

Reactivity of 1-Chlorobenzo[g]phthalazinone and 1,4-Dichlorobenzo[g]phthalazine towards some Nucleophilic Reagents

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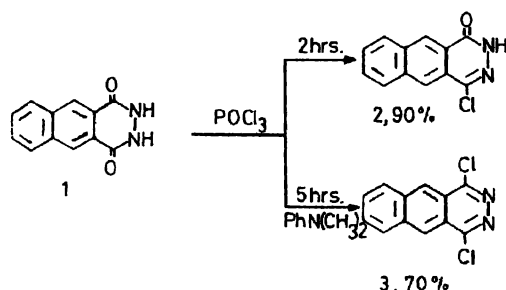
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1-Chlorobenzo[g]phthalazinone (2) and 1,4-dichlorobenzo[g]phthalazine (3) have been synthesised by the reaction of 1,2,3,4-tetrahydrophthalazine-2,4-dione (1) with phosphorus oxychloride. The chlorine atoms can be replaced by nucleophilic reagents such as morpholine, cyanide, amines, alkoxide, azide and hydrazine to give the corresponding products. Treating of hydrazino derivative (4) with formic acid afforded triazolophthalazinone derivative (5), while treating with acetic acid and/or acetic anhydride it gave triazolophthalazine derivatives, 6 and 7 respectively. Reaction of 4 with nitrous acid afforded azido derivative (8) which was also obtained from the reaction of 2 with sodium azide.

Some of the phthalazinone derivatives have found application in clinical medicine¹ due to their pronounced antipyretic, analgesic and tuberculostatic activity and some have shown interesting antihypertensive properties².

This presentation describes the synthesis of benzo[g]-phthalazine derivatives through the reaction of 1-chlorobenzo[g]phthalazinone (2) and 1,4-dichlorobenzo[g]phthalazine (3) with some nucleophilic reagents.

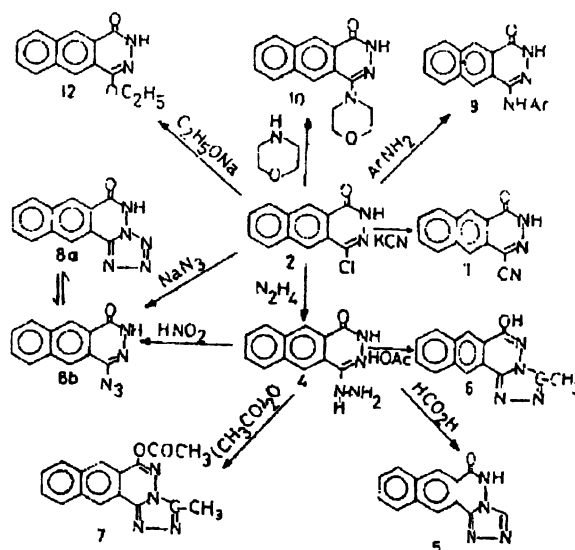
The starting material 1,2,3,4-tetrahydrobenzo[g]-phthalazin-2,4-dione (1) on treating with phosphorousoxychloride gave 1-chlorobenzo[g]phthalazinone (2) and 1,4-dichlorobenzo[g]phthalazine (3) depending on the reaction conditions (Scheme 1).



Scheme 1

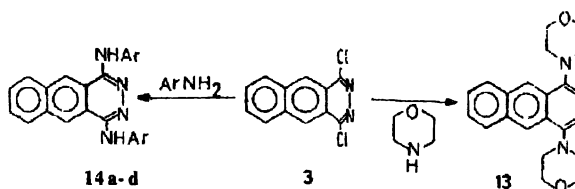
Treatment of 2 with hydrazine hydrate gave 1-hydrazinobenzo[g]phthalazin-4-one (4) which on boiling with formic acid afforded benzo[g]-s-triazolophthalazinone³ (5), while 4 on treatment with boiling glacial acetic acid gave 6-hydroxybenzo[g]-s-triazolophthalazine (6). Also 4 on treatment with acetic anhydride formed 7, which may be formed through the formation of 6 followed by acylation with acetic anhydride. Treatment of 4 with nitrous acid gave 1-azidobenzo[g]phthalazinone (8b) which showed ir bands at 2125 and 1280 cm⁻¹ characteristic to azido group. Also when compound 2 was treated with sodium azide it gave the azido derivative (8b). Chlorine atom in 2 is reactive towards some nucleophilic reagents such as

