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SYNTHESIS OF SOME NEW PHTHALAZINONE - SCHIFF BASES AND OTHER RELATED PRODUCTS OF POSSIBLE BIOLOGICAL ACTIVITY

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Several hydrazones, thiazolidinones, oxadiazoles and pyrazoles derived from phthalazine acetic acid hydrazide were prepared and tested for their antibacterial and antifungal activities.

Key words: Hydrazidomethyl phthalazinone, Phthalazinedone-schiff, Cyclocondensation.

Introduction

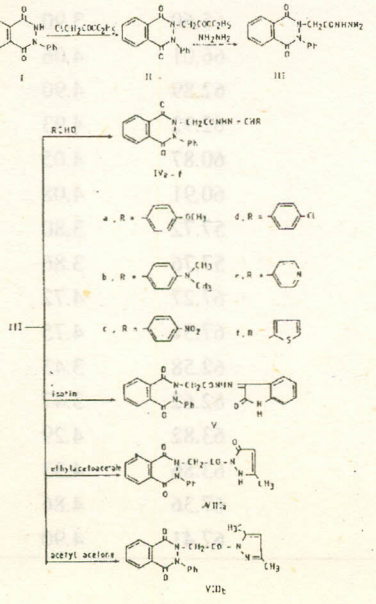
Diverse biological activities have been encountered in compounds having the phthalaizine ring system [1-3], including analgesic, antipyretic, CNS depressant actions [4], and anti- tubercular activity [5]. Furthermore, several heterocyclic Schiff bases, oxadiazoles, pyrazoles and thiazolidinone derivatives were found to possess antibacterial activity [6-10].

In view of the above, the title Schiff bases and related compounds were synthesized with a view to evaluating them for their antimicrobial activity *in vitro*.

The synthesis of the desired compounds was accomplished by allowing 2-phenyl-1,4-dioxophthalazine (I) [11] to react with ethylchloroacetate in dry DMF containing anhydrous potassium carbonate to give ethyl-2-phenyl-1, 4-dioxophthalazin-3-acetate (II) in 72% yield. Reaction of the ester II with hydrazine hydrate afforded the corresponding hydrazide-key intermediate III in 76% yield.

Reaction of the hydrazide III with different aromatic and heterocyclic aldehydes, gave the corresponding "hydrazone derivatives", IVa-f, respectively, in 78-83% yields.

In the same manner, condensation of III with isatin afforded the 2-indolone derivative V in 81% yield.



Scheme 1.

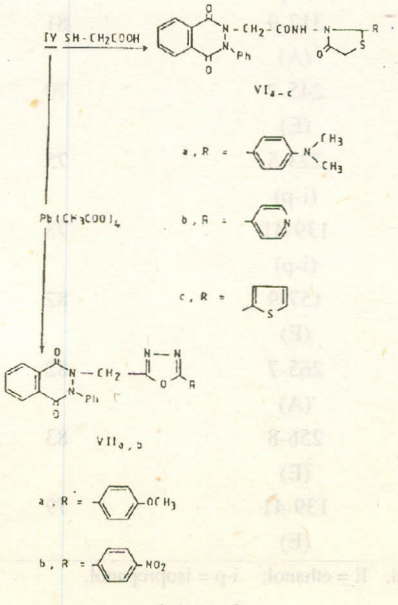
Cyclocondensation of compounds IVb,e and f with thioglycolic acid afforded the thiazolidinone derivatives VIa-c respectively.

Further, compounds IVa and IVc underwent oxidative cyclization using lead tetra acetate to give 1,3,4-oxadiazole derivatives VIIa and VIIb, respectively, in 82% yield.

On the other hand, cyclization of the hydrazide derivative III with ethylacetoacetate or acetylacetone, gave the corresponding pyrazole derivative VIIIa,b, respectively, in 80% yield (Scheme).

Antimicrobial activity . Compounds III, IVa, IVc, IVe, IVf, V, VIa, VIb, VIc, VIIa, VIIIa and VIIIb were screened against *Bacillus subtilus, staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans* and *Aspergillus niger*, according to a modified cup-test assay technique [12, 13].

It is observed that, compounds III, VIb show high activity against gram-positive bacteria, where these compounds show moderate activity against gram-negative bacteria. Compounds IVa, VIa and VIc show moderate activity against gram-positive bacteria, where these compounds show a slight activity against gram-negative bacteria. The compounds under test are inactive against yeast and fungi.



Scheme 2.

