (6). (3) reacted with diethyl malonate to give the pyrimidine derivative (4). The thione (9) reacted with hydrazine hydrate followed by anisaldehyde to give (10) and (11). The phthalazinone derivative (12) reacted with phenol and catechol to give (13a,b). Acetylation of (13b) gave the diacetate derivative (14). Finally (15) reacted with phenyl hydrazine gave the propenoic acid phenylhydrazide (16). The new compounds were synthesized with the objective of studying their antifungal and antimicrobial activity. Some of them gave positive results. The newly synthesized compounds were characterized on the basis of their spectral (1H-NMR, Mass spectrum, IR and Elemental analysis).

Keywords: Piperazine, phenylhydrazine, allyl bromide, diethyl malonate.

1. Introduction

Nitrogen-containing heterocycles possess diverse chemotherapeutic activities [1, 2]. Among a large variety of nitrogen-containing heterocyclic compounds, phthalazines (1H)-ones, they were reported to be used as efficient antitumor [3] and therapeutic agents [4]. On the other hand, phthalazines bearing a substituent at C-4 represent key intermediates in the synthesis of various compounds with highly interesting clinical applications of pharmacological properties, such as anti-atherosclerosis, antiplatelet aggregation inhibitors and cardiovascular antihypertensive agents [5-9]. In addition, a number of phthalazinone derivatives are well known to be active as anticonvulsant agents [5-9].

2. Results and Discussion

When the previously prepared phthalazinone (1) [14] was allowed to react with ethanolamine in oil bath at 150 °C, afforded 2-[2-aminomethyl] phthalazin-1-(2H)-one (2). The reaction possibly takes place via nucleophilic attack on the more electrophilic center of alcoholic moiety. The structure was deduced from correct microanalytical data. The IR spectrum revealed strong absorption bands at ν 1560, 3154 and 3407 cm⁻¹ attributable to C=O and NH. The IR spectrum revealed strong absorption bands at 1205, 1428, 1653, 1702, 2859 and 2927 cm⁻¹ attributable to C=O and laked any band for NH. The EIMS showed m/z 1156 and 1667 cm⁻¹ attributable to C=O and laked any band for NH. The EIMS showed m/z 522 corresponding to M+ (molecular ion peak). Also acetylation with acetic anhydride, afforded 2-[2-(acetylamo)ethyl]-4-tetrayl phthalazin-1(2H)-one (5). 1H NMR spectrum showed δ 1.2 (t, 2H, CH3), 1.7 (s, 4H, β-methylene protons of tetryl moiety), 2.05 (s, 3H, CH3), 2.3 (s, 6H, α-methylene protons of tetryl moiety and N-CH3), 2.7-7.2 (2m, 7H, Az-H), 10.29 (s, 1H, NH, exchangeable with D2O). The IR spectrum revealed strong absorption bands at ν 1666 and 3155 cm⁻¹ attributable to C=O and NH. Also interaction with piperonaldehyde (3,4-methylene dioxo-benzaldehyde) yielded 2-[2-(3,4-methylene dioxobenzylidene amino)-ethyl]-4-tetrayl phthalazin-2(1H)-one (6). The IR spectrum revealed strong absorption bands at ν 1658, 1701 cm⁻¹ attributable to C=O and NH. Among a large variety of antifungal and antitumor activity [1, 2]. The phthalazinone (1H)-one (1) was submitted to react with piperazine and formaldehyde in the presence of few drops of HCl yielded 2-piperidinomethyl-4-tetrayl phthalazin-1(2H)-one (7). The EI/MS showed m/z 373 corresponding to M+ (molecular ion peak). On the other hand when (1) was allowed to react with ethoxy carbonylpiperazine and formaldehyde in the presence of drops of HCl afforded (8). The IR spectrum revealed strong absorption bands at ν 1653, 1703, 2859 and 2927 cm⁻¹ attributable to two carbonyl groups (the lower frequency of C=O of ester is due to the presence of lone pair of electron on the adjacent nitrogen) and CH and devoid any band for NH. The 1H NMR spectrum showed δ 1.1 (t, 3H, CH3), 2.86 (s, 6H, α-methylene protons of tetryl moiety and N-CH3), 7.2-8.5 (3m, 12H, Ar-H), 10.49 (s, 2H, 2 NH, exchangeable with D2O). The IR spectrum was inferred chemically via its interaction with diethyl malonate and yielded (4). Its structures were deduced from correct microanalytical data. The IR spectrum revealed strong absorption bands at 1205, 1428, 1560, 3154 and 3407 cm⁻¹ attributable to C=O and NH. 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The EIMS showed m/z at 292, 293 and 294 corresponding to M⁺, M⁺+1 and M⁺+2. Also the structure of (9) was inferred chemically via its interaction with hydrazine hydrate to yield 1-hydrazino-4-tetraylphthalazine (10). The structure of (10) was inferred from correct microanalytical data. The IR spectrum showed strong absorption bands at 3100-3300 attributed to NH. The EIMS showed m/z at 291 corresponding to M⁺. Interaction of hydrazine derivative with 4-methoxybenzaldehyde in boiling ethanol yielded the hydrazine derivative (11). H NMR spectrum of (11) showed δ: 1.7 (s, 4H, β-methylene protons of tetryl moiety), 2.5 (s, 3H, CH3), 2.7 (t, 4H, α-methylene protons of tetryl moiety), 7.2-7.9 (3m, 11H, Ar-H), 11.92 (s, 2H, NH, exchangeable with D2O). The IR spectrum devoid any band of NH. The EIMS showed m/z at 409 corresponding to M⁺.

