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SYNTHESIS AND REACTIONS OF PHTHALOYL ACETOPHENONE AND THE BIOLOGICAL ACTIVITY OF SOME NEW COMPOUNDS

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Phthaloyl acetophenone 1 was prepared via Claisen condensation of diethyl phthalate with acetophenone. The behaviour of compound 1 towards hydrazines, diazonium salts and carbazides to give phthalazine derivatives 2,3 and 4, hydrazidoyl derivatives 5 and dipyrazole derivatives 6,7 and 8 respectively. The antimicrobial activity of some new compounds has been screened.

Key words: Synthesis, Biological activity, Compounds.

Introduction

As an extension of our previous work [1,2], this recent work reported the synthesis of some phthalazine derivatives and dipyrazole derivatives using diethyl phthalate and acetophenone as a key starting for their preparation.

It has been reported that pyrazoles and phthalazines have antimicrobial activities and recently they have respiratory and cardiovascular activities [3,4].

The aim of this work is to synthesis some new pyrazoles and phthalazines which might have antimicrobial and biological activities.

Results and Discussion

Phthaloyl acetophenone 1 was prepared via condensation of acetophenone with diethyl phthalate in the presence of sodium methoxide [5]. The ethanolic solution of 1 reacts with hydrazines, namely hydrazine hydrate and phenylhydrazine to afford the corresponding 1,4-bis-(benzoyl methylenyl)-2N-substituted-2,3- dihydrophthalazine 2a and 2b [6-9] (Table 1). These IR data infer that phthalazine 2 present in tautomeric forms 2 $\rightleftharpoons$ 2. The tautomeric forms of 2 has been established via acetylation and benzoylation of 2a with acetic anhydride and benzoyl chloride, to give the corresponding N-acetyl and N-benzoyl phthalazine derivative 3,4 respectively.

The new hydrazidoyl derivatives (5a,b) were prepared by coupling 1 with diazotized amines; namely, *p*-nitroaniline and *p*-chloroaniline in ethanol solution buffered with sodium acetate [10,11].

Condensation of 5a, b with hydrazine hydrate in boiling ethanol gave 1-[3´[(4-arylazo-5-phenyl)pyrazolyl] 2[3` (5 (phenyl) pyrazolyl]-benzene (6a, b) (Table 1).

The present work deals with the preparation of new heterocyclic compounds containing pyrazole and benzene moiety which are expected to show some antimicrobial activity. Consequently, compound 1 was allowed to react with carbazides, namely semicarbazide hydrochloride and thiosemicarbazide in pyridine to give the corresponding 1,2-[bis-[3´-(5-phenyl-1´-N- substituted) pyrazolyl]-benzene (7a, b) (Table 1). Acetylation of 7a,b with acetic anhydride gave N-diacetyl derivatives (8a,b) (Table 1).

The antimicrobial effect. Using acetone solutions with concentrations of 8, 40, 200 and 1000 mol/dm^3, all the newly synthesized compounds were tested for antimicrobial effect [12,13] against *Aspergillus niger, Penicillium cyclopium and Rhizopus oryzae*. After 24 hrs the growth in the broth was evaluated visually according to its turbidity. The results indicated that the compounds 1 and 5 a were outstanding in their MIC when compared with the other compounds tested and the control (without tested compound), and we can see that they inhibited the fungi tested more intensively. With the exception of compound 1 which inhibited the growth of *Bacillus subtilus* in a concentration 1000 x 10^{-6} mol/dm^3, the other compounds tested were biologically inactive against the strains tested. The results of screening the compounds synthesized have shown in Table 2.

Experimental

IR spectra were recorded in KBr on a Unicam SP 1200 spectrophotometer and PMR spectra on a Varian EM-360-60 MHz NMR spectrometer. All m.ps. reported are uncorrected.

