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Synthesis of Some New 4-Iodo Isoxazoles and Pyrazoles and Their Antimicrobial Activity

P.B. HEDA and B.J. GHIYA*
Chemistry Department, Institute of Science
Nagpur-440 001, India

Various propane 1,3-diones-(β-diketones) (I) were synthesized. (I) on iodination by iodine monochloride in dioxane gave 2-iodo-propane-1,3-dione (II). (II) was condensed with hydroxylamine hydrochloride, hydrazine hydrate and phenyl hydrazine in ethanol to get 4-iodo-3,5-(sub) diphenyl isoxazoles (III), 4-iodo-3,5-(sub) diphenyl pyrazoles (IV) and 4-iodo-1,3,5-triphenyl pyrazoles (V) respectively. The structures of synthesised compounds were confirmed by elemental analysis, chemical properties and IR, NMR and mass spectral data. Antimicrobial activity of some of the synthesized compounds was also studied.

INTRODUCTION

Isoxazoles and pyrazoles are well known to have a number of biological and antimicrobial activities[1, 2]. Earlier workers have reported 2-bromo-β-diketone derivative[3] and 4-bromoisoxazole[4]. Therefore, it was thought interesting to synthesise 4-iodo-3,5-(sub) diphenyl isoxazole (III), 4-iodo-3,5-(sub) diphenyl pyrazole (IV) and 4-iodo-1,3,5-triphenyl pyrazole (V) and study their antimicrobial activity. Substituted propane 1,3-diones commonly known as β-diketones (I) were prepared as reported earlier[5]. (I) was iodinated by specially developed method using ICl in dioxane to obtain 2-iodo-β-diketone (II). (II) was condensed with hydroxylamine hydrochloride, hydrazine hydrate and phenyl hydrazine to get (III), (IV) and (V) respectively (Scheme-1). The synthesised compounds were screened for their antimicrobial activity (Table-1) and m.p., yield, etc. in Table-2.

EXPERIMENTAL

The structures of these compounds were established by elemental analysis, chemical properties and spectral analysis. All melting points were taken in open capillaries and are uncorrected. Purity of compounds was checked by TLC on silica gel-G. Infrared spectra was recorded on Perkin Elmer spectrophotometer, mass spectra on Jeol D-300 (EI/CI) spectrophotometer and ^{1}H NMR spectra on Brucker AC 3000 F NMR spectrometer at 300 MHz.

The β-diketones (I) used for the synthesis of 4-iodo-β-diketones (II) were synthesised by base catalysed Baker Venketraman transformation of *o*-aroyloxy acetophenone as reported earlier[5].

TABLE-1
ANTIMICROBIAL ACTIVITY OF 4-IODO-ISOXAZOLES (III), 4-IODO-PYRAZOLES (IV) AND 4-IODO-1,3,5-TRIPHENYL PYRAZOLES (V) (zone of inhibition in mm)

S. No.	Organism tested	Compounds and zones of inhibition in mm				
		A	B	C	D	E
1.	*Salmonella typhi*	–	++ 1.6 mm	–	–	+ 1 mm
2.	*Escherichia coli*	–	+++ 1.6 mm	–	–	–
3.	*Staphylococcus aureus*	+ 0.8 mm	+ 1 mm	–	–	–
4.	*Bacillus megatherium*	–	+ 1.1 mm	–	–	–
5.	*Bacillus subtilis*	++ 1.3 mm	+ 0.7 mm	+ 0.5 mm	+ 0.5 mm	–
6.	*Pseudomonas aeruginosa*	++ 1.2 mm	+ 0.8 mm	–	++ 1.5 mm	+ 1 mm
7.	*Citrobacter*	–	+ 0.8 mm	–	–	–

+++ = Highly active; ++ = Moderately active; + = Active; – = Not active.

A = 3-(2-hydroxy-5-methyl phenyl)-4-iodo-5-phenyl isoxazole.

B = 3-(2-hydroxy-5-methyl phenyl)-4-iodo-5-phenyl pyrazole.

C = 1-phenyl-3-(2-hydroxy-5-methyl phenyl)-4-iodo-5-phenyl pyrazole.

D = 3-(2-hydroxy-5-chloro phenyl)-4-iodo-5-phenyl isoxazole.

E = 1-phenyl-3-(2-hydroxy-5-chloro phenyl)-4-iodo-5-phenyl pyrazole.

Preparation of 2-Iodo-β-diketone (II)

(I) (0.01 mol) was dissolved in dioxane (50 mL) and iodine monochloride (0.01 mol.) was added to it. The reaction mixture was kept at room temperature for 30 min. Yellowish crystalline product separated out was filtered, washed several times with dioxane, sodium bisulphite solution and water. It was finally crystallised from rectified spirit to get (II).

IIb: ν_{max} (cm^{-1}): 1640 ν(C=O), 2900 ν(O—H, H bonding), 580 ν(C—I). ^1H NMR: δ, 2.4 (s, CH_3), 6.8 (S, α-CH), 7.8 (m, 8H, ArH) 10 (s, OH). Mass: m/z 380.

