SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 6-ARYL-1,2,4 TRIAZOLO (3,4-a) PHTHALAZINES AND 6-ARYL-TETRAZOLO (5,1,-a) PHTHALAZINES

MOHAMMED A.E. SHABAN*
MAMDOUH A.M. TAHA**
ADEL Z. NASR**

SUMMARY: Reaction of 1-hydrazino-4-phenylphthalazine and 4-benzyl-1-hydrazinophthalazine with aromatic aldehydes gave the corresponding colored hydrazones. Catalytic dehydrogenative cyclization of these hydrazones afforded the 3,6-diaryl-1,2,4-triazolo (3,4-a) phthalazines. The latter compounds were also obtained from the reaction of 1-chloro-4-phenylphthalazine and 4-benzyl-1-chlorophthalazine with aromatic acid hydrazides. Oxalic and malonic acid dihydrazides reacted with two equivalents of the former imidoyl chloride to give bis-triazolophthalazine derivatives. Reaction of the two imidoyl chlorides with sodium azide gave the corresponding 6-aryl-tetrazolo (5, 1-a) phthalazines. Some of the prepared compounds were tested for their insecticidal and nematicidal activities and found to be inactive.

Key Words: Amidrazones, imidoyl chlorides, triazoles, tetrasoles, phthalazines.

INTRODUCTION

The chemistry of phthalazine derivatives has been of increasing interest since many of these compounds have found chemotherapeutic applications (1-3), especially as antihypertensive agents (1). Several phthalazines were found to exhibit tuberculostatic activity both *in vitro* and *in vivo* (2). It has also been reported that while several nitrogen heterocyclic Schiff bases possess biological activities as bactericides (4) and fungicides (5), some 1,2,4-triazolophthalazines showed anti-inflammatory (6), hypotensive, and cardiovascular (7) activities. Ishii *et al.* (8) reported that 1,2,4-triazolo (3,4-a) phthalazine, and 3-one, 3-methyl-1,2,4-triazolo (3,4-a) phthalazine, and 3-ethyl-1,2,4-triazolo (3,4-a) phthalazine, which are metabolites of the active hypotensive drugs "ecarazine" (1-ethoxycarbonylhydrazino-pthalazine) and "hydralazine" (1-hydrazinophthalazine), were potent inhibitors of cyclic adenosine monophosphate phosphodiesterase, equal to theophlylline in potency and that they possess smooth muscle relaxant activity. It was of interest, therefore, to synthesize the title compounds.

*From Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt.
**Department of Chemistry, Faculty of Education, Cairo University (Fayoum Branch), Egypt.

RESULTS AND DISCUSSION

Condensation of 1-hydrazino-4-phenylphthalazine (1) (3,9) or 4-benzyl-1-hydrazinophthalazine (2) (10) with aromatic aldehydes gave the corresponding yellow, or red hydrazones (3-14). The products were dicisively assigned hydrazone structures on the basis of their ir spectra which showed NH bands at 3400-3600 cm^{-1} and their pmr spectra which revealed the hydrazone NH signals as deuteratable one-proton singlets at δ 10.52-10.90. The

Table 1: Physical Properties and Spectral Data of aldehyde (4-aryl-1-phthalaziny) hydrazones.

