BEHAVIOUR OF [4-(3′,4′-DICHLOROPHENYL)-1-(2*H*)-PHTHALAZINONE-2-YL]-3-(4-CHLOROPHENYL)-2-PROPEN-1-ONE TOWARDS DIFFERENT NUCLEOPHILES

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In our previous work we have reported on the behaviour of α,β-unsaturated carbonyl compounds toward active methylene compounds[1].

In the present paper we report the results of further studies in this area in which carbonyl compounds bear a heterocyclic moiety.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were measured on a Perkin–Elmer infrared 137 spectrophotometer and are given in cm^{-1}. The ^1H NMR spectra were recorded on a Varian EM-360-L spectrophotometer 60 MHz using TMS as internal standard and $(CD_3)_2SO_4$ as a solvent. Physicochemical data of prepared compounds are given in Table I.

o-(3,4-Dichloro)benzoylbenzoic Acid (*I*)

To a mixture of phthalic anhydride (1 mol) and 100 ml of *o*-dichlorobenzene, anhydrous $AlCl_3$ (4 mol) was added gradually during stirring. The stirred reaction mixture was refluxed on steam bath for about 1 h. The reaction mixture was allowed to stand overnight at room temperature, then decomposed with ice and HCl and excess of the solvent was removed by steam distillation. The solid thus obtained was filtered, dried and crystallized from benzene. IR spectrum: 1 695 (C=O of acid); 1 675 (C=O of ketone); 3 250 – 3 450 (broad, OH). ^1H NMR spectrum: 7.2 – 8.3 m, 7 H (aromatic H); 10.3 s, 1 H (COOH).

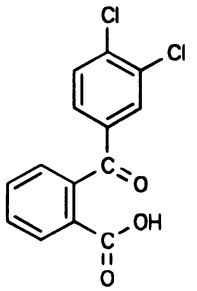
Formation of Phthalazinone Derivative *II*

A mixture of acid *I* (0.01 mol) and phenylacetylhydrazine (0.01 mol) was refluxed for 3 h. The solid that separated on concentration was filtered, dried and recrystallized from the proper solvent. IR spectrum: 1 640 (C=N); 1 665 (C=O of heterocyclic moiety); 1 690 (C=O). ^1H NMR spectrum: 3.3 s, 2 H (CH_2); 7.2 – 8.2 m, 12 H (aromatic H).

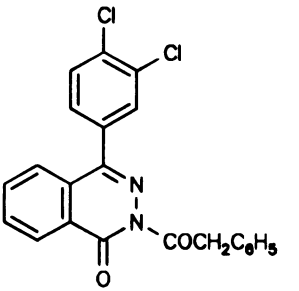
TABLE I
Physico-chemical data of prepared compounds