When (1) was submitted to react with 2-chloroethanol, benzoyl chloride and allyl bromide in boiling dry acetone and anhydrous potassium carbonate for 24 hours afforded 2-(2-hydroxyethyl)-4-tetraylphthalazin-1(2H)-one (12), 2-benzoyl-4-tetraylphthalazin-1(2H)-one (17) and 2-allyl-4-tetrayl-1(2H)phthalazinone (18) respectively. Their structures were inferred from correct microanalytical data. The IR spectrum of (12) revealed strong absorption bands at v 1632, 2852, 2921, and 3436 cm⁻¹ attributable to C=O, CH and OH. The EIMS showed m/z at 330 corresponding to M⁺(molecular ion peak). H NMR spectrum also showed δ: 1.7 (s, 4H, β-methylene protons of tetryl moiety), 2.7 (t, 6H, α-methylene protons of tetryl moiety and N-CH2), 4.1 (t, CH2OH), 7.2-7.9 (2m, 7H, Ar-H), 8.37 (s, 1H, OH, exchangeable with D2O). The reaction takes place via SN2 mechanism involving nucleophilic attack of lone pair of nitrogen atom of NH group of phthalazine moiety on the alkyl chloride moiety of 2-chloroethanol. The IR spectrum of (17) revealed strong absorption bands at v 1668, 2852 and, 2920 cm⁻¹ attributable to C=O and CH. The reaction proceeds via tetrahedral mechanism in which the N-C bond was formed before C-Cl bond which started to break and consequently a lot of energy is accumulated in the reaction medium, which offset the activation energy of the reaction and a facile conversion occurred. The IR spectrum of (18) revealed strong absorption bands at v 1660, 2853 and 2943 cm⁻¹ attributable to C=O and CH and devoid of any band for NH. The EIMS showed m/z at 316 corresponding to M⁺(molecular ion peak). The reaction takes place via SN2 mechanism and the role of K2CO3 is pulling of bromide ion as KBr and abstract of H⁺ and converted to KHCO3. The structure of (12) was verified chemically via its reaction with compounds containing an active hydrogen namely phenol and catechol in boiling ethanol to give Mannich bases type (13a,b). Their structures were inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at v 1665-1670 and 3400-3430 cm⁻¹ attributable to C=O and OH. H NMR spectrum of (13b) showed δ: 1.7 (t, 2H, CH3), 1.8 (s, 4H, β-methylene protons of tetryl moiety), 2.35 (t, 6H, α-methylene protons of tetryl moiety and N-CH2), 6.64-7.9 (3m, 11H, Ar-H), 10.28 (s, 2H, OH, exchangeable with D2O). Acetylation of (13b) yielded diacetoxyl derivative (14). The IR spectrum revealed strong absorption bands at v 1660 and 1761 cm⁻¹ attributable to two C=O and devoid any band for OH. On the other hand when (1) was submitted to react with ethyl cyanoacetate in boiling ethanol yielded ethyl-3-amino-3-(1-oxo-(4-1,2,3,4-tetrahydrophthalen-2-yl)phthalazin-2(1H)-y1)propanoate (15). The reaction takes place via nucleophilic addition on CN rather than tetrahedral nucleophilic substitution at acyl moiety(addition takes place easily than substitution involving bond breakage, while addition required bond polarization). The structure of (15) was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at v 1603, 1671, 1749, 2907, 2932, 3152 and 3296 cm⁻¹ attributable to C=C, two C=O, CH and NH. Also the structure was supported chemically from its interaction with phenyl hydrazine in boiling ethanol and yielded 3-amino-3-(1-oxo-(4-1,2,3,4-tetrahydrophthalen-2-yl)phthalazin(1H) ropenic acid phenylhydrazide (16). The structure of (16) was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at v 1604, 1665, 2854, 3932, 3100 and 3305 cm⁻¹ attributable to C=C, C=O, CH and NH. The IR spectrum also showed δ: 1.7 (s, 4H, β-methylene protons of tetryl moiety), 2.7 (t, 4H, α-methylene protons of tetryl moiety), 7.19-8.6 (3m, 12H Ar-H), 10.8 (broad, 4H, NH2), 2 NH, exchangeable with D2O). The EIMS showed m/z at 451 corresponding to M⁺. Interaction of (1) with phenylisothiocyanate in boiling benzene yielded 2-phenyl thiocarbonyl-4-tetraylphthalazin-1(2H)-one (19). The structure of (19) was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands at v 1156, 1665 and 3155 cm⁻¹ attributable to C=S, C=O and NH. The EIMS showed m/z at 411, 412 and 413 corresponding to M⁺, M⁺+1 and M⁺+2 (See Scheme 1 on last page).