Experimental

All melting points are uncorrected and were obtained on a Boetuis melting point microscope. The IR spectra were obtained on a Unicam spectrophotometer using KBr discs. The ^{1}HNMR spectra were determined on Varian EM-390 spectrometer 90 MHZ. 2-Phenyl-1, 4-dioxophthalazine (I) was prepared according to a reported method [11]. All analytical data, yields m.p.s. of the new compounds and crystallization solvents are presented in Table 1.

Ethyl-2-phenyl-1, 4-dioxophthalazin-3-acetate (II). To 2.38 g (0.01 mol) of 2-phenyl-1, 4-dioxophthalazine (I) and 2.07 g (0.015) of K_2CO_3 (anhydrous) was added to 20 ml of dry DMF and the reaction mixture was refluxed for one hr. Ethylchloroacetate (0.01 mole) was added to the reaction mixture which refluxed for 10 hr. After concentration, the reaction mixture was poured onto crushed ice and left overnight in a refrigerator. The crude ester was filtered, dried and recrystallized from ethanol to give white crystals of II : I.R. spectra (cm^{-1}) showed bands at 3010 (C-H aromatic); 1740 (C = O ester); 1680-1660 (C = O phthalazinone); 1460 (C = C aromatic).

The ^{1}HNMR spectrum (p.p.m.) showed signals at δ1.1 (t, 3H, CH_3), δ 4.0 (Q, 2H, CH_2), δ 4.9 (S, 2H, N-CH_2-) and δ 7.1 - 8.1 (m, 9H, $\overset{O}{\underset{C}{\|}}$ aromatics).

TABLE 1. ANALYTICAL DATA OF COMPOUNDS II - VIII.

Compound No.	m.p.°C (solvent)	Yield (%)	Formula (M.wt.)	Analysis Calcd. / Found C%	H%	N%
II	93-95	72	$C_{18}H_{16}N_2O_4$	66.65	4.98	8.64
	(E)		(324.36)	66.91	5.02	8.61
III	191-3	76	$C_{16}H_{14}N_4O_3$	61.92	4.56	18.06
	(E)		(310.34)	62.12	4.91	17.80
IVa	234-6	81	$C_{24}H_{20}N_4O_4$	67.28	4.71	13.08
	(A)		(428.43)	67.58	5.01	13.28
b	127-9	78	$C_{25}H_{23}N_5O_3$	68.01	5.25	15.87
	(A/H_2O)		(441.47)	68.31	5.51	15.69
c	284-6	82	$C_{23}H_{17}N_5O_5$	62.30	3.87	15.80
	(A)		(443.41)	62.35	3.90	15.83
d	177-9	80	$C_{23}H_{17}C1N_4O_3$	63.81	3.96	12.94
	(A)		(432.9)	63.85	4.00	12.97
e	233-5	79	$C_{22}H_{17}N_5O_3$	66.15	4.29	17.54
	(A)		(399.4)	66.02	4.90	17.00
f	227-9	83	$C_{21}H_{16}N_4O_3S$	62.36	3.99	13.85
	(A/H_2O)		(404.43)	62.61	4.03	13.88
V	317-9	81	$C_{24}H_{17}N_5O_4$	65.60	3.90	15.94
	(A)		(439.42)	66.01	4.06	16.11
VIa	245-7	70	$C_{27}H_{25}N_5O_4S$	62.89	4.90	13.59
	(E)		(515.63)	62.92	4.93	13.62
b	223-5	75	$C_{24}H_{19}N_5O_4S$	60.87	4.05	14.79
	(i-p)		(473.55)	60.91	4.08	14.83
c	139-41	73	$C_{23}H_{18}N_4O_4S_2$	57.72	3.80	11.71
	(i-p)		(478.57)	57.76	3.86	11.76
VIIa	157-9	82	$C_{24}H_{18}N_4O_4$	67.27	4.72	13.08
	(E)		(428.47)	67.31	4.75	13.11
b	265-7	82	$C_{23}H_{15}N_5O_5$	62.58	3.43	15.87
	(A)		(441.43)	62.62	3.47	15.90
VIIIa	256-8	83	$C_{20}H_{16}N_4O_4$	63.82	4.29	14.89
	(E)		(376.4)	63.86	4.33	14.92
b	139-41	79	$C_{21}H_{18}N_4O_3$	67.36	4.86	14.96
	(E)		(374.42)	67.41	4.90	14.01

A = acetic acid; E = ethanol; i-p = isopropanol.