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found		
			% C	% H	% N
I	228 – 230[a] 75	$C_{14}H_8Cl_2O_3$ (295.1)	57.14 56.03	2.71 2.55	– –
II	243 – 245[b] 65	$C_{22}H_{14}Cl_2N_2O_2$ (409.2)	64.55 64.32	3.42 3.32	6.85 6.73
IIIa	203 – 205[b] 70	$C_{29}H_{18}Cl_2N_2O_2$ (497.3)	70.20 69.81	3.62 3.42	5.63 5.34
IIIb	190 – 193[b] 65	$C_{30}H_{20}Cl_2N_2O_3$ (527.4)	68.31 68.00	3.80 3.62	5.32 5.11
IIIc	173 – 175[b] 90	$C_{29}H_{17}Cl_2N_2O_2$ (531.8)	65.48 65.02	3.20 3.00	5.27 5.02
IV	284 – 285[c] 40	$C_{32}H_{17}Cl_3N_4O_2$ (595.8)	64.48 64.29	2.86 2.61	9.40 9.02
V	238 – 240[b] 75	$C_{33}H_{20}Cl_3N_3O_3$ (612.9)	64.75 64.44	3.27 3.14	6.34 6.22
VI	203 – 205[b] 55	$C_{32}H_{18}Cl_3N_5O$ (594.9)	64.70 64.48	3.03 2.90	11.79 11.65
VIIa	218 – 220[b] 75	$C_{29}H_{19}Cl_3N_4O$ (545.8)	63.79 63.52	3.48 3.32	10.27 10.00
VIIb	194 – 195[b] 80	$C_{35}H_{23}Cl_3N_4O$ (621.9)	67.58 67.10	3.70 3.31	9.01 8.95
VIIIa	207 – 210[b] 70	$C_{30}H_{19}Cl_3N_4O_2$ (573.8)	62.77 62.18	3.31 3.21	9.76 9.60
VIIIb	189 – 190[a] 85	$C_{30}H_{19}Cl_3N_4OS$ (589.8)	61.07 61.00	3.22 3.01	9.50 9.34
IX	88 – 90[a] 60	$C_{29}H_{17}Cl_3N_2O_3$ (547.5)	63.56 63.34	3.10 3.06	5.11 5.00
Xa	173 – 175[d] 65	$C_{29}H_{19}Cl_3N_4O_2$ (561.8)	61.97 61.86	3.38 3.34	9.97 9.91
Xb	159 – 160[d] 70	$C_{35}H_{23}Cl_3N_4O_2$ (637.9)	65.88 65.76	3.61 3.58	8.78 8.66
XIa	213 – 215[b] 63	$C_{30}H_{22}Cl_3N_3O_3$ (578.9)	62.22 62.13	3.80 3.76	7.26 7.20
XIb	194 – 195[b] 65	$C_{35}H_{24}Cl_3N_3O_3$ (640.9)	65.67 65.52	3.75 3.60	6.57 6.33
XIc	206 – 208[b] 65	$C_{36}H_{26}Cl_3N_3O_3$ (654.9)	66.11 66.09	3.98 3.72	6.43 6.29
XII	275 – 277[a] 70	$C_{29}H_{17}Br_2Cl_3N_2O_2$ (691.8)	50.33 50.10	2.46 2.29	4.05 3.87

Crystallized from [a] benzene, [b] ethanol, [c] acetic acid, [d] toluene.



I



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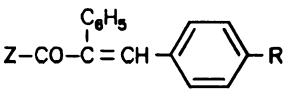
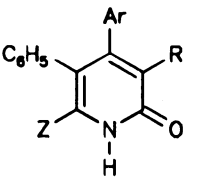
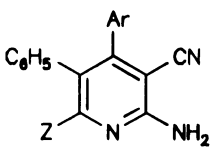


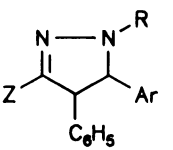
III a, R = H
III b, R = OCH_3
III c, R = Cl



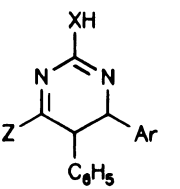
IV, R = CN
V, R = $COCH_3$



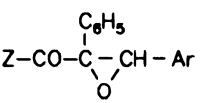
VI



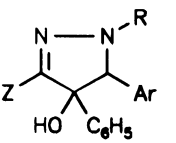
VII a R = H
VII b R = C_6H_5



VIII a X = O
VIII b X = S



IX



X a, R = H
X b, R = C_6H_5

4-(3′,4′-Dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl-3-(substituted)-2-propen-1-one Derivatives *IIIa – IIIc*

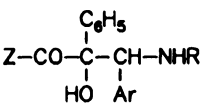
To a mixture of 2-(α-phenylacetyl)phthalazinone *II* (0.01 mol) and the appropriate aldehyde, (benzaldehyde, anisaldehyde *p*-chlorobenzaldehyde) in 40 ml of ethanol, a solution of 10% sodium hydroxide (10 ml) was added. The mixture was heated on a water bath for 30 min. The solid that separated was filtered, dried and recrystallized from the proper solvent to give *IIIa – IIIc*. IR spectra of *IIIa – IIIc*: 1 640 – 1 650 (C=N); 1 660 – 1 675 (C=O of heterocyclic moiety); 1 685 – 1 695 (C=O of amide). ^{1}H NMR spectrum of *IIIc*: 6.7 – 8.2 m, 17 H (aromatic H and =CH).

3-Cyano-4-[4′-chlorophenyl-5-phenyl-6-(4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl]-2-(2*H*)-pyridone (*IV*)

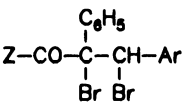
A mixture of ethyl cyanoacetate (0.01 mol), chalcone *IIIc* (0.01 mol) and ammonium acetate (0.08 mol) in butanol was refluxed for 10 h. During the reflux period a violet crystalline solid separated. The product was washed several times with water, then with ethanol and recrystallized to give the pyridone *IV*. IR spectrum: 1 630 (C=N); 1 670 – 1 680 (C=O); 2 200 (C=N); 3 400 (NH). ^{1}H NMR spectrum: 7.3 – 8.4 m, 16 H (aromatic H); 8.8 br, 1 H (NH).

