Synthesis of some Oxadiazolo-, Oxadiazolino-, Thiadiazolo- and Triazolothiazinophthalzinone Derivatives

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Summary: Reaction of the hydrazide (1) with aromatic aldehydes gave the corresponding hydrazones (2). Compounds (2) were cyclized either by sod. acetate/HOAc or acetic anhydride to give oxadiazoles and oxadiazolines (3) and (5) respectively. Also, compounds (6) were heated either with NaOH to give triazoles (7) or with phosphoric acid to give thiadiazoles (8). Moreover, compound (9) was reacted either with phenacyl bromides or benzoyl chlorides, yielding triazolothiadiazines (10) and triazolothiadiazoles (11) respectively.

Introduction

The present study is in continuation of our earlier work [1-3] on the synthesis of various heterocycles derived from phthalazine derivatives having pharmacological activities. 1,3,4-oxadiazoles have significant antitubercular and leprastatic properties [4,5]. Also, 1,2,4-triazoles and 1,3,4-thiadiazines are reported to have fungicidal, tuberculostatic and hypotensive activities [6,7].

Encouraged by the earlier results, we report herein the synthesis of 1,3,4-oxadiazolo-1,2,4-triazolo-1,3,4-thiadiazino phthalazinones. The sequence of the reactions followed in the preparation of the designed compounds are summarized in schemes [1-3].

Reaction of acid hydrazide (1) [8] with aromatic aldehydes in refluxing ethanol yielded 2-arylidene hydrazinocarbonylmethyl-4-benzyl-1-(2H) phthalazinones (2). The structure of compounds (2) were verified from correct elemental analysis and also from IR spectral data which

showed bands in the region 1680-1650 cm^{-1} characteristic of $\nu C=O$ of hydrazones and phthalazinones and in the region 3300-3200 cm^{-1} characteristic of NH.

Also the target oxadiazolophthalazinones (3) were obtained via reaction of hydrazones (2) with a mixture of acetic acid and sodium acetate [9]. The identification of compounds (3) were proved chemically, by the reaction of compounds (4) with Conc. H_2SO_4 [10] gave the desired compounds (3). Moreover, reaction of hydrazones (2) with acetic anhydride [11] gave the oxadiazolinophthalazinones (5). The structure of compounds (5) were deduced from its correct elemental analysis and also from IR spectral data which showed bands in the region 1610-1575 cm^{-1} characteristic of $\nu C=N$, in the region 1180-1115 cm^{-1} characteristic of νC-O of oxadiazolino ring and in the region 1650-1620 cm^{-1} characteristic of $\nu C=O$ of -$NCOCH_3$.

Furthermore, the acid hydrazide (1) was allowed to react with different isothiocyanates to yield thiosemicarbazides (6), which reacted with 2N NaOH [12] and gave triazolophthalazinones (7). The proposed structure of compounds (7) was confirmed by correct analytical data and IR spectra which showed bands in the region 3080-2930 cm^{-1} characteristic of νNH tautomeric at position 1 of triazol ring, in the region 3000-2930 cm^{-1} characteristic of νSH, in the region 1600-1540 cm^{-1} characteristic of $\nu C=N$ and $\nu C=C$ and in the region 1320-1300 cm^{-1} characteristic of $\nu C=S$ of the tautomeric thione.