2-Phenyl-1, 4-dioxophthalazin-3-yl acetic acid hydrazide (III). A mixture of the ester II (3.24 g; 0.01 mol), hydrazine hydrate (0.55 g; 0.011 mol) in 20 ml of absolute ethanol was refluxed for 7 hr. The reaction mixture was concentrated, cooled and the separated solid was filtered off. Recrystallization from ethanol gave pale yellow crystals. IR spectra (cm^{-1}) showed bands at 3320-3300 (N-H); 3200-3190 (NH_2); 3040 (C-H) aromatic); 2980 (C-H aliphatic); 1690-1680 (C = O phthalazinone).

2-Phenyl-1, 4-dioxophthalazin-3-yl arylidine acetic acid hydrazide (IVa-f). General method. To 3.1 g (0.01 mol) of compound III in 30 ml of ethanol was added (0.01 mol) of the appropriate aromatic or heterocyclic aldehyde and the reaction mixture was refluxed with stirring for 5 hr, then cooled and the precipitated product was filtered off. Recrystallization from the proper solvent gave compounds IVa-f respectively.

The I.R. spectra (cm^{-1}) of all compounds are in corre spondance with their structures and that of IVc showed bands at 3160 (NH - amide); 1720-1700 (C = O phthalazinc); 1678 (C = O amide); 1580 (C = N) and at 1345 (NO_2). The I.R. spectrum (cm^{-1}) of IVd showed bands at 3250 (NH - amide); 1760-40 (C = O phathalazinone); 1670-1650 (C = O amide); 1590 (C = N) and at 740 (C-Cl aromatic).

Reaction of (III) with isatin: Preparation of the indolone derivative (V). The foregoing method was applied using isatin instead of the aldehyde to give V from acetic acid.

Reaction of (IVb,e,f) with thioglycolic acid: Preparation of the thiazolidinones (VIa-c). Thioglycolic acid (2.7 ml; 0.03 mol) was added dropwise to 0.02 mol of the appropriate Schiff bases (IVb,e,f,) in 25 ml of dry benzene during 15 min. with stirring, which continued for 4 hr, then the reaction mixture was left overnight at room temperature. The solvent was distilled off, and the residue neutralized with sodium bicarbonate solution. The precipitated material was filtered off and recrystallized from the proper solvent to give VIa-c, respectively.

I.R. (cm^{-1}) of VIa : 3200 (C-H aromatic); 3050 (NH amide); 1690-1670 (C = O phthalazinone); 1640-1600 (C = O amide); and at 1475 (C = C aromatic).

I.R. (cm^{-1}) of VIb : 3250 (NH amide); 1730-1700 (C = O phthalazinone); 1670 (C = O amide); 1480 (C = C aromatic).

Reaction of (IVa,c) with lead tetraacetate. Preparation of the oxadiazoles (VIIa,b).. Lead tetra acetate (4.43 g; 0.01 mol) in CH_2Cl_2 (60 ml) was added to a solution of IVa or IVc (0.01 mole) in 90 ml of CH_2Cl_2 in a period of 1 hr with vigorous stirring. The reaction mixture was left overnight at room temperature, washed with water and the CH_2Cl_2 layer was dried with anhyd sodium sulfate. The solvent was distilled off and the precipitate was filtered and recrystallized from the proper solvent to give VIIa,b, respectively.

The ^{1}HNMR spectrum (p.p.m.) of VIIa showed signals at δ 3.9 (S, 3H, OCH_3), δ 5.6 (S, 2H, CH_2) and δ 7.0-8.2 (m, 13H, aromatics).

I.R. (cm^{-1}) of VIIb : 1695-1655 (C=O phthalazinone); 1355 (NO_2); 1180-1130 (C-O-C).

2-Phenyl-3-(5-methylprazolidine-3-one-2-yl) carbonylmethyl-1,4- dioxophthalazine (VIIIa). A mixture of the hydrazide III (3.1 g; 0.01 mol) and ethylacetoacetate (1.9 g; 0.015 mol) was heated on a boiling water bath for 9 hr. The reaction mixture was cooled and the product was recrystallized from ethanol to give VIIIa.

2-Phenyl-3-(3,5-dimethylpyrazol-2-yl)-cabonylmethyl-1,4- dioxophthalazine (VIIIb). The foregoing method was applied except that acetyl-acetone was used instead of ethylacetoacetate to give VIIIb from ethanol.

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