3-Acetyl-4-[(4′-chlorophenyl)-5-phenyl-6-(4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl)]-2-pyridone (*V*)

From compound IIIc: A mixture of ethyl acetoacetate (0.01 mol), chalcone *IIIc* (0.01 mol) and ammonium acetate (0.08 mol) in butanol (40 ml) was refluxed for 10 h. The dark crystalline solid was filtered, dried and recrystallized to give *V* as brownish-red crystals. IR spectrum: 1 625 (C=N);

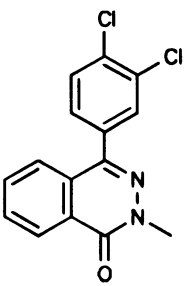


XIa, R = CH_3
XIb, R = C_6H_5
XIc, R = $CH_2C_6H_5$



XII

In formulae *III–XII*: Z =



IV–XII: Ar = *p*-ClC_6H_4

1 665 – 1 680 (C=O); 3 385 (NH). ^{1}H NMR spectrum: 2.5 s, 3 H (CH_3), 7.4 – 8.2 m, 16 H (aromatic H); 9.0 br, 1 H (NH).

From compound IV: A suspension of the 3-cyanopyridone *IV* (0.01 mol) in dry benzene (50 ml) was added dropwise to an ethereal solution of methyl magnesium iodide (prepared from 1.0 g magnesium, 7.0 g methyl iodide and 40 ml dry ether). The reaction mixture was refluxed on a steam bath for 2 h and then left at room temperature for 24 h, decomposed with cold diluted HCl to give *V* as brownish needles.

2-Amino-3-cyano-4-[(4′-chlorophenyl)-5-phenyl-6-(4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl)]pyridine (*VI*)

A mixture of malononitrile (0.01 mol), chalcone *IIIc* (0.01 mol) and ammonium acetate (0.08 mol) was refluxed for 8 h in boiling ethanol. The reaction mixture was hot filtered and concentrated, then left to cool in an ice bath. The separated product was filtered and recrystallized. IR spectrum: 1 670 (C=O); 1 625 (C=N); 2 100 (C≡N); 3 350 (NH_2). ^{1}H NMR spectrum: 4.3 s, 2 H (NH_2); 7.3 – 8.4 m, 16 H (aromatic H).

3-(4′-Chlorophenyl)-4-phenyl-5-[4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl]pyrazoline (*VIIa*) and its N-Phenyl Derivative (*VIIb*)

A mixture of the chalcone *IIIc* (0.01 mol) and hydrazine hydrate or phenylhydrazine, respectively (0.01 mol) was refluxed for 6 h in butanol (40 ml), then cooled and the separated product was filtered, dried and recrystallized. The IR spectra of *VIIa*, *VIIb*: 1 620 – 1 630 (C=N); 1 665 – 1675 (C=O). The ^{1}H NMR spectrum of *VIIb*: 3.6 d, 1 H (CHPh); 4.3 d, 1 H (CHN); 7.2 – 8.3 m, 21 H (aromatic H).

4,5-Dihydro-4-(4′-chlorophenyl)-5-phenyl-6-[4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl]pyrimidine-2-ol (*VIIIa*)

To a mixture of urea (0.01 mol), ethanol and HCl (enough to clear the solution), chalcone *IIIc* (0.01 mol) was added and the mixture was then heated on a steam bath for 8 h. After concentration and cooling, the reaction mixture was treated with 50 ml 5 M NaOH. The precipitate was filtered off and recrystallized from ethanol–benzene mixture (1 : 1) to give *VIIIa* as red crystals. IR spectrum: 1 630 (C=N); 1 685 (C=O); 3 390 (broad, OH). ^{1}H NMR spectrum: 2.8 s, 1 H (OH); 3.7 d, 1 H (CHPh); 4.5 d, 1 H (CHN–); 7.3 – 8.4 m, 16 H (aromatic H).