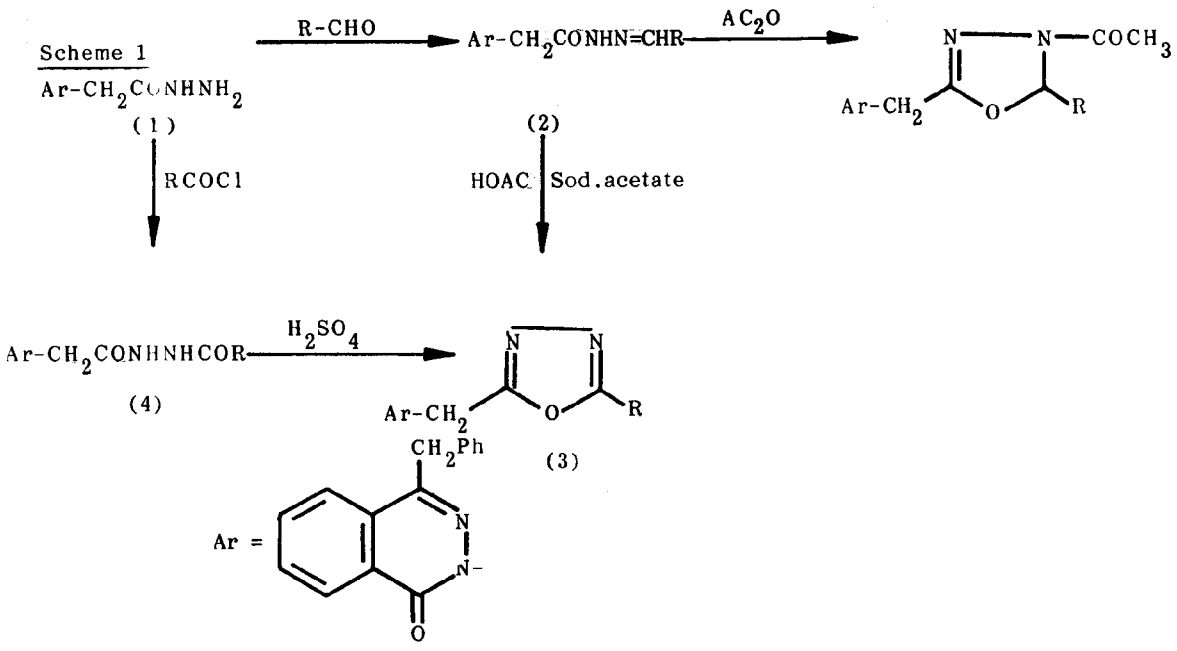
On the other hand, compounds (6) when heated with phosphoric acid [13] gave thiadiazolophthalazinone derivative (8).

Also, the acid hydrazide (1) was reacted with carbon disulphide in ethanolic KOH yielded the potassium salt of the corresponding dithiocarbazate in quantitative yield. This when reacted with hydrazine hydrate (99%) in water gave 2-(4-amino-5-mercapto-S-triazol-3-yl-methyl)-4-benzyl-l(2H) phthalazinone (9). Its IR spectrum showed bands at 3340-3100 cm^{-1} characteristic of νNH_2, at 2890 cm^{-1} characteristic of νS-H, at 1570 cm^{-1} characteristic of $\nu C=N$ and at 1460 cm^{-1} characteristic of νC-N.

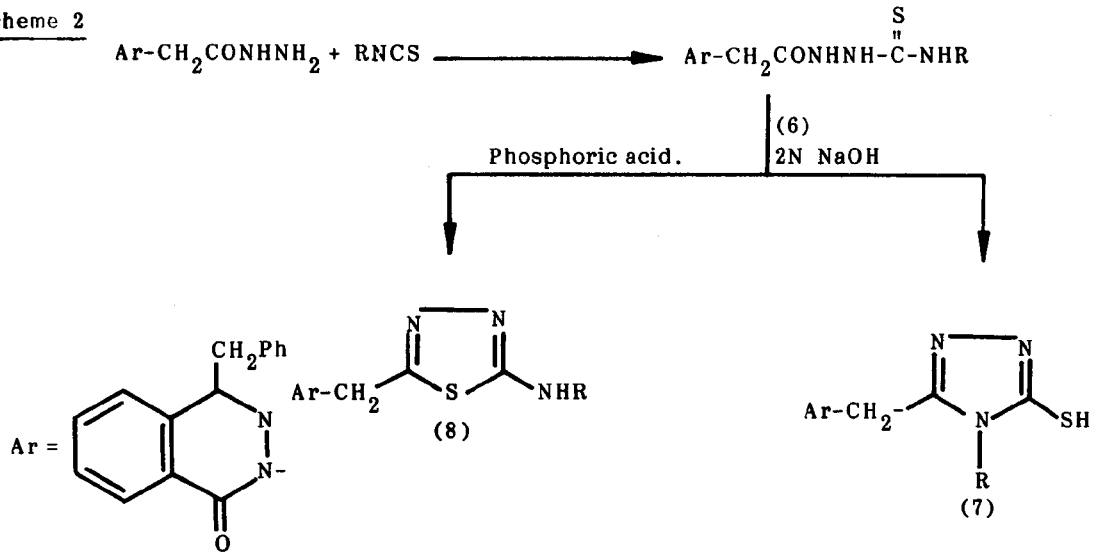
Condensation of compounds (9) with equimolar amount of phenacyl bromides in refluxing ethanol afforded the required 2-(6-aryl- (7H)-S-triazolo[3,4-b] 1,3,4-thiadiazin-3-yl-methyl)-4-benzyl-1- (2H) phthalazinones (10).

