

STUDIES ON HYDRALAZINES - PART-IX: PREPARATION AND ANTIMICROBIAL ACTIVITY OF 1- (PHTHALAZIN-1'-YL- AMINO)-3-CHLORO-4-ARYL- 4H-(OR 4-METHYL)-2-AZETIDINONE

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Abstract

1- (Phthalazin-1'-yl-amino)-3-chloro-4-aryl-4H-(or 4-methyl)-2-azetidinones (**3**) were prepared by cycloaddition of-methyl substituted benzal hydrazinophthalazine (**2**) with chloro acetylchloride. The hydrazone (**2**) was synthesised by the condensation of 1- hydrazinophthalazine (**1**) with substituted aromatic aldehydes, ketones & acetophenones. 1- Hydrazinophthalazine was prepared from the phthalaldehydic acid. All the compounds thus synthesised (**2** and **3**) were tested against different species of bacterial and fungi. Their structures have been determined by NMR and Mass spectroscopy.

Introduction

1- Hydrazinophthalazine [1] is found to possess antihypertensive activity [2] and despite its side effect, i.e. systematic lupus erythematosus, it is being widely used. Taking into consideration the antihypertensive activity of 1- hydrazinophthalazine and to reduce its side effect by taking an advantage of blocking amino group, we have tried to synthesise a new derivative of 1- hydrazinophthalazine with incorporating azetidinone moiety in it. We would like to report the synthesis and antimicrobial activity of 1- (phthalazin-1'-yl amino)-3-chloro-4-aryl-4H (or methyl)-2-azetidinone (**3**) for the first time.

Results and Discussion

In the present study, we have condensed 1- hydrazinophthalazine (**1**) with aromatic aldehyde and ketones to give 1- (substitued/ α - methyl benzal)

Keywords: 2-Azetidinone derivatives, Antibacterial Activity, Antifungal Activity

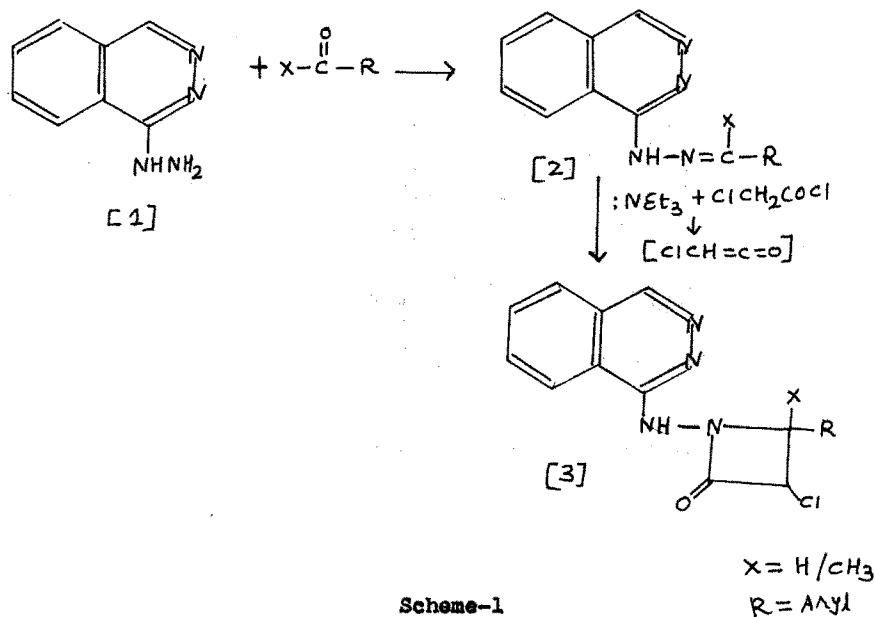
hydrazinophthalazine which, on reaction with chloroacetyl chloride and triethylamine in dioxan, afforded 1- (phthalazin-1'-yl amino)-3-chloro-4-aryl-2-azetidinone (Scheme-1, Table-1) through intermediate carbene formation.