amines, cyanide and alkoxide, so it reacted with aromatic amines, morpholine, potassium cyanide and sodium ethoxide to give 9, 10, 11 and 12 respectively (Scheme 2).



Scheme 2

On the other hand, 1,4-dichlorobenzo[g]phthalazine (3) being reactive towards some nucleophiles where the two chlorine atoms can be replaced specially, when treated with morpholin and aromatic primary amines it gave 1,4-dimorpholinobenzo[g]phthalazine (13) and 1,4-diarylaminobenzo[g]phthalazine derivatives (14a-d) (Scheme 3).



Scheme 3

Experimental

M.ps. were measured on a Galenkamp apparatus and are uncorrected. Ir spectra (KBr) were measured on a Perkin-Elmer 1340 spectrophotometer, mass spectra on MS 30 and MS 9 (Fa. AEJ, Manchester) spectrometer and nmr spectra on a Bruker HFX 90 (90 MHz) instrument using TMS as an internal standard.

1-Chlorobenzo[g]phthalazine-4-one (2) : A mixture of 1,2,3,4-tetrahydrobenzo[g]phthalazine-2,4-dione (1; 4.24 g, 0.02 mol) and phosphorus oxychloride (30 ml) was refluxed for 2 h. After cooling it was poured in ice/ NH_4OH solution. The resulting solid was washed with water and crystallised from 1,4-dioxane as pale brown crystals (4.15 g, 90%), m.p. 298° (Found : C, 62.13; H, 3.22; N, 12.22. $\text{C}_{12}\text{H}_7\text{N}_2\text{OCl}$ calcd. for : C, 62.49; H, 3.06; N, 12.15%; ν_{max} 3 177 (NH), 1 685 (C=O), 890 cm^{-1} (C-Cl); δ (DMSO- d_6 /TMS) 9.16 (1H, s, ArH), 8.80 (1H, s, ArH), 8.53–7.40 (4H, m, ArH); m/z 230 (M^+ , 100), 201 (8), 173 (34), 140 (29), 99 (7), 87 (10) and 63 (18).

1,4-Dichlorobenzo[g]phthalazine (3) : To 1 (3 g, 14 mmol) in phosphorus oxychloride (30 ml) drops of N,N' -dimethylaniline were added and the mixture was refluxed for 4 h. It was then cooled, poured into ice/ NH_4OH solution with stirring and the resulting brown solid was washed with water and crystallised from acetic acid (2.28 g, 70%), m.p. 258° (Found : C, 57.82; H, 2.66; N, 11.01. $\text{C}_{12}\text{H}_6\text{N}_2\text{Cl}_2$ calcd. for : C, 57.86; H, 2.43; N, 11.25%; ν_{max} 1 620, 1 592, (C=N), 671 cm^{-1} (C-Cl); δ (DMSO- d_6 /TMS) 8.86 (2H, s, ArH), 8.83–7.80 (4H, m, ArH); m/z 248 (M^+ , 100), 213 (19), 178 (18), 173 (28), 140 (11), 99 (11) and 77 (15).