The validity of the structure of compounds (10) were deduced from its correct elemental analysis and from IR spectral data which showed bands in the region 1630-1550 cm^{-1} due to $\nu C=C$,

Scheme 1



Scheme 2

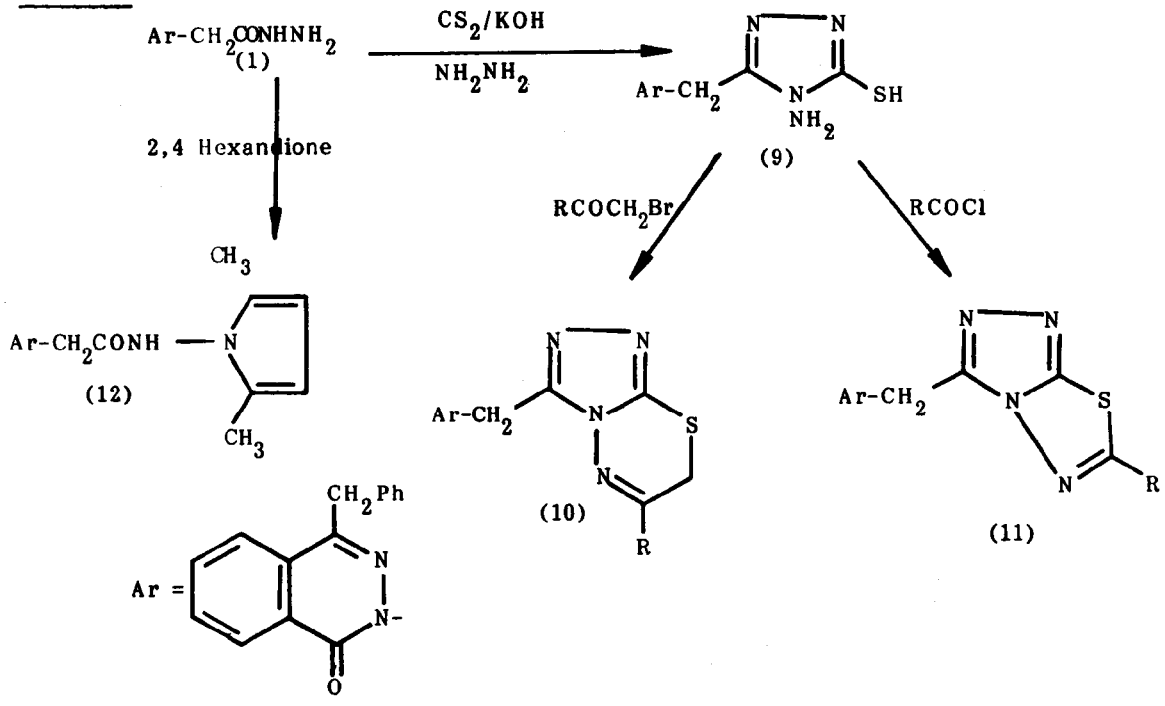


νC=N and νC-N, in the region 690-670 cm^{-1} characteristic of νC-S-C and at 840-410 cm^{-1} due to p-substituted phenyl. The abscence of signals in the region 3100-3600 cm^{-1} showed that no NH-tautomers of (10) are present.

Moreover, compound (9) was reacted with different acid chloride derivatives in pyridine, forming thiadiazoltriazolophthalazinones (11). Its IR spectra showed bands in the region 3100-3070 cm^{-1} characteristic of νC-H aromatic, in the region 2980-2865 cm^{-1} due to νC-H aliphatic, in the region 1610-1470 cm^{-1} due to νC-N and νC=C of aromatic rings and at 690 cm^{-1} of νC-S-C.

Also, 2,5-hexandione was reacted with acid hydrazide (1) in glacial acetic acid forming the pyrrolophthalazinone (12). Its IR spectrum showed bands at 3250-3180 cm^{-1} characteristic of νNH and at 1680-1660 cm^{-1} characteristic of νC=O.

Scheme 3



Experimental

Microanalysis and IR spectra were carried out in the micro- analytical center, Cairo University. IR (KBr) was carried out using a pye Unicam spectrophotometer. All m.p's are uncorrected.

