

Synthesis and Reactions of Phthalazine Derivatives

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Summary: O-arylbenzoic acids (1a and b) on treatment with hydrazine hydrate and hydrazine derivatives give the corresponding 2-substituted-4-aryl-1-(2H)-phthalazinones (2a-i). (2a) Reacts with POCl_3 to yield 1-chlorophthalazine (3) which reacts with hydrazine hydrate to give 1-hydrazino-4-(2,5-dimethyl)-phenylphthalazine (4). Phthalazinone (2a) undergoes alkylation to give 1-alkyl-4-arylphthalazine (5a and b) and also reacts with P_2S_5 to give the corresponding thione (7). Phthalazinones (2a and b) undergo Mannich reaction to give (8a and b).

Recently [1,2], 1(2H)-phthalazinones have been described as being useful as remedies for arteriosclerosis and thrombosis and have also been found useful as developable light-sensitive materials. This prompted us to synthesise some new phthalazinones via interaction of O-arylbenzoic acids with hydrazine derivatives.

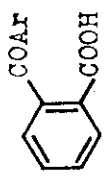
Acylation of aromatic hydrocarbons with phthalic anhydride under Friedel Craft's conditions give O-arylbenzoic acids (1a and b), which react with hydrazine hydrate and hydrazine derivatives, namely phenylhydrazine, 2,4-dinitro-phenylhydrazine, salicylic acid hydrazide, benzoylhydrazine and semicarbazide in boiling ethanol to give the corresponding 2-substituted-4-aryl-1-(2H)-phthalazinones (2a-i).

The structure (2a-i) is confirmed by correct analytical data and infrared spectral data. The I.R. spectra of (2a and b) exhibit bands corresponding $\nu\text{C}=\text{O}$ (1650 cm^{-1}), $\nu\text{C}=\text{N}$ (1610 cm^{-1}) and νNH (3160 cm^{-1}). The I.R. spectra of (2a-i) exhibit bands corresponding to $\nu\text{C}=\text{O}$ of amide ($1660\text{-}1640\text{ cm}^{-1}$), $\nu\text{C}=\text{N}$ ($1620\text{-}1605\text{ cm}^{-1}$) and absence of νNH .

Phthalazinones like pyridazinones exist in a lactam-lactim equilibrium. This has been confirmed by converting the lactim form of phthalazinone (2a) into 1-chlorophthalazine (3) by the action of phosphorous oxychloride [3].

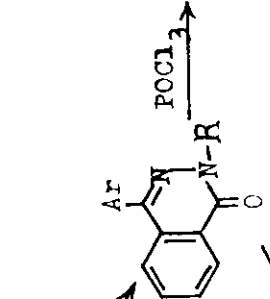
1-Chlorophthalazine undergoes nucleophilic substitution with hydrazine hydrate to give 1-hydrazino-4-(2,5-dimethyl)phenylphthalazine (4). The I.R. spectrum of (4) shows bands at 1605 cm^{-1} ($\nu\text{C}=\text{N}$).

Further proof for lactam-lactim equilibrium in phthalazinones has been gained from the alkylation of phthalazinone (2a) with ethylbromoacetate or diethylsulphate which in the presence of acetone using potassium carbonate as catalyst [4] gives rise to 1-alkyl-4-arylphthalazines (5a and b). The I.R. spectrum of (5b) shows bands at 1635 cm^{-1} ($\nu\text{C}=\text{N}$) and absence of νNH . The NMR spectrum (CDCl_3) for (5a) shows signals at δ 1.1-1.3 ppm (t, 3H, $-\text{CH}_2-\text{CH}_3$), δ 2.1 and 2.3 ppm (s, 6H, $\text{Ar}-\text{CH}_3$), δ 4.15-4.35 ppm (q, 2H, $-\text{COOH}-\text{CH}_2-$), δ 5.05 ppm (s, 2H, $\text{O}-\text{CH}_2-\text{COO}$) and δ 7.1 - 7.8 ppm (m, 7H, aromatic protons).



