Synthesis of condensed heterocyclic systems: Some ring closure reactions involving phthalazine

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Some new condensed heterocycles have been synthesized via condensation of 1,4-dichlorophthalazine with thiosemicarbazide followed by ring closure reactions. The constitution of the synthesized compounds have been delineated by elemental analysis and spectral data. All the products have been evaluated for their in vitro growth inhibitory activity against various microorganisms.

As an extension of our work on the synthesis of biologically active phthalazine derivatives, such as their thiosemicarbazide, thiazolidinones, triazoles, and triazines, the synthesis of some novel heterocyclic derivatives incorporating the phthalazine moiety has been undertaken and subjected to antimicrobial screening.

1,4-Dichlorophthalazine 1 on condensation with thiosemicarbazide in DMF afforded 1,4-bis(thiosemicarbazido)phthalazine 2. Compound 2 underwent cyclization with CS$_2$ in the presence of KOH to give 1, 4-bis(3'), 5'-dithioxy-s-triazol-1-yl)phthalazine 3. Compound 3 reacted with monochloroacetic acid in the presence of NaOH to give 1,4-bis[1'-thioxy-6'-oxo-s-triazolo[3, 4-b]1, 3-thiazol-2'-yl]phthalazine 4. 1, 4-bis[3'-thioxy-5'-substituted-s-triazol-1'-yl]phthalazines 5a-e were obtained by the treatment of 2 with triethylthioureaformate, AcOH-NaOAc and p-nitrobenzoyl chloride, respectively. 1, 4-bis[3'-thioxy-6'-oxo-1'-H-1', 2', 4'-triazin-1-yl]phthalazine 6 and 1, 4-bis[3'-thioxy-6'-H-5'- (p-bromophenyl)-1', 2', 4'-triazin-1-yl]phthalazine 7 were prepared by the action of 2 with dichloroacetic acid and p-bromophenacyl bromide in alkaline medium. The action of 2 with different phenylisothiocyanates gave 1, 4-bis-[4'(N-arylaminothiocarbonyl)-3'-thiosemicarbazido-yl]phthalazine 8a-d. Finally the action of monochloroacetic acid produced 1, 4-bis [5'-H-4'-oxo-2'-thiazolidin-2'-yl]hydrazino]phthalazine 9 (Scheme I).

The elemental analysis and spectral data prove the authenticity of the synthesized compounds. These products were evaluated for their in vitro growth inhibitory activity.

Antimicrobial activity

The activity was determined using cup-plate agar diffusion method by measuring the inhibition zones in mm. All the compounds were screened in vitro for their antimicrobial activity against S. aureus, S. citris, E. coli, Ps. flourescence and fungi A. flavus and C. albicans. Known antibiotics like ampicillin, cephalaxin, tetracycline and norfloxacin, were used for comparison. Significant activity was shown against S. citris by compounds 2, 5b, 6 and 7 (22-32 mm), while compounds 4, 5a-c, 7 showed good activity against E. coli and compound 9 against Ps. flourescence. Compounds 3, 5a, 6, 7 and 9 were most active against C. albicans (18-35 mm) and moderately active against A. flavus. The activity of other compounds were transitory (Table I).

Experimental Section

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-435-IR spectrophotometer ($\nu$ in cm$^{-1}$). Completion of the reaction was monitored by precoated plate of silica gel GF$254$ ([E. Merck], benzene : ethyl acetate, 85:15). The final products were purified by column chromatography using silica gel (200 mesh) in increasing percentage of ethyl acetate in benzene. Elemental analysis were quite compatible with their structures. Physical constants are recorded in Table I. 1, 4-Dichlorophthalazine 1 was prepared according to reported method.

