Synthesis, characterization and biological activities of some new acid hydrazones

R.N. SHARMA, K.P. SHARMA* and S.N. DIXIT

Chemical Laboratories, Government SMS Science College, Gwalior - 474 002 (India).

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ABSTRACT

A series of new acid hydrazones have been synthesised by the reaction of 2,3-dichloroanilido acetohydrazide with various carbonyl compounds in 58 to 92% yield. Newly synthesized compounds (1,3,4,7,8,9,12,13,15and16) have been tested for their anti-bacterial activity against gram positive bacteria S.albus, S.aureus and Gram negative bacteria E.coli and Pseudomonas piosineus. The compound 1,3,12,13 and 15 shown significant activity and compound 4,7,8 and 9 have shown moderate activity. The same compounds were tested for their anti-fungal activity against Candida albicans, Aspergillus niger and Alternaria alternate at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 12,13 and 15 were found to be moderately active against candida albicans and aspergillus niger. All the other compounds did not show significant activity against the fungi at the concentration used.

Key words: Malonicester, Acidhydrazide, Acidhydrazones, synthesis, Characterization, and Biological Activities.

INTRODUCTION

Hydrazones possessing an azometine -NHN=CH- Proton constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Acid hydrazides have frequently been investigated for testing their potentiality as tuberculostats. Hydrazides and their condensation products have displayed diverse range of biological properties such as bacteriocidal, anti-fungal, anti-convulsant, anti-helminthic, anti-tumor, anti-leprotic, anti-malarial, anti-cancer, anti-depressant, anti-HIV, analgesic-anti-inflammatory, leishmanicidal, vasodilator activities.

EXPERIMENTAL

All chemicals used were of A.R. grade (either of B.D.H. or Excel-R or extra pure E. Merk quality). The structure of the compounds were determined by elemental analysis, IR and NMR spectral data. IR spectra (KBr) are recorded on a perkin-Elmer 283 spectrophotometer. NMR spectra (CDCl3) are recorded on varian EM 360 L spectrophotometer. Melting point of the compounds are determined in open capillary tubes and are uncorrected. Purity of the compounds is checked on T.L.C. using silica gel-G. Elemental analysis is performed on Carlo-Erba 1108 analyser.
General procedure

Preparation of Ethyl-2-(2,3-dichloroanilido) ethanoate [1]

A mixture of 2,3-dichloro aniline (5 ml) and diethyl malonate (10ml) was refluxed for 50-55 minutes in a 100 ml r.b. flask fitted with an air condenser of such a length (14") that ethanol formed escaped and diethyl malonate flowed back in to the flask. Contents were cooled, 30 ml ethanol was added and kept over night, well precipitate found. It was filter under suction and purified by recrystallisation from ethanol.

IR Absorption band (cm⁻¹)
3150 (N–H stretching), 1665–1660 (C=O Ketone), 1090 (C–Cl Stretching), 760–755 (Di substituted benzene), NMR spectra (d Me₂CO), 1.1–1.2 (3 H, t, CH₃), 2.21 (2 H, s, CH₂), 4.0–4.22 (2 H, q, CH₂), 7.0–7.21 (4 H, m, ArH).

Preparation of Ethyl-2-(2,3-dichloro anilido) acetohydrazide [2]

Ethyl-2-(2,3-dichloroanilido) ethanoate [0.02 mol (5.52 gm)] was dissolved in rectified sprit in a small 3 neck r.b. flask kept on ice bath and set-up mechanical stirrer. Hydrazine hydrate (80%, 13 ml) was added by dropping funnel slowly drop by drop. The contents were stirred for 15-20 minutes. There were evolution of heat and reaction was spontaneous after 20 minutes, solid was filtered under suction and recrystallised from ethanol, then we get silver white crystals in good yield.

IR Absorption band (cm⁻¹)
3160 (N–H stretching), 1660 (C=O Ketone), 1095, 1520, 1450 (C=C ring stretching), 760–755 (2, 3 di substituted benzene), NMR spectra (d DMSO), 2.25 (2 H, s, CH₂), 3.15 (3 H, s, CH₃), 4.12–4.31 (1 H, t, NH), 6.95–7.2 (3 H, m, ArH).

