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Synthesis and antimicrobial activity of some pyridazinone derivatives

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ABSTRACT

Some new 6-phenyl–Pyridazine-3-One were synthesized by hydrazinolysis of appropriate β-(substituted aryl) propionic acid, there were converted into corresponding Bis-pyridazinone (IIIa toIIId). All these synthesized compounds were characterized on the bases of spectral data and evaluated for their antimicrobial activity.

Key word: Pyridazine-3-One, Antibacterial activity, Antifungal activity.

INTRODUCTION

Pyridazinones have been reported to possess variety of biological activities like antinociceptive1, anticancer[2], and anticonvulsant[3], antithrombotic[4], and antiinflammatory[5-6] activity. In present work we report the synthesis of compounds and their antimicrobial activity which is not done earlier and is quite significant.

Reaction between benzene with succinic anhydride in the presence of aluminium chloride produced benzoyl propionic acid (step-I). The product obtained from step-I react with hydrazine hydrate to produced 6-phenyl-2,3,4,5-tetrahydro Pyridazin-3-one (step-II). After this the product obtained from step-II react with different aromatic benzaldehydes in the presence of Acetic anhydride to produce different derivatives (IIIa to IIId).

MATERIAL AND METHODS

Melting points were determined by open capillary tube method in liquid paraffin bath. All the reactions were monitored by thin layer chromatography (TLC) using Toluene: Ethyl acetate: Formic acid (5:4:1) as solvent system. IR spectra (Kbr disc) were recorded on FTIR Perkin Elmer. ^{1}H NMR spectra were recorded in DMSO using Bruker Avance-II 400 mHz NMR spectrophotometer. The chemical shifts were expressed in terms of ppm downfield from TMS. And the mass spectra were recorded on Jeol SX-102 (FAB) Mass Spectrometer.

Synthetic Study

Step-I

Synthesis of benzoyl propionic acid

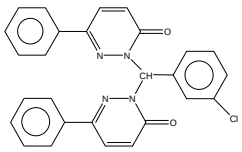
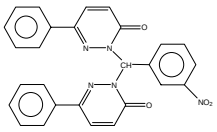
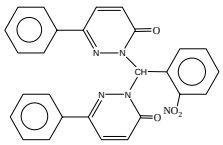
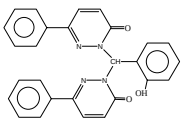
A mixture of benzene (30ml) and anhydrous aluminum chloride (0.10M) was refluxed on a water bath under anhydrous condition followed by addition of succinic anhydride (0.10M) in small quantities with continues stirring. Stirring and heating were continued for 4 hrs and the contents after leaving overnight at room temp were poured into ice cold hydrochloric acid (2.5% v/v) followed by steam distillation. The aqueous Solution was concentrated to a small volume by evaporating on a water bath to obtain the crude compound-(I). It was purified by dissolving in 5% w/v sodium bicarbonate solution, followed by extraction with