Comp. No					Analyses (%) Calcd/Found			Ir ν^{KBr} cm^{-1}		Pmr (δ) ppm (a), $CDCl_3$		
	Ar	Yield %	Mp (C)	Molecular Formula	C	H	N	NH	C=N	MH (b) (s)	aromatic H +-CH=N-(m)	CHp (s)
3	C_6H_5	73	160-163	$C_{21}H_{16}N_4$. $1/2H_2O$	75.68	5.11	16.82	3450	1600	10.90	8.55-7.10 (15H)	-
					76.10	5.50	16.70					
4	p-$OMeC_6H_4$	73	160	$C_{22}H_{18}N_4O$. $1/2H_2O$	70.97	5.38	15.05	3360	1623	-	8.80-7.33 (13H)	-
					70.41	5.52	14.81					
5	p-$NMe_2C_6H_4$	58	170-172	$C_{23}H_{21}N_5$	75.20	5.72	19.07	3400	1610	10.60	8.54-7.30 (14H)	-
					74.70	5.80	18.60					
6	p-ClC_6H_4	66	195-198	$C_{21}H_{15}N_4Cl$	70.20	4.18	15.60	3420	1623	10.72	8.60-7.25 (14H)	-
					69.62	4.43	15.73					
7	p-BrC_6H_4	58.5	190	$C_{21}H_{15}N_4Br$	62.53	3.72	13.90	3420	1625	10.84	8.46-7.33 (14H)	-
					62.63	3.66	13.95					
8	p-$NO_2C_6H_4$	64	260-263	$C_{21}H_{15}N_5O_2$. $2H_2O$	62.22	4.69	17.28	3400	1635	10.75	8.56-7.32 (14H)	-
					61.60	4.10	17.88					
9	C_6H_5	74	85-88	$C_{22}H_{18}N_4O$. $1/2H_2O$	76.08	5.48	16.14	3420	1620	10.70	8.60-7.15 (15H)	4.80
					76.60	5.50	15.50					
10	p-$OMeC_6H_4$	54	135-138	$C_{23}H_{20}N_4O$	75.00	5.44	15.22	3420	1630	10.64	8.60-7.00 (14H)	4.10
					74.50	5.60	14.50					
11	p-$NMe_2C_6H_4$	46	160-163	$C_{24}H_{23}N5_4O$. $1/2H_2O$	73.85	6.15	17.95	3400	1610	10.52	8.46-7.00 (14H)	4.05
					73.96	5.99	17.53					
12	p-ClC_6H_4	60	210-212	$C_{22}H_{17}N_4Cl$	70.87	4.56	15.00	3400	1625	10.64	8.50-6.90 (14H)	4.06
					70.45	4.69	14.90					
13	p-BrC_6H_4	48	198-200	$C_{22}H_{17}N_4Br$	63.31	4.08	13.43	3360	1620	10.59	8.53-7.00 (14H)	4.15
					62.80	4.50	13.50					
14	p-$NO_2C_6H_4$	65	255-258	$C_{22}H_{17}N_5O_2$	68.93	4.44	18.28	3400	1630	10.65	8.56-7.04 (14H)	4.20
					68.90	4.60	18.14					

(a) Multiplicies: s=singlet; m=multiplet, (b) Deuteratable

azomethine protons (-CH = N-) of these hydrazones were included in the downfield absorptions of the aromatic protons (Table 1). Catalytic dehydrogenative cyclization of the prepared hydrazones (3-14) by heating their methanolic solutions with 10% palladium-on-charcoal gave the corresponding 3, 6-diaryl-1,2, 4-triazolo (3,4-a) phthalazines 15-29). These compounds lacked the ir NH absorption and the azomethine proton signal present in the spectra of the parent hydrazones (Table 2). Compounds (15-29) were also prepared by the reaction of the cyclic imidoyl chlorides 30 and 31 (9,10) with the appropriate aroylhydrazine. The un-isolable intermediate hydrazides 32 were formed and concomitantly dehydratively cyclized to the triazolopthalazines (15-29).

Reaction of two equivalents 30 with oxalic and malonic of acid dihydrazides yielded the bis (6-phenyl-1,2,4-triazolo (3,4-a) phthalazin-3-yl) (33) and bis (6-phenyl-1,2,4-triazolo (3-4a) phthalazin-3-yl) methane (34).

The ir spectra of the products obtained from the reaction of 30 and 31 with sodium azide did not show absorption bands at 2130 cm^{-1} diagnostic of azido functions (11) and were, consequently, assigned the structure of 6-penyl-and 6-benzyl-tetrazolo (5, 1-a) pthalazines 35 and 36, respectively.