2.1 Antimicrobial Activity

The antibacterial activity of the synthesized compounds was tested against Bacillus subtilis, Staphylococcus aureus (Gram-positive bacteria), Escherichia coli, Pseudomonas sp. (Gram-negative bacteria) using nutrient agar medium. The antifungal activity of the compounds was tested against Candida albicans and Aspergillus niger using Sabouraud dextrose agar medium.

2.2 Agar Diffusion Medium

All compounds were screened in vitro for their antimicrobial activity against, by agar diffusion method (Cruickshank et al.1975) [15]. A suspension of the organisms were added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer). An amount of 0.1 ml of the synthesized compounds was poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. The plates were then incubated at 37°C for 24 h and observed for antimicrobial activity. The diameters of zone of inhibition are presented in Table 1.
6.20, N 11.97  

C=O and NH. Anal cald for C

chromatography (TLC) was performed on Merk TLC  

All melting points are uncorrected and were measured on an  

Weakly active (+) = (inhibition zone 11-12) nm  

Slightly active (++) = (inhibition zone 13-15) nm  

Moderately active (+++) = (inhibition zone 16-29) nm  

3. Experimental  

All melting points are uncorrected and were measured on an electrothermal melting point apparatus. Elemental analyses  

Experimental  

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−ve ++ ve  

−ve + ve  

−ve -ve  

Table 1: Antibacterial and antifungal activities of the newly synthesized compounds  

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1-2-(1-Oxo-4-(5, 6, 7, 8-tetrahydro-4-phenyl-2-thioxodihydropyrimidine-1(2H)-yl)ethyl)-3-phenyl-2-thioxodihydropyrimidine-4, 6(1H, 5H)-dione (4)  

A mixture of (3) (0.003 mol) 1.3 gm and (0.003 mol) 0.48  

gm diethylmalonate in 20 mL ethanol was heated under reflux for 3 hs. After cooling a solid was separated and  

crystalized from ethanol to give (4), 50 % yield, m.p. 240 ℃. M + (M+1)1, 522 (1.5), 524 (0.6). IR (KBr) ν 1156, 1666 and 3155 cm−1 attributable to C=S and C=O. Anal cald for C18H12N4O3S: C 68.95, H 5.10, N 10.72; found C 67.48, H 5.29, N 10.21.