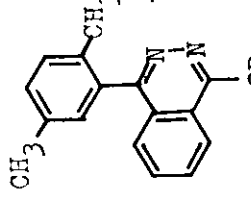
(1)

- a, Ar=2,5(CH₃)₂C₆H₃
- b, Ar=p-(CH₃)₂CHC₆H₄



(2)

- a) 2,5(CH₃)₂C₆H₃
- b) p-(CH₃)₂CHC₆H₄
- c) 2,5(CH₃)₂C₆H₃
- d) p-(CH₃)₂CHC₆H₄
- e) 2,5(CH₃)₂C₆H₃
- f) 2,5(CH₃)₂C₆H₃
- g) p-(CH₃)₂CHC₆H₄
- h) 2,5(CH₃)₂C₆H₃
- i) p-(CH₃)₂CHC₆H₄

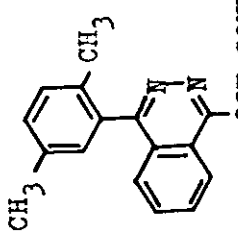


(3)

- a) R=CH₂COOEt
- b) R=C₂H₅



(4)



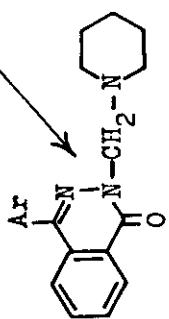
(5)



(6)

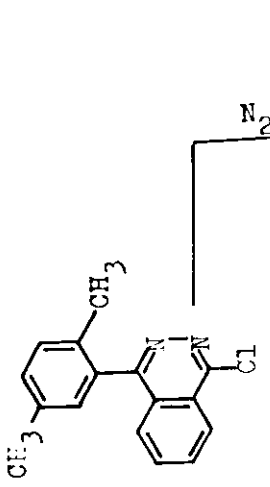


(7)



(8)

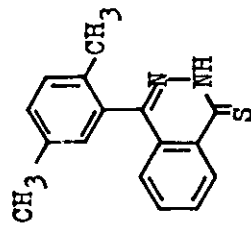
- a) Ar=2,5(CH₃)₂C₆H₃, b) Ar=p-(CH₃)₂CHC₆H₄



(9)

- R: H, H, C₆H₅, C₆H₅, 2,4(NC₂)₂C₆H₃, o-CH(CO)C₆H₄, o-OHC₆H₄CO, C₆H₅CO, H₂HCO

(10)



(11)

Table-1: Physical data of phthalazinones derivatives.

Compd.	M.p.(°C)	Solv. yield %	Mol.formula (M.Wt.)	Analysis %	
	colour			Calcd.	Found
2a	187	Benz/P.E. 60-80° (70)	C ₁₆ H ₁₄ N ₂ O (250)	C: 76.80	76.80
	Colourless			H: 5.60	5.50
2b	247	Ethanol (73)	C ₁₇ H ₁₆ N ₂ O (264)	C: 77.27	77.00
	Colourless			H: 6.06	5.80
2c	156	Methanol (60)	C ₂₂ H ₁₈ N ₂ O (326)	C: 80.98	81.20
	Colourless			H: 5.52	5.60
2d	258	Ethanol (70)	C ₂₃ H ₂₀ N ₂ O (340)	C: 81.17	80.70
	Colourless			H: 5.88	6.10
2e	190	Methanol (70)	C ₂₂ H ₁₆ N ₄ O ₂ (368)	C: 71.73	71.40
	Brown			H: 4.34	4.50
2f	Over 280	Ethanol (60)	C ₂₃ H ₁₈ N ₂ O ₃ (370)	C: 74.59	74.30
	Brown			H: 4.86	4.80
2g	248	Ethanol (60)	C ₂₄ H ₂₀ N ₂ O ₃ (384)	C: 75.00	75.30
	Colourless			H: 5.20	5.10
2h	207-210	Methanol (70)	C ₂₃ H ₁₈ N ₂ O ₂ (354)	C: 77.96	77.60
	Pale- yellow			H: 5.08	5.20
2i	248	Toluene (30)	C ₁₈ H ₁₇ N ₃ O ₂ (307)	C: 70.35	70.80
	Colourless			H: 5.53	5.20
				N: 13.68	13.10

Treatment of (5a) with benzylamine gives the corresponding amide (6). The I.R. spectrum of (6) shows bands at 1655 cm⁻¹ (νCO of amide), 1605 cm⁻¹ (νC=N) and 3145 cm⁻¹ (νNH).

The reaction of phthalazinone (2a) with phosphorous pentasulphide in boiling xylene [5] gives the corresponding phthalazine thione (7).