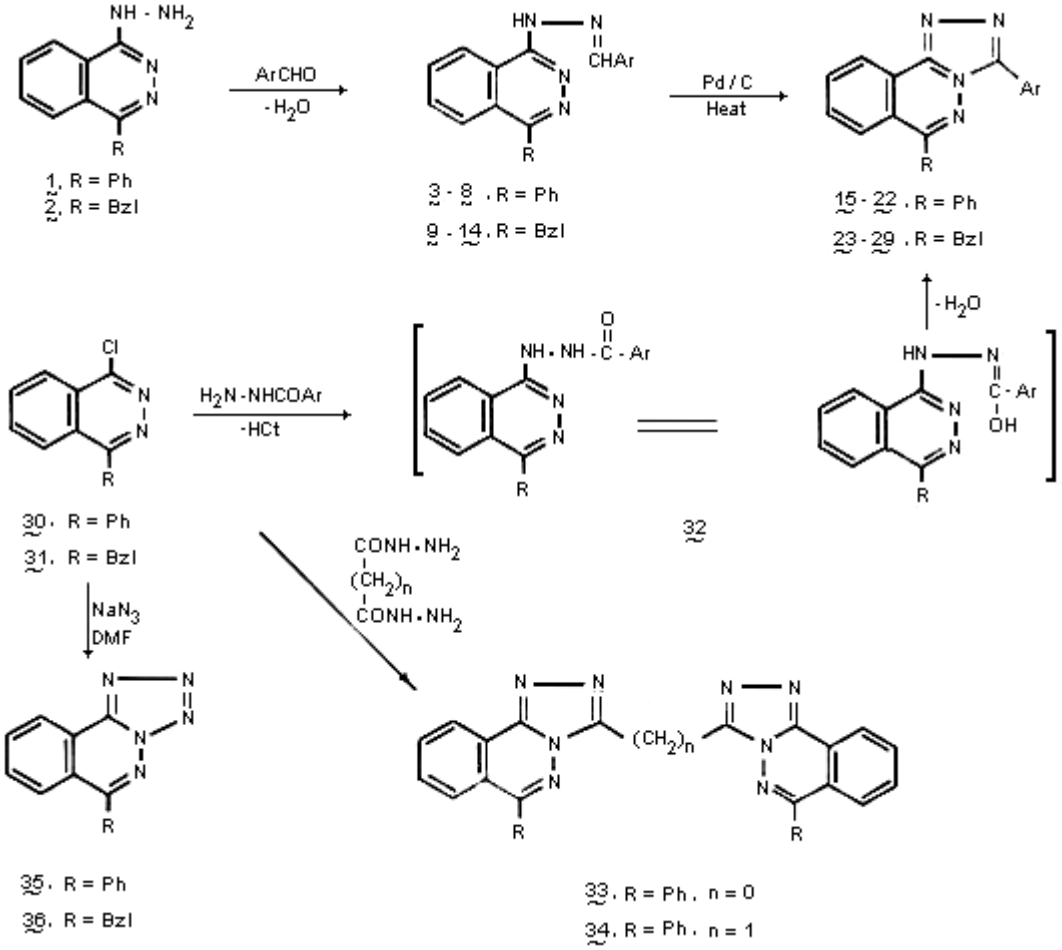
Table 2: Physical Properties and Spectral Data of 3,6-Diaryl-1,2,4-Triozolo (3,4-a) phthalazines.