Thus 1-hydrazinophthalazine [1] which was prepared from phthaladehydic acid was condensed with different substituted aromatic aldehyde and ketone to yield hydrazone of type-2. The NMR and MS spectrum was totally in agreement with the proposed structure.

Reaction of chloroacetylchloride and triethylamine with **2** in 1,4- dioxane gave azetidinone of type-3. The constitution of the product was supported by mass spectral study.

Experimental Section

All the melting points are uncorrected. The IR spectra were recorded on Shimadzu DR-1, 435-IR spectrophotometer using KBr pellet in the range of 4000



Scheme-1

Table 1- Physical constants of 1-(Methyl substituted benzal) hydrazinophthalazine (2-a) and 1-(phthalazin-1-yl-amino)-3-chloro-4-aryl-methyl-2-Azetidinone (3-a).

Sl. No.	R	Hydrazones of type 2		Azetidinone of type 3	
		Yield %	M.P. °C	Yield %	M.P. °C
1.	2- Aminophenyl	65	206	55	300
2.	3- Aminophenyl	72	142	57	129(d)
3.	4-Aminophenyl	69	191	53	300
4.	2,4- Dihydroxyphenyl	48	240	56	oily
5.	2,5- Dihydroxyphenyl	86	208	64	144
6.	2,6- Dihydroxyphenyl	60	213	58	oily
7.	4- Ethoxyphenyl	66	196	57	149
8.	2- Hydroxy-5- methylphenyl	71	211	48	101
9.	2- Hydroxyphenyl	49	215	59	118
10.	3- Hydroxyphenyl	52	185	61	oily
11.	4-Hydroxyphenyl	63	232	58	oily
12.	1-Naphthyl	75	220	53	300
13.	2- Naphthyl	78	210	89	171-3
14.	4- Nitrophenyl	72	235	54	300
15.	2- (1-Thienyl)	64	121	62	300
16.	Phenyl*	-	-	52	245-7

*Reported

to 400 cm^{-1} . NMR spectra were recorded on Varian CFT-20 (200 MHz) using tetramethylsilane as internal standard and Mass spectra were recorded on Varian BG-7070F mass spectrometer at 90 ev.

Preparation of 1-(α -methyl benzal) hydrazinophthalazine (2):

1- Hydrazinophthalazine (1.60 gm, 0.01 mole) in methanol (10 ml) was refluxed in a water bath for 20-30 min. with acetophenone (0.01 mole). The reaction mixture was then cooled to give the product. It was crystallised from ethanol. Yield 72%, M.P. 151°C. IR max (KBr pellet) in cm^{-1} : 3350 (N-H sec. str. assym.), 2900, 1440, 1370 (C-H str. asym., def. asym., & sym.), 1610 (N=C str.), 1590, 1570, 1470, 1410 (C=C + C=N & Ring str.), NMR (CDCl_3): 10.49 (s, 1H, -NH), 7.6-8.5 (m, 5H, Ar-H), 7.23-7.55 (m, 4H, Ar-H), 2.58 (s, 3H, C- CH_3); MS m/z (%) 262 (M^+ , 26), 247 (M^+ - CH_3 , 100) (base peak), 185 (M^+ - C_6H_5 , 43), 144 (M^+ - $\text{NC}(\text{CH}_3)\text{C}_6\text{H}_5$), 131(14), 129(6), 119(9), 103(18), 89(14), 77(27), 63(5), 57(5), 57(14). (Found: C, 62.41; H, 4.15; N, 22.75; $\text{C}_{16}\text{H}_{14}\text{N}_4$ required C, 62.54; H, 4.23; N, 22.80 %).

Similarly, other hydrazones of type-2(a) were

prepared by condensing 1-hydrazinophthalazine with different acetophenone. Their physical data are recorded in Table-I. Various aromatic aldehydes were condensed with compound-1 to get Schiff's bases [3] of type-2(b).