Preparation of 1, 4-bis(thiosemicarbazido)phthalazine 2. Compound 1 (0.01 mole) was taken in
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Scheme I

Reagents: (a) NH₂NHCSNH₂, DMF; (b) Cs₂/KOH; (c) CICH₂COOH; (d) Cl₂CHCOOH; (e) Triethyl orthoformate, AcOH-NaOAc, p-nitrobenzoyl chloride; (f) R-NCS; (g) p-bromophenacetyl bromide; (h) CICH₂COOH

<table>
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<tr>
<th>Compd</th>
<th>R</th>
<th>Mol. formula</th>
<th>Nitrogen %*</th>
<th>m.p.</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
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<tr>
<td>2</td>
<td></td>
<td>C₆H₄N₂S₂</td>
<td>36.30 (36.36)</td>
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<tr>
<td>3</td>
<td></td>
<td>C₆H₄N₂S₂</td>
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<td>4</td>
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<td>C₆H₄N₂S₄0₂</td>
<td>24.79 (24.78)</td>
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<td>++</td>
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<tr>
<td>5a</td>
<td>H</td>
<td>C₆H₄N₂S₂</td>
<td>34.11 (34.14)</td>
<td>181</td>
<td>++</td>
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<tr>
<td>5b</td>
<td>CH₃</td>
<td>C₆H₄N₂S₂</td>
<td>31.44 (31.46)</td>
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<tr>
<td>5c</td>
<td>C₂H₄NO₂</td>
<td>C₂H₄N₂S₂O₄</td>
<td>24.46 (24.48)</td>
<td>125d</td>
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<td>6</td>
<td></td>
<td>C₂H₂N₂S₂O₂</td>
<td>29.13 (29.17)</td>
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<td>7</td>
<td>C₂H₂Br</td>
<td>C₂H₂N₂S₂Br₂</td>
<td>16.79 (16.82)</td>
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<tr>
<td>8a</td>
<td>C₂H₄H₂</td>
<td>C₂H₄N₂S₂</td>
<td>24.20 (24.22)</td>
<td>70</td>
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<tr>
<td>8b</td>
<td>C₂H₂Br</td>
<td>C₂H₂N₂S₂Br₂</td>
<td>19.00 (19.03)</td>
<td>100</td>
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<td>++</td>
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<tr>
<td>9</td>
<td>C₂H₂F</td>
<td>C₂H₂N₂S₂F₂</td>
<td>22.75 (22.80)</td>
<td>96</td>
<td>+++</td>
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*All Compounds gave satisfactory elemental analysis within ±0.05% of theoretical values.

**S.A. = Staphylococcus Aureus; S.C. = Staphylococcus citrus; E.C. = Escherichia coli; P.F. = Pseudomonas fluorescens; C.A. = Candida albicans; A.F. = Aspergillus flavus. □ zone of inhibition after 24 hr: 10-15mm=++, 16-20mm= +++ , 21-25mm=++++, DMF= +
DMF and thiosemicarbazide (0.02 mole) in DMF added to it with stirring. The reaction mixture was refluxed for several hours, till the spot of thiosemicarbazide disappeared on TLC plate. It was cooled and the excess solvent removed in vacuo to obtain a crude solid which was purified over a column of silica gel and recrystallized from CH₂Cl₂-EtOH to give 2 in 58% yield, mp 196°C (Found: C, 38.94; H, 3.87; N, 36.30; S, 20.70. C₁₀H₈N₂S₂ requires C, 38.96; H, 3.90; N, 36.36; S, 20.78%).

IR (KBr): 3420 (-NH₂ def), 3150 (-CH₂ str), 3050, 2901 (-CH str), 2950 (-CH₂ str), 1660 (-C=N), 1650 (-C=O), 1570-1550 (-C=N-), 1330 (-NCSN-), 1180 (-C=N-S), 1130 (-NCSN-), 1240 (-C-N-S), 1180 (C=S), 1030, 980, 800 cm⁻¹ (phenyl group).

1, 4-Bis[3',5'-dithioxy-s-triazol-1'-yl]phthalazine 3. To a mixture of 2 (0.02 mole) and carbon disulphide (60 mL) a solution of KOH (4N, 100 mL) in ethanol was added dropwise and the reaction mixture refluxed for 6-8 hr, till TLC showed the absence of 2. It was cooled and poured on to crushed ice. The solution was filtered and the clear filtrate was acidified with dil. HCl. The resultant precipitate was filtered, dried and recrystallized from acetic acid to get light yellow crystals of 3 in 62% yield, m.p. 201°C (Found: C, 35.95; H, 3.98; N, 27.94; S, 31.85. C₁₀H₈N₂S₂ requires C, 36.00; H, 4.00; N, 28.00; S, 32.00%).