1-Hydrazinobenzo[g]phthalazin-4-one (4) : To a stirred suspension of compound 2 (0.6 g, 2.6 mmol) in dioxane (25 ml), hydrazine hydrate (2 ml; 98%) was added and boiled for 4 h. It was then cooled and the resulting solid was washed with ether (5 ml) and crystallised from ethanol as orange-red crystals (0.5 g, 85%), m.p. 310° (Found : C, 63.92; H, 4.68; N, 25.01. $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$ calcd. for : C, 63.71; H, 4.46; N, 24.76%; ν_{max} 3 320–3 120 (NHNH_2), 1 680 (C=O), 1 610 cm^{-1} (C=N); δ (CDCl_3 /TMS) 9.16 (1H, s, ArH), 8.80 (1H, s, ArH), 8.50–7.50 (4H, m, ArH), 4.6 (3H, bs, NHNH_2); m/z 226 (M^+ , 5), 211 (14), 196 (42), 180 (71), 153 (14), 139 (16), 126 (26), 85 (15), 71 (26), 44 (100), 43 (41).

Triazolobenzo[g]phthalazinone (5) : A mixture of compounds 4 (0.2 g, 0.9 mmol) and formic acid (40 ml) was boiled for 5 h. On cooling, the reaction mixture was diluted with water and the resulting white solid was washed with water, dried and crystallised from ethanol, (0.14 g, 66%), m.p. $290\text{--}92^\circ$ (Found : C, 65.82; H, 3.59; N, 23.46. $\text{C}_{13}\text{H}_8\text{N}_4\text{O}$ calcd. for : C, 66.10; H, 3.41; N, 23.72%; ν_{max} 3 180 (NH), 1 676 cm^{-1} (C=O); m/z 236 (M^+ , 100), 210 (21), 165 (18), 126 (32), 71 (38).

6-Hydroxy-3-methylbenzo[g]-s-triazolo[3,4-a]phthal-

azine (6) : A mixture of 4 (0.15 g, 0.66 mmol) and glacial acetic acid (20 ml) was refluxed for 6 h. It was then cooled and the resulting solid was washed with water, dried and crystallised from glacial acetic acid as a colourless crystals (0.119 g, 72%), m.p. 325° (Found : C, 67.48; H, 4.33; N, 22.02. $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}$ calcd. for : C, 67.19; H, 4.03; N, 22.39%; ν_{max} 3 407 (OH), 1 619, 1551, 1 537 cm^{-1} (C=N) and no $\nu_{\text{C=O}}$ band observed; m/z 250 (M^+ , 100), 180 (37), 153 (14), 126 (24), 77 (9), 63 (15).

6-O-Acetyl-3-methylbenzo[g]-s-triazolo[3,4-a]phthalazine (7) : Compound 4 (0.12 g, 0.53 mmol) was boiled in acetic anhydride (20 ml) for 6 h. The solvent was then removed under reduced pressure and the residual solid was suspended in ethanol, filtered off and crystallised from acetic acid as colourless crystals (0.105 g, 68%), m.p. 172° (Found : C, 65.60; H, 4.22; N, 19.34. $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$ calcd. for : C, 65.75; H, 4.14; N, 19.17%; ν_{max} 1 730 (C=O) and no NH or OH was observed; δ (CDCl_3 /TMS) 8.86 (1H, s, ArH), 8.50 (1H, s, ArH), 8.3–7.6 (4H, m, ArH), 4.12 (3H, s, COCH_3), 3.24 (3H, s, CH_3).

1-Azidobenzo[g]phthalazinone (8a) : (a) A mixture of compound 2 (0.5 g, 2.1 mmol) and sodium azide (0.5 g, 6.7 mmol) in DMF (20 ml) was boiled for 5 h. On cooling and dilution with water (10 ml), the pale brown solid that yielded was crystallised from dioxane, (0.17 g, 34%), m.p. $266\text{--}68^\circ\text{d}$ (Found : C, 61.09; H, 3.28; N, 29.11. $\text{C}_{12}\text{H}_7\text{N}_5\text{O}$ calcd. for : C, 60.76; H, 2.97; N, 29.52%; ν_{max} 3 180 (NH), 1 685 (C=O), 1 620 (C=N), 1 270 (N_3); m/z 237 (M^+ , 6), 195 (21), 152 (18), 126 (100), 71 (29), 63 (25).