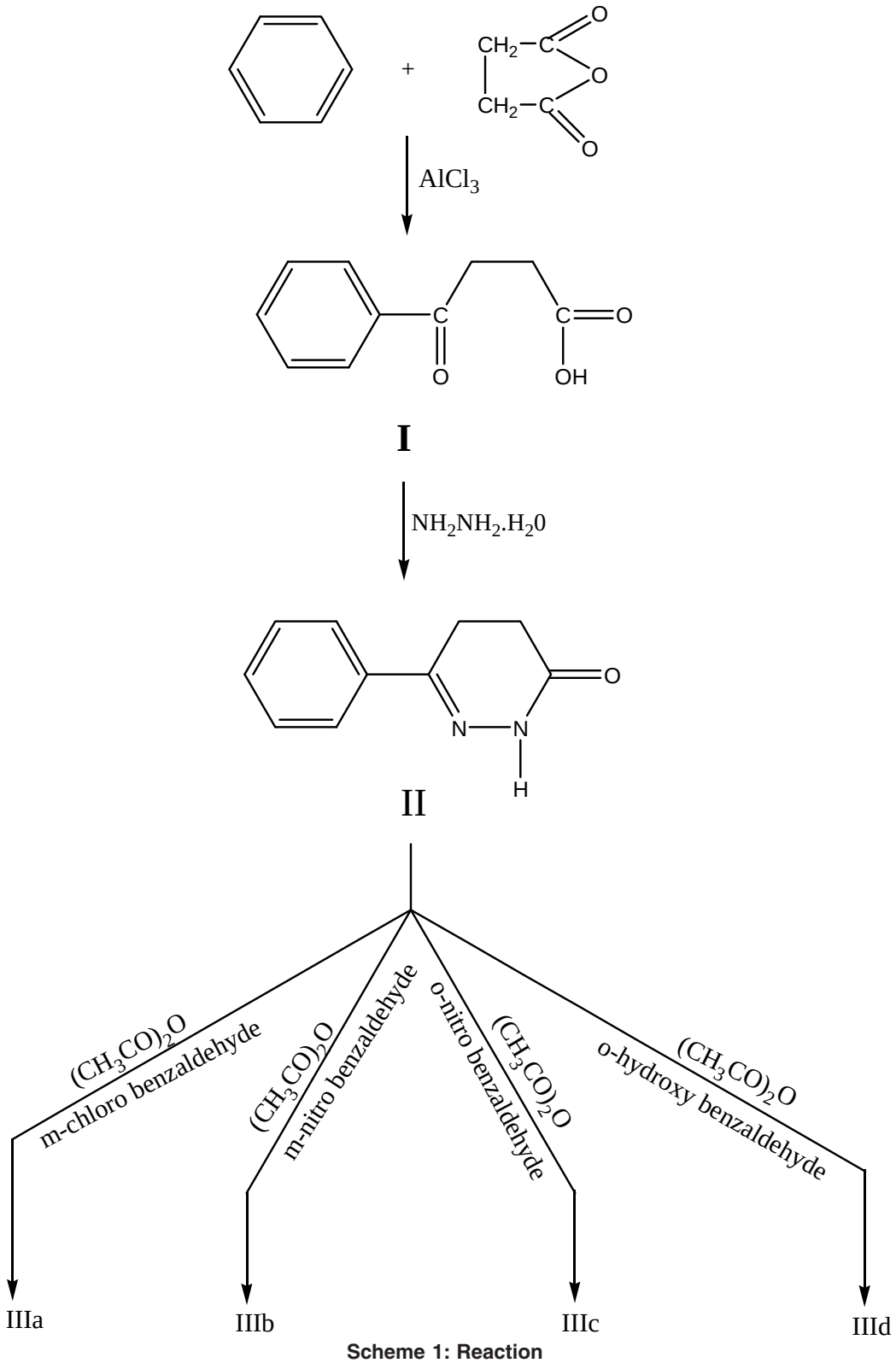
Table 1: Antimicrobial activity

S. No.	Compounds	Bacteria				Fungus	
		Gram-positive		Gram-negative			
		S. pyogen	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. niger*	*C. albicans*
1.	IIIa	+ + +	+ +	+ +	+++	+	+
2.	IIIb	+	+	-	-	-	-
3.	IIIc	+	-	+	-	-	-
4.	IIId	-	+ +	+	-	+ +	++
5.	Standard	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
6.	Control	-	-	-	-	-	-

Excellent : +++ , Very Good : ++ , Good : + , No Activity : - , Control : N.Saline(0.9%w/v)

Table 2: Structure & Physiochemical data of derivatives

S.No.	Compound	Structure of derivatives	I.U.P.A.C No	M.P.	Yield %	Rf value
1	IIIa		m-chloro phenyl di-(6-phenyl, Pyridazin-3-one-yl) Methane	185°C	65	0.65
2	IIIb		m-nitro phenyl di-(6-phenyl, Pyridazin-3-one-yl) Methane	205°C	72	0.55
3	IIIc		o-nitro phenyl di--(6-phenyl, Pyridazin-3-one-yl) Methane	160°C	55	0.62
4	IIId		O-Hydroxy phenyl-(6-phenyl, Pyridazin-3-one-yl) Methane	165°C	65	0.65



Scheme 1: Reaction

ether. The aqueous layer on acidification with dil. hydrochloric acid gave benzoyl propionic acid, crystallized from aq. ethanol.

M.P.122°C, Yield 70% , Rf 0.65

IR (cm^{-1}): 3250 (OH), 1720 (C=O), ^{1}H-NMR (δppm): 3.32(2H,m), 7.47(2H,m), 7.63(2H,m), 7.97(2H,m)

Step-II

Synthesis of 6-phenyl-2,3,4,5-tetrahydro pyridazin-3-one

Compound-I (0.1M) was refluxed for 8hrs with hydrazine hydrate (1ml) in ethanol (25ml). The reaction mixture was concentrated and then poured into ice cold water to obtain compound-(II) which was crystallized from ethanol.