As a point of interest the authors investigated the behaviour of phthalazinones (2a and b) toward secondary amines under Mannich reaction conditions. Thus (2a and b) react with formaldehyde in the presence of piperidine to give 2-(piperidyl)-methyl-4-aryl-1-(2H)-phthalazinones (8a and b). The I.R. spectra of (8a and b) show strong bands at 1655

Table-2: Physical data of chlorophthalazinone, hydrazide phthalazinone, alkylphthalazinone, N-benzylcarboxamide, phthalazinone thione and Mannich base

Compd.	M.p.(°C) Colour	Solvent yield %	Mol.formula (M.Wt.)	Analysis %	
				Calcd.	Found
3	146 yellow	P.E.60-80° (40)	C ₁₆ H ₁₃ N ₂ Cl (268.5)	C: 71.50 H: 4.84 N: 10.42 Cl:13.22	71.40 4.60 10.70 12.80
4	196 yellow	Benzene (70)	C ₁₆ H ₁₆ N ₄ (264)	C: 72.72 H: 6.06 N: 21.21	72.80 6.00 21.60
5a	121 Colourless	P.E.60-80° (60)	C ₂₀ H ₂₀ N ₂ O ₃ (336)	C: 71.42 H: 5.95 N: 8.33	71.90 6.00 8.50
5b	133 Colourless	P.E.60-80° (50)	C ₁₈ H ₁₈ N ₂ O (278)	C: 77.69 H: 6.47 N: 10.07	77.60 6.31 9.80
6	132 Colourless	P.E.60-80° (70)	C ₂₅ H ₂₃ N ₃ O ₂ (397)	C: 75.56 H: 5.79 N: 10.57	75.80 5.50 10.30
7	156 Yellow	P.E.60-80° (30)	C ₁₆ H ₁₄ N ₂ S (266)	C: 72.18 H: 5.26 N: 10.52 S: 12.03	72.40 5.30 10.30 12.60
8a	182 Colourless	P.E.60-80° (60)	C ₂₂ H ₂₅ N ₃ O (347)	C: 76.08 H: 7.20 N: 12.10	76.60 6.90 12.50
8b	258 Yellow	Toluene (66)	C ₂₃ H ₂₇ N ₃ O (361)	C: 76.45 H: 7.47 N: 11.60	76.60 7.50 11.30

cm⁻¹ (,C=O) and absence of ,NH.

Experimental

All melting points are uncorrected. I.R. spectra were determined with a Unicam SP 1200 spectrophotometer using KBr wafer technique.

The NMR spectra were determined by a Varian (60 MHz), Jeol JNMFX200

and EM 390 A Varian (90 MHz) using TMS as internal standard. All compounds gave satisfactory C,H and N analyses.

Formation of phthalazinones derivatives (2_{a-i})

A mixture of acids (1a and b) (0.01 mole) and hydrazines namely: hydrazine hydrate, phenylhydrazine,

2,4-dinitrophenylhydrazine, salicylic acid hydrazide, benzoyl-hydrazine and semicarbazide (0.01 mole) was refluxed in ethanol (60 ml) for 3 hrs. The solids separated were filtered off and crystallised from a suitable solvent to give (2a-i). The results are listed on Table-1.

Synthesis of 1-chlorophthalazinone (3):

Phthalazinone (2a) (0.01 mole) was refluxed with POCl_3 (5 ml) and PCl_5 (0.5 gm) on a water bath for 2 hrs, cooled and the reaction mixture poured gradually into ice-water. The solid separated was filtered off and crystallised from the proper solvent to give (3). Results are given on Table-2.

Formation of 1-hydrazino-4-(2,5-dimethyl)phenylphthalazinone(4):

A mixture of (3) (0.01 mole) and hydrazine hydrate was refluxed in (50 ml) ethanol for 3 hrs. The solid obtained was filtered off and crystallised from an appropriate solvent to give (4). Results are listed on table (2).

Formation of N-benzylcarboxamide derivative (6):

A mixture of (5a) (0.01 mole) and benzylamine (0.01 mole) was refluxed in ethanol (50 ml) for 3 hrs; the solid separated was filtered off and crystallised from a suitable solvent to give (6). The results are listed on Table-2.

Synthesis of phthalazinone thione (7):

A mixture of (2a) (0.01 mole) and P_2S_5 (0.02 mole) was refluxed in xylene (50 ml) for 30 min. The reaction mixture was filtered while hot and the solid separated was crystallised from the proper solvent to give (7). Results are listed on Table-2.

Formation of Mannich base (8a and b):

A mixture of (2a and b) (0.01 mole) and piperidine (0.02 mole) in methanol (20 ml) and aqueous formaldehyde (35%, 2 ml) was heated on a water bath for 5 hrs., kept overnight at room temperature, diluted with water and the solid obtained was crystallised from the proper solvent to give Mannich base (8a and b). The results are listed on Table-2.

References

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