(b) To a stirred solution of compound 4 (0.2 g, 0.88 mmol) in 1 N HCl (30 ml), sodium nitrite (0.1 g, 1.4 mmol) was added portionwise. The reaction mixture was then stirred for 1 h at room temperature, and the resulting solid was washed with water, dried and crystallised from EtOH/ CHCl_3 , (0.1 g, 48%) which was identified by its spectra and m.m.p. to be compound 8a.

1-Arylamino benzo[g]phthalazinone (9a-d) : A mixture of compound 2 (0.5 g, 2.1 mmol) and the primary aromatic amine (4 mmol) (namely, aniline, *p*-toluidine, *p*-anisidine and *p*-chloroaniline) in ethanol (30 ml) was refluxed for 5–7 h. It was then cooled and the resulting solid was washed with light petrol (b.p. $60\text{--}80^\circ$) and crystallised from a suitable solvent to give 9a-d (yields 67–81%) (Table 1).

1-Morpholinobenzo[g]phthalazine-4-one (10) : A mixture of 2 (0.6 g, 2.6 mmol) and morpholine (20 ml) was boiled for 4 h. The excess of morpholine was then removed under reduced pressure and the residue was triturated with ethanol and the solid product was crystallised from ethanol as scarlet red needles (0.496 g, 68%), m.p. 287° (Found : C, 68.01; H, 6.11; N, 15.33. $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$ calcd. for : C, 68.31; H, 5.75; N, 14.94%; ν_{max} 3 185 (NH), 1 685 (C=O), 1 625 cm^{-1} (C=N); δ (CDCl_3 /TMS) 8.84 (2H, s, ArH), 8.82–7.80 (4H, m, ArH), 4.40–4.0 (8H, m,

TABLE 1—PHYSICAL AND SPECTRAL DATA OF COMPOUNDS 9 AND 14*

Compd. no.	Ar	M. p.** °C	ν_{\max} cm ⁻¹	<i>m/z</i> (rel. int. %)
9a	C ₆ H ₅	312 ^a	3 192 (NH), 1 680 (C=O)	287 (M ⁺ , 100), 242 (5), 215 (20), 189 (4), 136 (9), 108 (14), 94 (15), 85 (8), 71 (12), 57 (20), 43 (19)
9b	C ₆ H ₄ .CH ₃ - <i>p</i>	> 325 ^b	3 190 (NH), 1 682 (C=O)	301 (M ⁺ , 100), 286 (12), 258 (18), 196 (20), 152 (9), 126 (55), 99 (10), 74 (9), 43 (86)
9c	C ₆ H ₄ .OCH ₃ - <i>p</i>	296–98 ^b	3 186 (NH), 1 685 (C=O)	317 (M ⁺ , 100), 302 (12), 259 (26), 126 (62), 99 (22), 85 (12), 79 (18), 43 (61)
9d	C ₆ H ₄ .Cl- <i>p</i>	> 325 ^c	3 200 (NH), 1 692 (C=O)	321 (M ⁺ , 100), 278 (8), 194 (22), 127 (42), 126 (44), 99 (18), 85 (14), 43 (17)
14a	C ₆ H ₅	284 ^d	3 373 (NH), 1 625 (C=N)	362 (M ⁺ , 12), 232 (92), 202 (75), 191(25), 174 (100), 166 (71), 152 (50), 139 (92), 126 (29), 76 (29)
14b	C ₆ H ₄ .CH ₃ - <i>p</i>	271–72 ^e	3 376 (NH), 1 624 (C=N)	390 (M ⁺ , 19), 388 (84), 269 (16), 195 (19), 152 (20), 126 (9), 91 (100), 65 (73)
14c	C ₆ H ₄ .OCH ₃ - <i>p</i>	159–61 ^f	3 385 (NH), 1 621 (C=N)	422 (M ⁺ , 100), 407 (24), 285 (11), 230 (8), 211(6), 179 (6), 152 (5), 122 (7), 106 (8)
14d	C ₆ H ₄ .Cl- <i>p</i>	> 300 ^g	3 315 (NH), 1 618 (C=N)	—

*All compounds gave satisfactory C, H and N analysis.