Reaction of acetophenone with diethyl phthalate: Formation of 1. A mixture of acetophenone (0.02 mol) and diethyl phthalate (0.01 mol) in 50 mL sodium methoxide solution (0.005gm atom sodium/ 25 mL methanol) was fused in an oil bath at 105° for 6 hrs. The reaction mixture was cooled and the solid obtained was washed with dilute hydrochloric acid and recrystallized from an appropriate solvent to give 1 (Table 1).

Reaction of 1 with hydrazines : Formation of 2a,b. A solution 1 (0.01 mol) and the hydrazine derivative namely, hydrazine hydrate and phenylhydrazine) in ethanol (70 mL) was refluxed for 6 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 2a,b (Table 1).

TABLE 1. CHARACTERISATION AND PHYSICAL DATA OF THE COMPOUNDS (1:8).

Compd.	M.P. °C (Colour)	Crystallized (Yield%)	Mol. formula	Analysis% Found (%) (Calcd) C	H	N	Cl	S	IR data υ_{max} (cm^{-1})	PMR data value
1.	102	Ethanol	$C_{24}H_{18}O_4$	(77.8	4.86	–	–	–)	1710-1690 (CO ketonic)	4.5 (s, 4H, 2x$COCH_2CO$)
	(Pale yellow)	(45)	(370)	77.6	4.83	–	–		1605-1600 (C=C)	7.3-8.1 (m, 14H, Ar-H)
2a	250	Ethanol	$C_{24}H_{18}N_2O_2$	(78.68	4.91	7.65	–	–)	1700-1670 (CO ketonic),	–
	(Pale yellow)	(55)	(366)	78.34	4.87	7.56	–	–	1620 (C=N), 3240 (NH)	–
2b	125	Ethanol	$C_{30}H_{22}N_2O_2$	(81.44	4.97	6.33	–	–	–	–
	(Orange)	(50)	(442)	81.27	4.92	6.09	–	–	–	–
3	200	Acetic acid	$C_{28}H_{22}N_2O_4$	(74.66	4.88	6.20	–	–	1740(CO N-acetyl),1695	–
	(Yellow)	(65)	(450)	74.56	4.83	6.01	–	–	(CO–ketonic), 1600(C=C)	–
4	150	Ethanol	$C_{36}H_{26}N_2O_4$	(78.54	4.72	5.09	–	–	1710(CO N-benzoyl),1680	6.3(s,2H, 2xCHCO)
	(Brown)	(45)	(550)	78.49	4.25	5.01	–	–	(COketonic),1600(C=C)	7.4-8.4(m, 24H,Ar-H)
5a	240	Benzene	$C_{30}H_{21}N_3O_6$	(69.36	4.04	8.09	–	–)	1715-1680(CO)	4.3 (s,2H, $COCH_2CO$)
	(Pale red)	(35)	(519)	68.98	3.87	8.39	–	–	1620 (C=C)	7.1-8.3 (m, 18H, Ar-H
5b	201	Benzene	$C_{30}H_{21}N_2ClO_4$	(70.79	4.12	5.50	6.98	–)	–	–
	(Pale yellow)	(40)	(508.5)	70.65	4.00	5.29	6.80	–	–	–
6a	205	Ethanol	$C_{30}H_{21}N_7O_2$	(70.45	4.10	19.10	–	–)	1630(C=N), 1610(C=C),	6.8-8.3(m, 18H, Ar-H
	(Red)	(55)	(511)	70.12	3.90	18.90	–	–	3300(NH) and absence	and heterocyclic);
									anyband (CO).	11.6 (s, 2H, NH).
6b	315	Ethanol	$C_{30}H_{21}N_6Cl$	(71.92	4.19	16.78	7.04	–)	–	–
	(Yellow)	(45)	(500.5)	71.89	4.07	16.57	6.98	–	–	–
7a	240	Ethanol	$C_{26}H_{20}N_6O_2$	(69.64	4.46	18.75	–	–)	1690-1660(CO amide),	–
	(Pale yellow)	(60)	(448)	69.49	4.35	18.69	–	–	1615(C=C), 3200 and	–
									3380 (NH of amino group).	–
7b	>350	Acetic acid	$C_{26}H_{20}N_6S_2$	(65.00	4.16	17.50	– 13.33)		Absence of any bands	–
	(Orange)	(65)	(480)	65.03	4.02	17.39	– 13.29		Characteristic (CO).	–
8a	190	Ethanol	$C_{34}H_{28}N_6O_6$	(66.23	4.54	13.63	–	–)	1740(CO N-acetyl),	–
	(Yellow)	(63)	(616)	66.01	4.45	13.36	–	–	1700 (CO amide), 1610(C=N)	–
									and absence any band (NH of	–
									amino group)	–
8b	278	Acetic acid	$C_{34}H_{28}N_6S_2O_4$	(62.96	4.32	12.96	– 9.97)		1740(CO N-acetyl),	–
	(Pale yellow)	(55)	(648)	62.82	4.13	12.75	– 9.79		1610(C=N) and absence any	–
									band (NH of amino group).	–