Comp. No	Ar	Yield %	Method of prep.	MP (C)	Molecular Formula	Analyses (%) Calcd/Found			Ir v KBr cm^{-1}	Pmr (δ) ppm (a), $CDCl_3$	
						C	H	N	C=N	aromatic H +-CH=N-(m)	CH_2 hp(s)
15	C_6H_5	67	A, B	282-285	$C_{21}H_{14}N_4$	78.26	4.35	17.39	1620	8.95-7.40 (14H)	-
						78.37	4.67	17.30			
16	p-MeC_6H_4	72	B	290-293	$C_{22}H_{16}N_4$	78.57	4.76	16.67	1615	8.90-7.30 (13H)	-
						77.95	5.10	16.20			
17	p-$OMeC_6H_4$	62	A, B	298-302	$C_{22}H_{16}N4_4O$	75.00	4.55	15.91	1620	8.98-7.45 (13H)	-
						74.70	4.70	15.60			
18	p-$NMe_2C_6H_4$	60	A	290-293	$C_{23}H_{19}N_{15}$. $1/2H_2O$	73.80	5.35	18.72	1620	8.88-7.42 (13H)	-
						74.30	5.59	18.60			
19	p-ClC_6H_4	61	A, B	285-288	$C_{21}H_{13}N_4Cl$	70.59	3.64	15.69	1620	8.75-7.25 (13H)	-
						70.68	3.25	15.70			
20	p-BrC_6H_4	66	A, B	269-273	$C_{21}H_{13}N_4Br$	62.84	3.24	13.97	1600	8.80-7.38 (13H)	-
						62.35	2.72	14.30			
21	p-IC_6H_4	64	B	272-276	$C_{21}H_{13}N_4I$	56.25	2.90	12.50	1620	8.96-7.50 (13H)	-
						55.98	2.59	12.87			
22	p-$NO_2C_6H_4$	79	A, B	320	$C_{21}H_{13}N_5O_2$. $1/2H_2O$	67.02	3.72	18.62	1600	8.95-7.46 (13H)	
						67.02	3.80	18.50			
23	C_6H_5	61	A, B	255	$C_{22}H_{16}N_4$. $1/2H_2O$	76.52	4.93	16.23	1620	8.80-7.07 (14H)	4.25
						76.20	5.00	16.20			
24	p-MeC_6H_4	58	B	279-281	$C_{23}H_{18}N_4$. $1/2H_2O$	76.88	5.29	15.59	1610	8.80-7.05 (13H)	4.53
						77.03	5.42	15.42			
25	p-$OMeC_6H_4$	70	A, B	242-245	$C_{23}H_{18}N_4O$. $1/2H_2O$	73.60	5.07	14.93	1620	8.75-6.88 (13H)	4.50
						73.80	5.10	14.71			
26	p-$NMe_2C_6H_4$	60	A	258-260	$C_{24}H_{21}N_5O.2$ $1/2H_2O$	67.92	6.13	-	1605	8.80-7.20 (13H)	4.55
						68.05	5.69	-			
27	p-ClC_6H_4	69	A, B	265-268	$C_{22}H_{15}N_4Cl.3H_2O$	62.19	4.95	13.19	1630	8.80-7.22 (13H)	4.53
						62.52	5.64	12.88			
28	p-BrC_6H_4	55	A, B	275-278	$C_{22}H_{15}N_4Br.1/2H_2O$	62.26	3.77	-	1630	8.90-7.35 (13H)	4.67
						62.40	4.40	-			
29	p-$NO_2C_6H_4$	60	A, B	295-298	$C_{22}H_{15}N_5O_2$	69.29	3.94	18.37	1600	8.85-7.26 (13H)	4.60
						68.60	3.90	17.74			

(a) Multiplicies: s=singlet; m=multiplet, (b) Deuteratable

Compounds 19, 22, 33, and 34 showed no insecticidal activity when applied at the rate of 1000 ppm to the following insect species/host plant systems: Mexican beet beetls (*Epilachna varivestis* Muslant)/pinto bean (*Phaseolus vulgaris*); pea aphid (*Acyrthosiphon pisum* Harris)/fave bean (*Vicia faba*); southern armyworm (*Spodoptera eridania* Grammer)/pinto bean; and the two-spotted spider mite (*Tetranychus urticae*)/pinto bean.

Compounds 3, 6, 8, 15, 19, 22 and 34 also showed no nematicidal activity at an application rate of 10 ppm against root-knot nematode (*Meloidogyne incognita*) hosted on cucumber (*Cucumis sativus*).