**Solvent for crystallisation : ^aAcOH, ^bDMF, ^cEtOH-CHCl₃, ^dEtOH, ^eEtOH-Et₂O, ^fEtOH-C₆H₆, ^gMeOH.

CH₂).

1-Cyanobenzo[g]phthalazine-4-one (11) : A mixture of 2 (0.4 g 1.7 mmol) and KCN (0.5 g, 7.6 mmol) in DMF (30 ml) was refluxed for 8 h. On cooling and dilution with water, the resulting solid was washed with water, dried and crystallised from 1,4-dioxane as a pale brown needles (0.236 g, 63%) m.p. 301–03° (Found : C, 70.21; H, 3.17; N, 18.57. C₁₃H₇N₃O calcd. for : C, 70.58; H, 3.19; N, 18.99%); ν_{\max} 3 180 (NH), 2 250 (C≡N), 1 682 cm⁻¹ (C=O); *m/z* 221 (M⁺, 12), 194 (18), 151 (9), 126 (100), 73 (7), 64 (11), 43 (68).

1-Ethoxybenzo[g]phthalazin-4-one (12) : To a solution of sodium (0.5 g, 21.7 mmol) in ethanol (20 ml) was added compound 2 (0.3 g, 1.3 mmol) and the mixture was boiled for 5 h. On cooling, the solvent was removed under reduced pressure and the residue was triturated with water and acidified with acetic acid. The solid which was formed was crystallised from ethanol as pale yellow crystals (0.181 g, 58%), m.p. 269–71° (Found : C, 69.51; H, 5.46; N, 11.42. C₁₄H₁₂N₂O₂ calcd. for : C, 69.99; H, 5.03; N, 11.66%); ν_{\max} 3 189 (NH), 1 653 cm⁻¹ (C=O); *m/z* 240 (M⁺, 74), 224 (11), 212 (100), 180 (10), 154 (72), 126 (77), 97 (7), 95 (12), 71 (19), 57 (32), 43 (25).

1,4-Dimorpholinobenzo[g]phthalazine (13) : A mixture of 3 (1 mmol) and morpholine (20 ml) was refluxed for 6 h. It was then cooled and the resulting orange solid was washed with light petrol (b.p. 60–80°) and crystallised from ethanol, (0.283 g, 81%), m.p. 310–11° (Found : C, 68.12; H, 6.52; N, 14.71. C₂₀H₂₂N₄O₂ calcd. for : C, 68.55; H, 6.33; N, 15.99%); ν_{\max} 1 550, 1 500 cm⁻¹ (C=N), and no

ν_{NH} or $\nu_{\text{C=O}}$ bands observed; δ (CF₃COOD; TMS) 8.86 (2H, s, ArH), 8.66–7.80 (4H, m, ArH), 4.66–3.11 (16H, m, aliphatic H); *m/z* 350 (M⁺, 88), 319 (27), 305 (38), 292 (96), 264 (42), 208 (46), 180 (100), 152 (77), 87 (85).

*1,4-Diarylamino*benzo[g]phthalazines (14a–d) : A mixture of 3 (1 mmol) and aromatic primary amines (4 mmol) in 1,4-dioxane (30 ml) was refluxed for 5 h. The solvent was then removed by a rotatory evaporator and the residue was triturated with ethanol, filtered, and the products were crystallised from a proper solvent giving 14a–d (yields 68–81%) (Table 1).

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