Synthesis of new Acidhydrazones [3]

Ethyl-2-(2,3-dichloroanilido)acetohydrazide (.001 mol) and (.001 mol) of aromatic aldehyde or ketone dissolve in absolute alcohol and added 2-drops of conc. H₂SO₄ and stirred for 15 minutes. It was filtered under suction and recrystallised from hot ethanol. Synthetic strategy has been out lined in scheme I,II&III. Mechanism for the formation of acid hydrazones is given in chart-I.

IR Absorption band (cm⁻¹)
3150 (N–H stretching), 2960–2970 (C–H aliphatic), 1662–1660 (C=O Ketone), 785–778 (C–Cl Stretching), 760 (2,3-disubstituted benzene),

Scheme 1.

[Ethyl-2-(2,3-dichloro anilido) ethanoate]
☆ colour – light cream
☆ MP – 90°C
☆ MF – C₂H₅0.HCl
☆ Yield – 99%

[2-(2,3-dichloro anilido) ethanoate]
☆ colour – light yellow
☆ Yield – 79%
☆ MP – 166°C
☆ MF – C₂H₅0.HCl
Table 1: Physical and analytical data of new compounds: Acid hydrazones derived from 2-(2,3-dichloroanilido) acetohydrazide

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Aldehyde / Ketone</th>
<th>R₁</th>
<th>R₂</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Formula Weight</th>
<th>Molecular formula</th>
<th>Colour</th>
<th>Elemental analysis</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Benzaldehyde</td>
<td>H</td>
<td>Ph</td>
<td>208</td>
<td>91</td>
<td>C₁₆H₁₃O₂N₃Cl₂</td>
<td>White</td>
<td>54.85</td>
<td>3.71  9.14  12.00 20.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(54.83) (3.70) (9.10) (11.99) (20.25)</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Vanilline</td>
<td>H</td>
<td>Ph</td>
<td>197</td>
<td>84</td>
<td>C₁₇H₁₅O₄N₃Cl₂</td>
<td>White</td>
<td>51.51</td>
<td>3.78  16.16 10.60 17.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(51.50) (3.75) (16.16) (10.50) (17.90)</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>5-Chlorosalicylaldehyde</td>
<td>H</td>
<td>OH₂Cl₂ (3)</td>
<td>214</td>
<td>88</td>
<td>C₁₆H₁₁O₃N₃Cl₃</td>
<td>White</td>
<td>48.06</td>
<td>2.75  12.01 10.51 26.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(48.00) (2.72) (12.00) (10.50) (26.60)</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>5-Bromo-</td>
<td>H</td>
<td>OH₂Br₂ (3)</td>
<td>210</td>
<td>92</td>
<td>C₁₆H₁₂O₃N₃Cl₃Br</td>
<td>Silver</td>
<td>39.02</td>
<td>2.43  9.75  8.53 14.43</td>
</tr>
<tr>
<td></td>
<td>salicylaldehyde</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>(39.01) (2.42) (9.72) (8.51) (14.42)</td>
<td></td>
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<tr>
<td>5.</td>
<td>2-Nitro vanilline</td>
<td>H</td>
<td>NO₂</td>
<td>195</td>
<td>75</td>
<td>C₁₇H₁₄O₆N₄Cl₂</td>
<td>Cream</td>
<td>46.25</td>
<td>3.17  21.76 12.69 16.09</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(46.25) (3.15) (21.74) (12.67) (16.00)</td>
<td></td>
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<tr>
<td>6.</td>
<td>O-Nitro</td>
<td>H</td>
<td>NO₂</td>
<td>220</td>
<td>90</td>
<td>C₁₆H₁₂O₄N₄Cl₂</td>
<td>White</td>
<td>48.60</td>
<td>3.03  16.20 14.17 17.97</td>
</tr>
<tr>
<td></td>
<td>benzaldehyde</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(48.58) (3.01) (16.19) (14.15) (17.96)</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>2-Nitro</td>
<td>H</td>
<td>NO₂</td>