Reaction of 2a with acetic anhydride : Formation of 3 . A solution of 2a (0.01 mol) in 20 mL acetic anhydride/acetic acid (molar ratio 1:1) was heated under reflux for 4 hrs. The solid that after cooling, was filtered off and crystallized from an appropriate solvent to give 3 (Table 1).

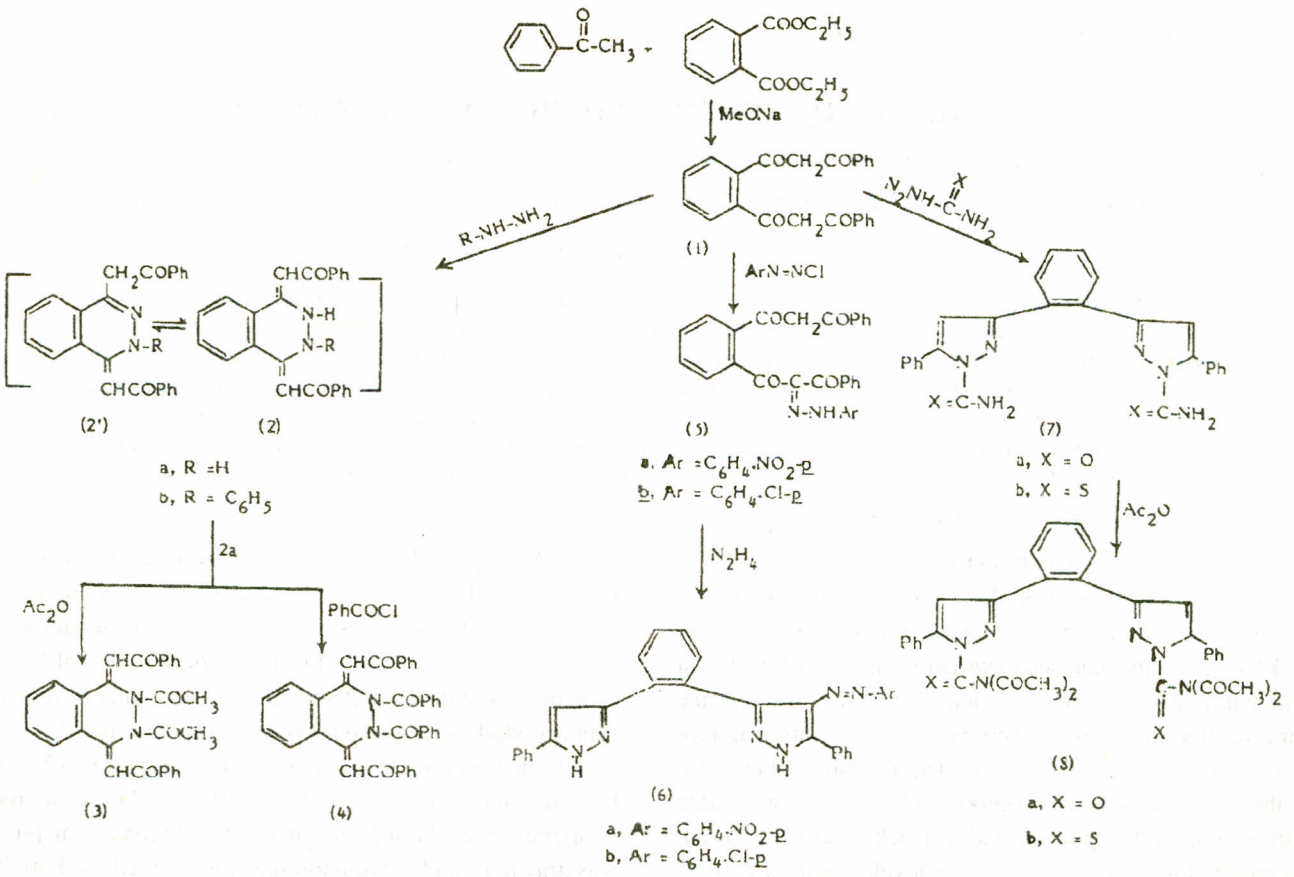
Reaction of 2a with benzoyl chloride : Formation of 4 . A solution of 2a (0.01 mol) in 10 mL benzoyl chloride was heated under reflux for 3 hrs. The reaction mixture poured into water. The solid that separated was washed with 1N $NaHCO_3$ and recrystallized from an appropriate solvent to give 4 (Table 1).