MATERIALS AND METHODS

Melting points were determined with a kofler block and are uncorrected. Infrared spectra (ir) were recorded for potassium bromide discs on Unicam SP-1025 or Pye-Unicam SP-2000 spectrophotometers. Proton magnetic resonance spectra (pmr) were recorded at 90 MHz with an EM-390 spectrometer for solutions in $CDCl_3$. Follow up of the reactions and checking the homogeneity of the prepared compounds were made by thin-layer chromatography (tlc) on Silica gel G (Merck) precoated plates (layer thickness 0.25 mm) used without pretratment. The distance of solvent travel was 5 cm and the sports were detected by exposition to iodine vapour. All solvent evaporations were performed in a rotary evaporator under diminished pressure, with an outside bath temperature kept below 50°C. Elemental microanalyses were performed in the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, Alexandria University using a Perkin-Elmer model PE-240 analyzer and in the Microanalysis Unit, Cairo University, Cairo, Egypt.

Aldehyde (4-aryl-1-phthalazinyl) hydrazones (3 - 14).

To a solution of 1-hydrazino-4-phenylphthalazine (3, 9) (1, 0.004 mole) or 4-benzyl-1-hydrazinophthalazine (10) (2, 0.004 mole) in methanol (20 ml), a solution of the aromatic aldehyde (0.004 mole) in methanol (10 ml) was added and the mixture was heated for 15 minutes on a boiling water-bath. The product which separated upon cooling, was filtered, washed, and crystallized from chloroform (Table 1).

3.6-Diaryl-1, 2,4-triazolo (3,4-a) phthalazines (15-29).

Method A:

A solution of the aldehyde (4-phenyl-1-phthalazinyl) hydrazone (3 - 8, 0.003 mole) or aldehyde (4-benzyl-1-phthalazinyl) hydrazone (9 - 14, 0.003 mole) in methanol (50 ml) was treated with 10% palladium-on-charcoal (0.6 g) and heated under reflux for 2 hours. The mixture was left to attain ambient temperature and the catalyst was filtered on a layer of celite. Evaporation of most of the solvent gave the product which was filtered, washed, and crystallized from chloroform (Table 2).

Method B:

A solution of the appropriate aroylhydrazine (0.004 mole) in methanol (15 ml) was treated with 1-chloro-4-phenylphthalazine (9) (30, 0.004 mole) or 4-benzyl-1-chlorophthalazine (10) (31, 0.004 mole) in the same solvent (15 ml) and the mixture was heated for 20 minutes on a boiling water-bath. The mixture was allowed to attain ambient temperature and the product which separated was filtered, washed with methanol and crystallized from chloroform (Table 2).

Bis (6-phenyl-1, 2, 4-triazolo (3,4-a) phthalazin-3-yl) (33).

1-chloro-4-phenylphthalazine (30, 1 g) was gradually added to a boiling solution of oxalic acid dihydrazide (0.25 g) in methanol (40 ml) and the mixture was refluxed for one hour. The product which separated upon cooling was filtered, washed methanol, and crystallized from chloroform to give 0.8 g (78%) of 33 mp > 330°; tlc in 9:1 chloroform: methanol, R+: 0.50; υ^{KBr} 1650 and 1625 cm^{-1} (C = N); pmr ($CDCl_3$: δ 9.00-716 (m, 18H, aromatic H).

Anal. Calcd. for $C_{30}H_{18}N_8 1/2H_2O$: C, 72.14; H, 3.81; N, 22.45. Found: C, 71.58; H, 3.99; N, 22.50.

Bis (6-phenyl-1, 2, 4-triazolo (3,4 a) phthalazin-3-yl) methane (34).

To a solution of 30 (1 g) in benzene (20 ml) a solution of malonic acid dihydrazide (0.27 g) in benzene (20 ml) was added and the mixture was heated under reflux for one hour. The product which separated upon cooling was filtered, washed with benzene, and crystallized from chloroform to give 0.7 (67%) of 34, mp 305-308°; tlc in 9:1 chloroform: methanol, R+: 0.45; υ^{KBr} 1620 cm^{-1} (C=N) pmr ($CDCl_3$): δ 8.76-7.71 (m, 18H, aromatic H) and 5.15 (s, 2H, CH_2).