<td>216</td>
<td>58</td>
<td>C₁₇H₁₃O₆N₄Cl₂Br</td>
<td>Cream</td>
<td>35.97</td>
<td>2.29  16.93 9.87 12.52</td>
</tr>
<tr>
<td></td>
<td>5-Bromo vanilline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(35.96) (2.29) (16.92) (9.86) (12.51)</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>3, 5 di chloro-2-hydroxy benzaldehyde</td>
<td>H</td>
<td>Cl(3)</td>
<td>214</td>
<td>68</td>
<td>435</td>
<td>C16H13O3N3Cl4</td>
<td>White</td>
<td>44.13</td>
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<tr>
<td>9.</td>
<td>3-Nitro-6-hydroxyacetophenone</td>
<td>CH3</td>
<td>NO2</td>
<td>220</td>
<td>49</td>
<td>425</td>
<td>C16H14O3N3Cl2</td>
<td>Cream</td>
<td>48.00</td>
</tr>
<tr>
<td>10.</td>
<td>Acetone</td>
<td>Me</td>
<td>Me</td>
<td>194</td>
<td>44</td>
<td>302</td>
<td>C13H13O2N3Cl2</td>
<td>Cream</td>
<td>47.68</td>
</tr>
<tr>
<td>11.</td>
<td>2-Chloro benzaldehyde</td>
<td>H</td>
<td>C6H4-Cl(2)</td>
<td>228</td>
<td>81</td>
<td>384.5</td>
<td>C16H13O2N3Cl3</td>
<td>White</td>
<td>49.93</td>
</tr>
<tr>
<td>12.</td>
<td>4-N-N-Bis-2’ cyanoethyl amino benzaldehyde</td>
<td>H</td>
<td>C6H4-N2-Cl(2)</td>
<td>206</td>
<td>64</td>
<td>471</td>
<td>C22H20O2N6Cl2</td>
<td>Light brown</td>
<td>56.05</td>
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<tr>
<td>13.</td>
<td>2-Methyl-4-N-N-bis 2’ cyano ethyl amino benzaldehyde</td>
<td>H</td>
<td>C6H4-N2-Cl(2)</td>
<td>204</td>
<td>86</td>
<td>485</td>
<td>C23H22O2N6Cl2</td>
<td>Brown</td>
<td>56.90</td>
</tr>
<tr>
<td>15.</td>
<td>Acetophenone</td>
<td>Me / Ph</td>
<td>CH3</td>
<td>212</td>
<td>91</td>
<td>364</td>
<td>C17H15O2N3Cl2</td>
<td>White</td>
<td>56.04</td>
</tr>
<tr>
<td>17.</td>
<td>Anisic aldehyde</td>
<td>H</td>
<td>Ph-OCH3(2)</td>
<td>222</td>
<td>71</td>
<td>380</td>
<td>C16H13O3N3Cl2</td>
<td>Yellow</td>
<td>53.68</td>
</tr>
<tr>
<td>18.</td>
<td>β-Ionone</td>
<td>Me / CH3</td>
<td></td>
<td>180</td>
<td>28</td>
<td>446</td>
<td>C23H25O2N3Cl2</td>
<td>Buff</td>
<td>61.88</td>
</tr>
</tbody>
</table>
NMR spectra (d DMSO), 2.25 (2 H, s, CH₂), 4.21 (1 H, s, NH), 6.95–7.2 (10 H, m, ArH).

**Biological evaluation**

**Anti-bacterial activity**

Ten new acid hydrazones (1,3,4,7,8,9,12,13,15 and 16) were screened for their anti-bacterial activity against the gram positive bacteria *S. albus*, *S. aureus* and gram negative bacteria *E. coli* and *pseudomonas piosineus* using cup-plat agar diffusion technique at 10,15,25 mg/ml concentrations. Maximum inhibition (13-14 mm) was found in 12,13 and 15 against *S. albus*. Compounds 4,7,8,9 showed moderate activity against *S. aureus*. No significant activity was displayed by other compounds.

| Chart 1: [Mechanism of formation of new acid hydrazones] |

**Anti-fungal activity**

The same compounds were tested for their anti-fungal activity against *candida albicans*, *aspergillus niger* and *alternaria alternate* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds 12,13 and 15 were found to be moderately active against *candida albicans* and *aspergillus niger*. All the other compounds did not show significant activity against the fungi at the concentration used.

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REFERENCES