Action of diazotized amines on 1 : Preparation of 5a,b . A solution of 1 (0.01 mol) in ethanol (50 mL) was stirred with sodium acetate (3 gm) and the mixture was then chilled in ice to 0-5°. A cold aqueous solution (0-5°) of the diazonium salt (0.01 mol) was added dropwise with stirring during 45 mins. After addition, the mixture was stirred for further 30 mins and then left for 2 hrs in an ice-chest. The precipitated products were collected, washed with water and recrystallized from an appropriate solvent to give 5a,b (Table 2).

TABLE 2. ANTIMICROBIAL ACTIVITY OF SOME PREPARED COMPOUNDS.

Compd. No.	*A. Niger*	*P.Cyclopium*	*R.Oryzae*	*E.Coli*	*B. Subtilus*
	MIC (X 10^{-6} mol/dm3)				
1	1000	1000	>1000	>1000	1000
2a	>1000	>1000	>1000	>1000	>1000
2b	>1000	>1000	>1000	>1000	>1000
3	>1000	>1000	>1000	>1000	>1000
4	>1000	>1000	>1000	>1000	>1000
5a	>1000	>1000	>1000	>1000	>1000
6a	>1000	>1000	>1000	>1000	>1000
6b	>1000	>1000	>1000	>1000	>1000
7b	>1000	>1000	>1000	>1000	>1000

Action of hydrazine hydrate on 5a,b : Formation of 6a,b. A solution of 5a,b (0.01 mol) and hydrazine hydrate (0.03 mol)



in ethanol (50 mL) was refluxed for 8 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 6a,b (Table 1).

Reaction of 1 with carbazide derivatives : Formation of 7a,b. A solution of 1 (0.01 mol) and carbazide derivative (0.03 mol) (namely semicarbazide hydrochloride and thiosemicarbazide) in pyridine (50 mL) was refluxed for 10 hrs. The reaction mixture was cooled, then poured upon ice - HCl. The solid that separated was crystallized from an appropriate solvent to give 7a,b (Table 1).

Reaction of 7a,b with aceitc anhydride : Formation of 8a,b. A solution of 7a,b (0.01 mol) in 20 mL acetic anhydride/ acetic (molar ratio 1:1) was refluxed for 4 hrs. The solid that after cooling was filtered off and crystallized from an appropriate solvent to give 8a,b (Table 1).

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