Preparation of 1-(phthalazin-1'-yl-amino)-3-chloro-4-aryl-4-methyl-2-azetidinone (3):

To 1-(α -methyl benzal) hydrazinophthalazine (2.62 gm, 0.01 mole) in dry 1,4-dioxane (25 ml) chloroacetylchloride (2.24 ml, 0.02 mole) was added slowly at room temperature and stirred constantly. After adding triethylamine (1.08 ml, 0.02 mol) the reaction mixture was stirred and kept for three days at room temperature (25°C). The reaction mixture was then poured on crushed ice, filtered and washed with cold water. The product was crystallised from ethanol. The purity of the product was checked by TLC and column chromatographed with Alumina (neutral) with chloroform as eluting solvent. Yield: 54%, M.P. 245°C. IR (KBr pellet) max cm^{-1} 3300 (N-H sec. str. asym.), 1660 (C=O str.), 740 (C-Cl), 1610 (C=C + C=N str. phthalazine moiety), MS: m/z (%) 338 (M^+ %) 302(5), 287(9), 279(14), 256(11), 213(5), 185(7), 169(5), 167(23), 155(6), 149(51), 113(23), 111(24), 105(7), 97(36), 93(11), 91(7), 79(10), 77(8), 67(27), 57(100, base peak), 55(66), 53(8); (Found: C, 63.75; H, 4.38;

Table 2- PHYSICAL CONSTANTS OF 1-(PHTHALAZIN-1'-YL-AMINO)-3-CHLORO-4-ARYL-2-AZETIDINONE: (3-b)

Sr. No.	R	M.P. °C	Yield %
1.	Phenyl	183	54
2.	2- Hydroxyphenyl	195	60
3.	4- Hydroxyphenyl	326	62
4.	3- Anisyl	124	55
5.	4- Anisyl	160	54
6.	3,4- Dimethoxyphenyl	171	50
7.	3- Methoxy-4-hydroxyphenyl	161	45
8.	4- Dimethylaminophenyl	179	48
9.	3- Nitrophenyl	175	59
10.	4- Nitrophenyl	232	48
11.	2- Chlorophenyl	135	46
12.	4- Chlorophenyl	155	52
13.	2,6- Dichlorophenyl	132	50
14.	2,4- Dichlorophenyl	176	45
15.	Cinnamyl	168d	52

N, 16.39; C₁₈H₁₅ClN₄O required: C, 63.81; H, 4.43; N, 16.54 %).

Similarly, other hydrazones of type-2 (a) and (b) were condensed with chloroacetylchloride. Their physical data are recorded in Tables I and II respectively.

Antimicrobial Activity [4]:

Antibacterial and Antifungal activity of the purified product were tested against different species of bacteria and fungi at a concentration of 50 ug/ml in DMF using the cup-plate method. The gram positive bacteria used were *S. aureus*, *S. citreus*, *B. magaterium*, *B. subtilis* and gram negative bacteria were *P. aeruginosa*, *P. fluorescence* and *E. coli*. Antifungal activity was tested against *A. flavus*, *A. niger* and *C. albicans*.

The comparable antibacterial and antifungal activity was observed in compound (3a) having R= 3-hydroxyphenyl and was active against all the bacteria and fungi tested and results were comparable with standards i.e. ampicillin and cephalixin.

The comparable activity were observed in compound 3(b) having R= 4'-dimethylaminophenyl, 3'-nitrophenyl, 2',6'- dichlorophenyl, 2',4'- dichlorophenyl

against *B. magaterium*, 3- Anisyl, 3- methoxy-4'-hydroxyphenyl, cinnamyl, against *B. subtilis*; 3-methoxy-4'-hydroxyphenyl, 4'- dimethylaminophenyl against *P. aeruginosa*, 4'- hydroxyphenyl against *E. coli*.

The comparable antifungal activity was observed in compound 3(b) having R=2'- chlorophenyl against *A. niger*.

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