2-(2-[Acetylamino]ethyl)-4-(5,6,7,8-tetrahydrophthalan-2-yl)phthalazin-1(2H)-one (5)  

Acetic anhydride (0.002 mol) 0.19 mL was added rapidly to a boiling solution of (2) (0.001 mol) 0.3 gm in 20 mL ethanol was heated under reflux for 2 hs, cooled and poured on cold water to give a solid which was separated and crystalized from benzene to give (5), 65 % yield, m.p. 190 ℃. H NMR δ: 1.2 (t, 2H, CH3) 1.7 (s, 4H, β- methylene protons of tetryl moiety), 2.05 (s, 3H, CH3), 2.8 (t, 6H, α- methylene protons of tetryl moiety and N-CH3), 2.7-7.2 (7m, 7H, Ar-H), 10/29 (s, 1H, NH, exchangeable with D2O). IR (KBr) ν 1666 and 3155 cm−1 attributable to C≡O and NH. Anal cald for C15H12N2O3: C 73.11, H 6.41, N 11.63, found C 73.48, H 5.90, N 11.21.

2-[3-(4-Methylenedioxybenzylidenemino)ethyl]-4-(5, 6, 7, 8-tetrahydrophthalacen-2-yl)phthalazin-2(1H)-one (6)  

A mixture of (2) (0.001 mol) 0.3 gm and piperonaldehyde (0.001 mol) 0.18 gm in 20 mL ethanol was heated under reflux for 3 hs. After cooling a solid was separated and crystalized from ethanol to give (6), 40 % yield, m.p. 220 ℃. M + (M+1)1, 373 (13), 276 (73) and 248 (20), 230 (17), 161 (100). IR (KBr) ν 1662 and 1675 cm−1 attributable to C≡N and C=O. Anal cald for C19H12N2O2: C 74.48, H 5.58, N 9.31; found C 74.58, H 5.90, N 9.97.

2-(Piperidin-1-ylmethyl)-4-(5, 6, 7, 8-tetrahydrophthalacen-2-yl)phthalazin-1(2H)-one (7)  

A mixture of (1) (0.001 mol) 2.7 gm, (0.002 mol) 1.2 gm of 2  

aminoethanol in 20 mL pyridine was heated under reflux for 3 hs. After cooling, the mixture was poured on  

ice/HCl to separate a solid which was separated, filtered and  

crystallized from ethanol to give (7), 90 % yield, m.p. 235 ℃. IR (KBr) ν 1658, 3154 and 3407 cm−1 attributable to C≡N and C=O .Anal cald for C18H16N4O3S: C 75.21, H 6.63, N 10.36, found C 75.48, H 5.90, N 10.13.
Ethyl 4-(1-oxo-4-(5,6,7,8-tetrahydro-2-naphthalen-2-yl)phthalazin-2(1H)-yl)methylpiperazine-1-carboxylate (8)

A mixture of (1) (0.01 mol) 2.7 gm and 2 gm of phosphorous pentasulphide in 20 mL xylene was heated under reflux for 2 hrs. After cooling a solid was formed and crystallized from ethanol to give (8), 60 % yield, m.p. 170 °C. IR (KBr) ν 1604, 1665, 2854, 2932, 3100 and 3208 cm⁻¹ attributable to C=C, C=O, CH and OH. Anal cald for C₂₇H₂₅N₅O: C 71.82, H 5.58, N 15.51; found C 71.38, H 5.29, N 16.11.

1-Hydrazinyl-4-[(5,6,7,8-tetrahydro-2-(1H)-thione) (9)

A mixture of (1) 1gm and 1 mL of hydrazine hydrate was refluxed for 2 hrs. After cooling a solid was obtained and crystallized from ethanol to give (9), 40 % yield, m.p. 190 °C. MS, m/z (%) M⁺, 291 (26), 273 (28), 264 (30). IR (KBr) ν 1205, 1428, 2855, 2932 and 3147 cm⁻¹ attributable to C=S, CH and NH. Anal. cald for C₁₃H₁₄N₂S: C 73.94, H 5.52, N 9.58, found C 73.48, H 5.90, N 8.71.