IR (KBr): 3300-3205 (-NH), 3170-3015 (-CH), 1570-1550 (C=N), 1335 (-NCSN-), 1230 (-CNS), 1150 (C=S), 1050 cm⁻¹ (phenyl group).

1, 4-Bis[1'-thioxy-6'-oxo-1'-H-1', 2', 4'-triazin-1'-yl]phthalazine 6. Compounds 2 (0.01 mole) and dichloroacetic acid (0.02 mole) in dry ethanol (200 mL) was refluxed for 3-5 hr, till spots of 2 disappeared on pre-coated silica gel plate (E. Merck). It was cooled and poured onto ice. The resultant solid was isolated and recrystallized from ethanol to give orange crystals in 70% yield, m.p. 170°C (Found: C, 43.71; H, 2.00; N, 29.11; S, 16.60. C₁₀H₈N₂S₂ requires C, 43.75; H, 2.08; N, 29.17; S, 16.67%).

IR (KBr): 3140 (-NH), 3020 (-CH), 1680 (-C=O), 1330 (-C=N), 1130 (-NCSN-), 1180 (-C=S), 1050, 980, 800 cm⁻¹ (phenyl group).

1, 4-Bis[3'-thioxy-6'-oxo-1'-H'-1', 2', 4'-triazin-1'-yl]phthalazine 6. Compound 2 (0.01 mole) and substituted phenylisothiocyanate (0.02 mole) in dry ethanol (100 mL) was refluxed for 18-14 hr. After cooling, the reaction mixture was filtered and concentrated to yield a crude solid which was chromatographed over silica gel, elution with benzene in ethyl acetate (20:80) gave pure 7 in 80% yield, m.p. 101°C (Found: C, 46.84; H, 2.68; N, 16.78; S, 9.60. C₁₀H₈N₂S₂Br₂ requires C, 46.86; H, 2.70; N, 16.82; S, 9.61%).

IR (KBr): 3050, 2901 (-CH₃), 1550 (-C=N), 1150 (-C=S), 1050, 1000, 820 (phenyl group), 600-550 cm⁻¹ (-C-Br).

1, 4-Bis[4'-(N-arylaminothiocarbonyl)-3'-thiosemicarbazidophthalazine 8a-d. A mixture of 2 (0.01 mole) and substituted phenylisothiocyanate (0.02 mole) in dry ethanol (200 mL) was refluxed for
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5-8 hr, till silica gel precoated TLC plate showed the absence of 2. The excess solvent was removed under reduced pressure to obtain a crude solid which was purified over a column of silica gel. It was recrystallized from DMF to give pure 8 in 49% yield, m.p. 76 °C (Found: C, 49.80; H, 3.79; N, 24.19; S, 22.10. C$_2$H$_2$N$_2$S$_4$ requires C, 49.83; H, 3.81; N, 24.22; S, 22.15%); IR (KBr) for 8a: 3150 (-NH-), 3020 (-CH-Str), 1630 (-acyclic C=N), 1580 (-cyclic C=N), 1510 (-NCSC -), 1320 (NCNS), 1250 (-CNS), 1170 (-C=S), 1000, 980, 700 cm$^{-1}$ (phenyl group).

1,4-Bis(5'-H-4'-oxo-thiazolidin-2'-yl)hydrazino-phthalazine 9. To a stirred mixture of 2 (0.01 mole) and chloroacetic acid (0.02 mole), 10 % NaOH (50 mL) was added. The mixture was stirred for 30 min and refluxed for 6-8 hr. It was cooled and cold water added. The solid obtained after acidification was filtered, dried and recrystallized from light petroleum to get colourless crystals of 9 in 71% yield, m.p. 220°C (Found: C, 43.29; H, 3.00; N, 28.84; S, 16.40. C$_{14}$H$_{12}$N$_2$S$_2$O$_2$ requires C, 43.50; H, 3.09; N, 28.87; S, 16.49%); IR (KBr): 3100 (-NH), 3020 (-CH), 1600 (-C=O), 1175 (-C=O), 1100, 1000, 980 cm$^{-1}$ (phenyl group).

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References

9 Mansour A K, Awad S B & Amour S, Z Naturforsch, B 29, 1974, 792; Chem Abstr, 82, 1975, 100 84Z.