2-Arylidenehydrazinocarbonylmethyl-4-benzyl-1-(2H) phthalazinones (2):

A solution of compound (1) (0.01 mol.) and the appropriate aldehyde (0.01 mol) in ethanol was heated under reflux for one hour. The precipitate which was obtained by cooling was filtered and crystallized from ethanol (Table 1).

2-(5-aryl 1,3,4-oxadiazol-2-yl-methyl)-4-benzyl-1-(2H) phthalazinones (3):

A mixture of compound (2) (0.01 mol), anhydrous sodium acetate (0.01 mol) and 15 ml of glacial acetic acid was heated under reflux for one hour. The reaction mixture was concentrated and cooled. The precipitated product was filtered off, dried and crystallized from acetic acid (Table 2).

2-N-benzoylhydrazinocarbonylmethyl-4-benzyl-1-(2H) phthalazinones (4)

The acid hydrazide (1) (0.01 mol) was dissolved in pyridine (30 ml), the aryl acid chlorides (0.01 mol) was added and the mixture was heated on a water bath for one hour. The reaction mixture was cooled and poured on crushed ice. The precipitated product was separated by filteration, washed with water and recrystallized from ethanol. For compound (4a): R = C_6H_5- m.p. 90°C, ($C_{24}H_{20}N_4O_3$) (412) (Calc. C, 69.90; H, 4.85; N, 13.95) (Found. C, 69.93; H, 4.89; N, 13.59). For compound (4b) R = p-Cl-C_6H_4- m.p. 140°C ($C_{24}H_{19}ClN_4O_3$) (446.5). (Calc. C, 64.50; H, 4.25; N, 12.54) (found. C, 64.53; H, 4.27; N, 12.51).

2-(4-acetyl-5-aryl-1,3,4-oxadiazolin-2-yl-methyl)-4-benzyl-1- (2H) phthalazinones (5):

One gram of the appropriate arylidenehydrazide (2) was refluxed with acetic anhydride (30ml) for one hour. The reaction mixture was neutralized after cooling with ammonium

Table 1: 2-arylidenhydrazinocarbonylmethyl-1-4-benzyl-1-(2H) phthalazinones (2)

Comp.	R	Yield	m.p.°C	M.F.M.Wt.	Analysis (Calc./F.)		
					C%	H%	N%
2a	C_6H_5	89	218	$C_{24}H_{20}N_4O_2$ (396)	72.72 72.70	5.05 5.07	14.14 14.16
2b	p-Cl-C_6H_4	80	225	$C_{24}H_{19}ClN_4O_2$ (430.5)	66.89 66.82	4.41 4.41	13.00 13.11
2c	m.Cl-C_6H_4	85	173	$C_{24}H_{19}ClN_4O_2$ (430.5)	66.89 66.92	4.41 4.46	13.00 13.10
2d	p.OCH_3-C_6H_4	79	197	$C_{25}H_{22}N_4O_3$ (426)	70.42 70.44	5.16 5.22	13.14 13.16
2e	p.NO_2-C_6H_4	75	240	$C_{24}H_{19}N_5O_4$ (455)	65.30 65.36	4.30 4.24	15.87 15.84
2f	p.$N(CH_3)_2$-C_6H_4	70	255	$C_{26}H_{25}N_5O_2$ (453)	71.07 71.11	5.69 5.72	15.94 15.90

Table 2: 2-(5-aryl-1,3,4-oxadiazol-2-yl-methyl-4-benzyl-1-(2H) phthalazinones (3)

Comp.	R	Yield	m.p.°C	M.F.M.Wt.	Analysis (Calc./F.)		
					C%	H%	N%
3a	C_6H_5	69	310	$C_{24}H_{18}N_4O_2$ (394)	73.09 73.12	4.56 4.55	14.21 14.26
3b	p.Cl-C_6H_4	75	305	$C_{24}H_{17}ClN_4O_2$ (428.5)	67.21 67.20	3.96 3.96	13.07 13.11
3c	m.Cl-C_6H_4	55	280	$C_{24}H_{17}ClN_4O_2$ (428.5)	67.21 67.18	3.96 3.89	13.07 13.12
3d	p.OCH_3-C_6H_4	65	278	$C_{25}H_{20}N_4O_3$ (452)	70.75 70.71	4.72 4.74	13.21 13.18
3e	p.NO_2-C_6H_4	80	273	$C_{24}H_{17}N_5O_4$ (453)	65.60 65.63	3.87 3.86	15.94 15.90
3f	p.$N(CH_3)_2$-C_6H_4	71	290	$C_{26}H_{23}N_5O_2$ (451)	71.39 71.33	2.63 2.65	16.02 16.03