4-(5,6,7,8-Tetrahydrophanthalen-2-yl)phthalazin-1(2H)-thione (10)

A mixture of (1) (0.01 mol) 2.7 gm and 2 gm of phosphorous pentasulphide in 20 mL xylene was heated under reflux for 2 hrs. After cooling a solid was obtained and crystallized from ethanol to give (10), 40 % yield, m.p. 190 °C. MS, m/z (%) M⁺, 291, 229 (100), 293 (20) and 294 (8) corresponding to M⁺ and M⁺+1, 295 (21). IR (KBr) ν 1205, 1428, 2855, 2932 and 3147 cm⁻¹ attributable to C=S, CH and NH. Anal. cald for C₁₃H₁₄N₂S: C 73.94, H 5.52, N 9.58; found C 73.48, H 5.90, N 8.71.

4-(5,6,7,8-Tetrahydrophanthalen-2-yl)-1,2-dihydrophthalazine (11)

A mixture of (10) (0.01 mol) 0.7 gm, (0.01 mol) 1.3 gm anisaldehyde in 20 mL ethanol was refluxed for 3 hrs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give (11), 30 % yield, m.p. 140 °C. H NMR δ: 1.7 (s, 4H, β- methyl protons of tetryl moiety), 2.5 (s, 3H, CH₃), 2.7 (t, 4H, α- methyl protons of tetryl moiety), 7.2-7.9 (3m, 11H, Ar-H), 11.92 (s, 2H, NH, exchangeable with D₂O). MS, m/z (%) M⁺, 409 (22), 273 (18), 135 (100). IR (KBr) ν 1601, 1508 cm⁻¹ attributable to C=N. Anal. cald for C₂₉H₂₅N₅O: C 76.07, H 6.38, N 13.65; found C 75.68, H 5.90, N 14.41.

2-(2-Hydroxyethyl)-4-(8, 6, 7, 8-tetrahydrophanthalen-2-yl)phthalazin-1(2H)-one (12)

A mixture of (1) (0.01 mol) 2.7 gm, (0.01 mol) 0.8 gm chloroethanol and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give (13), 50 % yield, m.p. 110 °C. H NMR δ: 1.7 (s, 4H, β- methyl protons of tetryl moiety), 2.7 (t, 4H, α- methylene protons of tetryl moiety), 7.19-8.6 (3m, 12H Ar-H), 10.8 (broad, 4H, NH₂, 2 NH, exchangeable with D₂O). MS, m/z (%) M⁺, 451 (6), 434 (4), 317 (4). 276(100). IR (KBr) ν 1604, 1665, 2854, 2932, 3100 and 3208 cm⁻¹ attributable to C=C, C=O, CH and NH. Anal. cald for C₂₇H₂₅N₅O: C 71.82, H 5.58, N 15.51; found C 71.38, H 5.29, N 16.11.
2-Benzoyl-4-(5, 6, 7, 8-tetrahydronaphthalen-2-yl) phthalazin-1(2H)-one (17)

A mixture of (1) (0.01 mol) 2.7 gm, (0.04 mol) 5 gm benzoyl chloride and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give (17), 60 % yield, m.p. 100 °C. IR (KBr) ν 1668, 2852 and, 2920 cm⁻¹ attributable to C=O and CH. Anal cald for C₂₅H₂₀N₂O₂: C 78.93, H 5.30, N 7.36; found C 78.75, H 5.35, N 7.61

2-Allyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (18)

A mixture of (1) (0.01 mol) 2.7 gm, (0.01 mol) 1 gm allyl bromide and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give (18), 50 % yield, m.p. 110 °C. MS, m/z (%); M⁺, 316 (7.6), 290 (18), 276 (33). IR (KBr) ν 1660, 2853 and 2923 cm⁻¹ attributable to C=O and CH. Anal cald for C₂₁H₂₀N₂O: C 79.72, H 6.37, N 8.85; found C 80.38, H 5.90, N 8.21

1-Oxo-N-phenyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-carbothioamide (19).

A mixture of (1) (0.001 mol) 0.2 gm and (0.001mol) 0.13 gm of phenyl isothiocyanate in 20 mL methanol was refluxed for 5 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give (19), 30 % yield, m.p. 95 °C. IR (KBr) ν: 1156, 1665 and 3155 cm⁻¹ attributable to C=S, C=O and NH. MS, m/z (%), M⁺, 411, (3), 412 (5) and 413 (2) corresponding to M⁺, M⁺+1 and M⁺+2, 275 (100), 247 (30). Anal cald for C₂₅H₂₁N₃OS: C 72.97, H 5.14, N 10.21; found C 73.25, H 5.85, N 10.70

References

Scheme 1