M.P. 248°C, Yield 72% , Rf 0.60

IR (cm^{-1}): 3350 (NH), 1685 (C=O), ^{1}H-NMR (δppm): 5.7(1H,d), 6.49(1H,d), 7.0(4H,s), 7.5(3H,m), 7.9(2H,m).

Step-III

Compound-II (0.02M) was reflux with different aromatic benzaldehydes (0.01M) in the presence of acetic anhydride (10ml) for 26hrs and then poured into ice cold water to get compound-(IIIa-IIId) which was also crystallized from ethanol. Similarly other derivatives also prepared by the above method.

Antimicrobial activity

All the synthesized compound were screened for their antibacterial activity at concentration 50µg/ml against *Escherichia coli, Pseudomonas aureoginosa* (gram-ve) using Gentamycin as standard drug where as Ceftizoxime was used as standard against *Staphylococcus aureus* where as ampicilline was used as standard against *Staphylococcus pyogen* (gram +ve) by disc diffusion method. The zone of inhibition was measured and compared againt standard.

Table 3: Characterization of derivatives

S. No.	Derivatives	IR (cm^{-1})	^{1}H-NMR (δppm)	Mass Spectral data (m/z)
1	IIIa	C = O : 1683, C-H: 2923, C=N : 1623, C – Cl : 712, 1313	7.52 (6H,m), 7.98 (4H,m), 6.98 (1H, s), 5.7 (2H,s), 6.49 (2H,s) 7.27 – 7.52 (4H,m)	466.12
2	IIIb	Ar- C – H : 3100, 3084, C = O : 1684, Ar – NO_2 : 1347, 1523, C – H : 2923	7.52 (6H,m), 7.98 (4H,m), 6.98 (1H,s), 5.7 (2H,s), 6.49 (2H,s), 7.59-8.49 (4H,m)	477.14
3	IIIc	Ar- C – H : 3100, 3084, C = O: 1684, Ar- NO_2 : 1347, 1523 C – H : 2923,	7.52 (7H,m), 7.98(4H,m), 6.98 (1H,s), 5.7 (2H,s), 6.49 (2H,s), 6.71 – 7.96 (3H,m)	478.10
4	IIId	Ar- C-H : 3100, 3084, C = O : 1684, C – H : 2923, O – H : 3373, C – O : 1224	7.52 (6H,m), 7.98 (4H,m), 6.98 (1H,s), 5.7 (2H,s), 6.49 (2H,s), 9.68 (1H,s) 6.83 – 7.09 (4H, m)	448.15

Compound IIIa shows excellent activity against *S.pyogen* and *E. coli.* Compound IIIb shows good activity against *S.pyogen* and *S.aureus* and it doesn't show any activity against P.aureginosa and *E.coli.* Compound IIIc shows good activity against *S. pyogen* and *P. aeruginosa* is not active against *S.aureus* and *E.coli.* Compound IIId shows very good activity against *S. aureus* and good activity against *P. aureginosa* while no activity against *S. pyogen* and *E.coli.*

The same compound were also tested for antifungal activity against *Aspergillus niger* and *Candida albicans* using Fluconazole as standard drug.

Compound IIIa shows good activity against *A. niger* and *C. albicans* where as IIIb and IIIc don't show any activity against A.niger and C.albicans. Compound IIId shows very good activity against *A. niger* and *C. albicans*.

RESULTS AND DISCUSSION

The derivatives were synthezied as shown in reaction scheme friedel-crafts acylation of appropriate hydrocarbons with succinic anhydride in the presence of aluminium chloride to get β-(substituted aryl) propionic acid (I) cyclization of β-(substituted aryl) propionic acid with hydrazine hydrate to from pyridazinones-(II). On treatment of compound-(II) with acetic anhydride and corresponding aromatic benzaldehydes. The desired derivatives (viz: IIIa, IIIb, IIIc, IIId) where produced as shown and their structure were shown in Table 1. From the antimicrobial screening data it has been found that derivative IIIa have excellent antibacterial activity against both Gram +ve (*S. pyogen*) and Gram –ve (*E. coli)* strain where as derivative IIId has very good antifungal activity.

Ampicillin was taken as std drug against *S. pyogen* while Ceftizoxime was taken as std drug against *S. aureus*. While as Gentamycin was taken as std drug against *P. aeruginosa* and *E. coli*. While as Fluconazole was taken as std drug against *Aspergillus niger* and *Candida albicans.*

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