4,5-Dihydro-4-(4′-chlorophenyl)-5-phenyl-6-[4-(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl]pyrimidine-2-thiol (*VIIIb*)

A mixture of chalcone *IIIc* (0.01 mol), thiourea (0.01 mol), KOH (1 g), ethanol (50 ml), and water (2 ml) was refluxed for 3 h. The formed precipitate was filtered, dried and recrystallized from the proper solvent to give the pyrimidine thiol *VIIIb* as yellow crystals. IR spectrum: 1 190 (C=S); 1 630 (C=N); 1 670 (C=O); 2 550 (S–H).

2-(α,β-Epoxydihydrocinnamoyl)phthalazinone Derivative *IX*

A mixture of 30% H_2O_2 (10 ml) in 4 M NaOH, and methanol (20 ml) was added to a solution of *IIIc* (0.01 mol) in acetone (30 ml) with stirring, then kept at 0 °C for 2 h. The reaction mixture was poured onto ice-cooled 20% HCl, the solid separated was filtered, dried and recrystallized from

methanol. IR spectrum: 1 290 (epoxy linkage); 1 625 (C=N); 1 675 (C=O). ^{1}H NMR spectrum: 4.2 s, 1 H (CH–O); 7.3 – 8.4 m, 16 H (aromatic H).

4,5-Dihydro-4-hydroxypyrazoline Derivatives *Xa*, *Xb*

A mixture of compound *IX* (0.01 mol) and hydrazine hydrate or phenylhydrazine, respectively, in ethanol (40 ml) was refluxed for 6 h. The reaction mixture was hot filtered, concentrated and cooled. The solid separated was filtered, dried and recrystallized from the proper solvent. The IR spectra of *X*: 1 620 – 1 635 (C=N); 1 670 – 1 685 (C=O); 3 250 – 3 400 (NH and OH).

N-Aralkyl Propanone Derivatives *XIa* – *XIc*

A solution of compound *IX* (0.01 mol) in ethanol (30 ml) was treated with methylamine, aniline or benzylamine, respectively. The reaction mixture was refluxed for 5 h, filtered while hot and left to cool in an ice bath. The solid that separated was filtered, dried and recrystallized to give *XIa* – *XIc*. IR spectra of *XI*: 1 620 – 1 635 (C=N); 1 665 – 1 680 (C=O); 3 200 – 3 400 (NH and OH). ^{1}H NMR spectrum of *XIb*: 3.9 s, 1 H (CH–NH); 4.8 s, 1 H (NH); 5.6 s, 1 H (OH); 7.3 – 8.3 m, 21 H (aromatic H).

Bromination of the Chalcone *IIIc*: Formation of 2,3-Dibromo-1-[(3′,4′-dichlorophenyl)-1-(2*H*)-phthalazinone-2-yl]-2-phenyl-3-(4′-chlorophenyl)propan-1-one (*XII*)

A mixture of the chalcone *IIIc* (0.01 mol) in CCl_4 (60 ml) was cooled and bromine (0.01 mol) was added with stirring. After complete addition, the reaction mixture was left overnight. The precipitate formed was filtered off and washed several times with 5 portions of ethanol and recrystallized to give *XII* as red crystals. IR spectrum of *XII*: 1 625 (C=N); 1 665 (C=O).

Appendix – Biological Activity

Compounds *II*, *IIIc*, *IV*, *V*, *VI*, *XII* were tested for their antibacterial activity against gram-positive bacteria (*Bacillus subtilis*, *Bacillus cereus*) and gram-negative bacteria (*Escherichia coli*, *Pseudomonas fluorescens* using cup-plate method[2,3] and for their antifungal activity against *Aspergillus niger*, *Aspergillus flavus* and *Penicillium cyclopium* using agar plate diffusion technique[4] (see Table II).

TABLE II
Antimicrobial activity of selected compounds (MIC in μmol l^{-1})

Compound	*A. niger*	*A. flavus*	*P. cyclopium*	*E. coli*	*P. fluorescens*	*B. subtilis*	*B. cereus*
II	>1 000	>200	200	1 000	1 000	40	200
IIIc	>1 000	>1 000	1 000	200	1 000	200	>1 000
IV	>1 000	>1 000	200	1 000	200	>1 000	>1 000
V	40	200	1 000	200	200	1 000	40
VI	1 000	>1 000	200	1 000	>1 000	200	1 000
XII	200	1 000	1 000	1 000	1 000	200	200

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