Table 3: 2-(4-acetyl-5-aryl-1,3,4-oxadiazolin-2-yl-methyl)-4-benzyl-1-(2H) phthalazinones (5)

Comp.	R	Yield	m.p.°C	M.F.M.Wt.	Analysis (Calc./F.)		
					C%	H%	N%
5a	C_6H_5	52	130	$C_{26}H_{22}N_4O_3$ (438)	71.23 71.33	5.02 5.01	12.78 12.75
5b	p.Cl-C_6H_4	66	240	$C_{26}H_{21}ClN_4O_3$ (472.5)	66.03 66.03	4.44 4.42	11.85 11.82
5c	m.Cl-C_6H_4	61	125	$C_{26}H_{21}ClN_4O_3$ (472.5)	66.03 66.03	4.44 4.42	11.85 11.82
5d	p.OCH_3-C_6H_4	69	180	$C_{27}H_{24}N_4O_4$ (468)	69.23 69.20	5.13 5.20	11.96 11.92
5e	p-NO_2-C_6H_4	72	185	$C_{26}H_{21}N_5O_5$ (473)	65.96 65.56	4.43 4.36	14.80 14.51
5f	p.$N(CH_3)_2$-C_6H_4	56	150	$C_{28}H_{27}N_5O_3$ (481)	69.85 69.89	5.61 5.58	14.55 14.57

hydroxide. The precipitate obtained was filtered, washed with water and crystallized from dioxane (Table 3).

Cyclization of compounds (4a,b) to compounds (3a,b):

One gram of compound (4a) or (4b) was added to sulphuric acid (10 ml) and left overnight. The mixture was diluted with water and filtered and the precipitate was washed with water, dried in air and crystallized from acetic acid to give the compounds (3a) or (3b) respectively.

2-N-substituted methylcarboxthiosemicarbazide-4-benzyl-1- (2H) phthalazinones (6):

A solution of acid hydrazide (1) (0.01 mol) and the appropriate isothiocyanate (0.01 mol) in dioxane (10 ml) was heated under reflux for one

Table 4: Physical and analytical data of compounds (6-8)

Comp.	R	Yield	m.p.°C	M.F.M.Wt.	Analysis (Calc./F.)		
					C%	H%	N%
6a	C_2H_5	85	225	$C_{20}H_{21}N_5O_2S$ (385)	60.75 60.71	5.32 5.34	17.72 17.69
6b	C_6H_5	79	240	$C_{24}H_{21}N_5O_2S$ (433)	65.01 65.03	4.74 4.70	15.80 15.78
6c	p.F-C_6H_4	71	210	$C_{24}H_{20}FN_5O_2S$ (451)	62.47 62.47	4.34 4.31	15.18 15.20
7a	C_2H_5	60	260	$C_{20}H_{19}N_5OS$ (367)	63.66 63.63	5.04 5.02	18.57 18.53
7b	C_6H_5	73	280	$C_{24}H_{19}N_5OS$ (415)	67.76 67.78	4.47 4.45	16.47 16.49
7c	p.F-C_6H_4	67	225	$C_{24}H_{18}FN_5OS$ (433)	65.01 65.03	4.06 4.08	15.80 15.77
8a	C_2H_5	77	305	$C_{20}H_{19}N_5OS$ (367)	63.66 63.68	5.04 5.06	18.57 18.51
8b	C_6H_5	62	310	$C_{24}H_{19}N_5OS$ (415)	67.76 67.79	4.47 4.44	16.47 16.45
8c	p.F-C_6H_4	58	262	$C_{24}H_{18}FN_5OS$ (433)	65.07 65.04	4.06 4.04	15.80 15.82

hour. The resulting solution is cooled, diluted with water and where a crystalline precipitate was formed filtered, washed with water and crystallized from aqueous ethanol (Table 4).

2-(4-substituted-5-mercapto-S-5-triazol-3-yl-methyl)-4- benzyl-l-(2H) phthalazinones (7):

One gram of compound (6) was refluxed with 2N aqueous sodium hydroxide solution (20 ml) for 2 hours. The solution was cooled and neutralized with dilute hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from aqueous dioxane (Table 4).