Anal. Calcd. for $C_{31}N_{20}N_8$: C, 73.81; H, 3.97; N, 22.22. Found: C, 73.80; H, 4.30; N, 21.50.

6-Phenyl-tetrazolo (5, 1-a) phthalazine (35).

A solution of 30 (1 g) in dry dimethylformamide (15 ml) was treated with sodium azide (0.3 g) and the mixture was heated under reflux for 4 hours. The reaction mixture was allowed to attain ambient temperature and then poured onto crushed ice. The product which separated was filtered, washed several times with water, and crystallized from methanol-chloroform to give 0.7 (68%) of 35, mp 210-212°; tlc in 9:1 chloroform: methanol, R+: 0.60; υ^{KBr} 1615 cm^{-1} (C=N); pmr ($CDCl_3$): δ 8.95-7.52 (m, 9H, aromatic H).

Anal. Calcd. for $C_{14}H_9N_5$: C, 68.02; H, 3.64; N, 28.34. Found: C, 67.75, H, 3.90; N, 28.80.

6-Benzyl-tetrazolo (5, 1-a) phthalazine (36).

The title compound (36) was prepared from 31 (1 g) and sodium azide (0.3 g) as described for the preparation of 35 (yield: 0.8 g, 78%); mp 120-123°; tlc in 9:1 chloroform: methanol, R+: 0.65; υ^{KBr} 1630 cm^{-1} (C=N); pmr ($CDCl_3$): δ 8.75-7.00 (m, 9H, aromatic H) and 4.56 (s, 2H, CH_2ph).

Anal. Calcd. for $C_{15}H_{11}N_5$: C, 68.97; H, 4.22; N, 26.82. Found: C, 68.80; H, 4.35; N, 26.70.

REFERENCES

1. De Stevens G : Medicinal Research Reviews, Wiley-Interscience New York. NY, Vol 1, p 73, 1981.

2. Drain DJ, Seymour DE : Some compounds related to 1:2-dihydro-hydroxy-1-oxo-2-phenylphthalazine. J Chem Soc, 852-855, 1955.

3. Druey J, Ringier BH : Hydrazinderivate der phthalazin und pyridazinreihe. Helv Chim Acta, 34:195-210, 1951.

4. Attia A, Islam AM, El-Maghraby AA, Ammar Y : Synthesis of newer xanthotoxin derivatives with potential antibacterial effects. J Prakt Chem, 321(6):1036-1046, 1979.

5. Badawi A, El-Maghraby AA, Haroun B, Soliman H : Dihydroxybenzene derivatives of antimicrobial activity. Pharmazie 35(12):748-751, 1980.

6. Kadota M, Honda K : 1,2,4-triazolo (3,4-a) (5,6,7,8) tetrahydrophthalazines, Japan Patent 78, 21, 197, (1978); Chem. Abstr, 89:43471 J, 1978.

7. Faid-Allah HM, Soliman R : Synthesis and spectra of some triazolo and tirazinophthalazines of possible hypotensive activity. J Heterocycl Chem, 24:667-671, 1987.

8. Iszhii A, Kubo K, Deguchi T, Tanaka M : Inhibition of cyclic AMP phosphodiesterase activity by ecarazine hydrochloride, hydralazine and their metabolites. Yakugaku Zasshi 99(5):533-536, (1979); Chem Abstr, 91; 133826 z, 1979.

9. Shaban MAE : unpublished results.

10. Shaban MAE, Taha MAM : unpublished results.

11. Reynolds GA, Van Allan JA, Tinker JF : Cyclization of heterocyclic azides, J Org Chem, 24:1205-1209, 1959.

Correspondence:
MAE Shaban
Department of Chemistry,
Faculty of Science,
Alexandria University,
Alexandria, EGYPT.