2-(5-substituted amino-1,3,4-thiaiazol-2-yl-methyl)-4-benzyl- 1-(2H) phthalazinones (8):

One gram of compound (6) was added to sulphuric acid (10 ml) and heated with stirring for one hour at 120°C, then cooled and 40 ml of water was added. The reaction mixture was neutralized with ammonia solution and the precipitated product was filtered off, washed with water, dried and crystallized from ethanol (Table 4).

2-(4-amino-5-mercapto-S-triazol-3-yl-methyl)-4-benzyl-1-(2H) phthalazinone (9):

The acid hydrazide (1) (0.01 mol) was added to ethanolic KOH (absolute alcohol 100 ml, KOH 1.6 gm) at room temperature. Carbon disulphide was added (2.3 gm, 0.013 mol) and the mixture stirred at room temperature for 10 hours until a saffron coloured product precipitated. The mixture was diluted with ether (100 ml) and stirred for further 1 hour. The separated solid was filtered, washed with ether and dried m.p. 135°C. The potassium salt was used for the next stage without further purification. Hydrazine hydrate (99%) (0.02 mol) was gradually added to the above potassium salt (0.01 mol) dissolved in water (40 ml) with stirring and the mixture was refluxed gently for 3 hours during which hydrogen sulphide evolved and the

colour of the reaction mixture changed to high green colour. The resulting solution was diluted with water (30 ml), cooled to 5°C and acidified with concentrated HCl to pH 1.00. When a yellow solid separated out, it was filtered washed with cold water and crystallized from ethanol to afford the triazole (9) of m.p. 180°C. ($C_{18}H_{16}N_6OS$) (364) (Calc. C, 59.34; H, 4.39; N, 23.08) (found. C, 59.31; H, 4.37; N, 23.09).

2-(6-aryl-(7H)-S-triazolo[3,4-b]1,3,4-thiadiazin-yl-methyl)- 4- benzyl-1-(2H)-phthalazinones (10)

A mixture of compound (9) (0.01 mol) and the appropriate p- substituted phenacyl bromides (0.01 mol) in anhydrous ethanol (40 ml) was heated under reflux for 5 hours. After cooling, the mixture was neutralized with concentrated ammonia solution and the separated free base was filtered, washed with water and crystallized from ethanol. For compound (10a) R = C_6H_5 m.p. 189°C, ($C_{26}H_{20}N_6OS$) (464) (Calc. C, 67.24; H, 4.31; N, 18.10) (Found. C, 67.22; H, 4.33; N, 18.13). For compound (10b) R = p-Br-C_6H_4-; m.p. 172°C; ($C_{26}H_{19}BrN_6OS$) (543); (Calc. C, 57.46; H, 3.50; N, 15.74) (Found. C, 57.44; H, 3.47; N, 15.45).

2-(6-aryl-S-triazolo-[3,4-b]-1,3,4-thiadiazol-3-yl-methyl)-4- benzyl-1-(2H) phthalazinones (11):

A mixture of equimolecular amounts (0.01 mol) of compound (9) and the appropriate acid chloride in 10 ml pyridine was heated under reflux for ten hours. The reaction mixture was then cooled, diluted with water and acidified with HCl. The precipitated product was separated by filteration and crystallized from ethanol to give compounds (11). For compound (11a) R = C_6H_5-; m.p. 195°C ($C_{25}H_{18}N_6OS$) (450) (Calc. C, 66.66; H, 4.00, N, 18.66) (Found. C, 66.62; H, 4.02; N, 18.63). For compound (11b) R = p.Cl-C_6H_4-, m.p. 167°C, ($C_{25}H_{17}ClN_6OS$) (484.5), (Calc. C, 61.91; H, 3.51; N, 17.34) (Found. C, 61.89; H, 3.48; N, 17.31).

2-(2,5-dimethylpyrrol-1-yl-aminocarbonylmethyl)-4-benzyl-1- (2H) phthalazinone (12):

A mixture of acid hydrazide (1) (0.01 mol) and 2,5-hexadione (0.01 mol) in glacial acetic acid (30 ml) was stirred at room temperature for 12 hours. The reaction mixture was diluted with water, the separated solid was filtered off and recrystallized from dioxane to give compound (12) in 60% yield, m.p. 225°C, ($C_{23}H_{22}N_4O_2$) (386), (Calc. C, 71.50; H, 5.70; N, 14.51) (Found. C, 71.53; H, 5.87; N, 14.54).

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