Preparation of 4-Iodo-3-5-(Sub) diphenyl isoxazole (III)

(II) (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and ethanol (25 mL) were refluxed for 3 h. The reaction mixture was poured into water. The product formed was filtered, washed with water, dried and crystallised from rectified spirit to get (III).

TABLE-2

S. No.	Compound	R	Mol. formula	% N		m.p. (°C)	Yield (%)
				Calcd.	Found		
1.	IIa	H	$C_{15}H_{11}O_3I$	—	—	148	90
2.	IIb	CH_3	$C_{16}H_{13}O_3I$	—	—	140	90
3.	IIc	Cl	$C_{15}H_{10}O_3ICl$	—	—	160	90
4.	IIIa	H	$C_{15}H_{10}O_2NI$	3.85	3.84	115	60
5.	IIIb	CH_3	$C_{16}H_{12}O_2NI$	3.71	3.70	182	60
6.	IIIc	Cl	$C_{15}H_9O_2NICl$	3.52	3.49	175	50
7.	IVa	H	$C_{15}H_{11}N_2OI$	7.73	7.71	100	50
8.	IVb	CH_3	$C_{16}H_{13}N_2OI$	7.44	7.40	175	50
9.	IVc	Cl	$C_{15}H_{10}N_2OICl$	7.06	7.00	185	50
10.	Va	H	$C_{21}H_{15}N_2OI$	6.39	6.37	96	50
11.	Vb	CH_3	$C_{22}H_{17}N_2OI$	6.19	6.15	180	50
12.	Vc	Cl	$C_{21}H_{14}N_2OICl$	5.92	5.85	174	60

(IIIa) ν_{max} (cm^{-1}): 1600 ν(C=N), 2800 ν(OH, H bonded), 1380 ν(—CH_3), 580 ν(C—H). ^1H NMR: δ, 2.4 (S, —CH_3), 6.8–7.8 (m, 8H, ArH), 8.0 (s, —OH). Mass: m/z 377.

Preparation of 4-Iodo-3,5-(Sub) diphenyl pyrazole (IV)

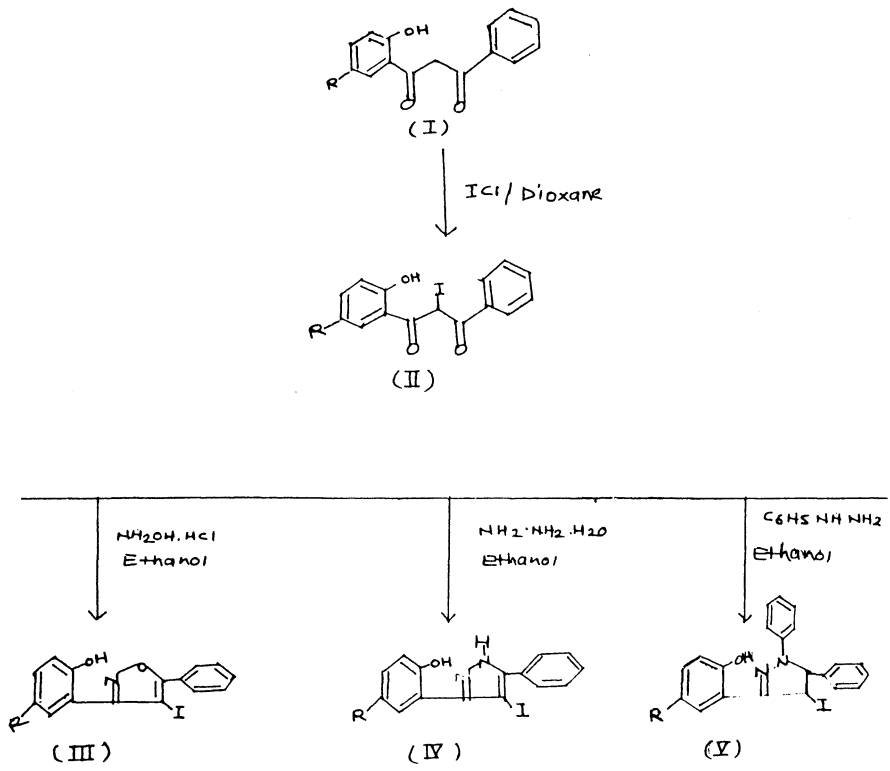
(II) (0.01 mol), hydrazine hydrate (0.01 mol) and ethanol (25 ml) were refluxed for 3 h. The reaction mixture was poured into water. The product formed was filtered, washed with water, dried and crystallised from rectified spirit to get (IV).

IVb: ν_{max} (cm^{-1}): 1640 ν(C=N), 2800 (OH—H bonded), 580 ν(C—I) 1440 ν(—NH), 1370 ν(—CH_3). ^1H NMR: δ, 2.46 (s, CH_3), 6.8–7.8 (m, H8, ArH), 8.1 (s, NH). Mass: m/z 376.

Preparation of 4-Iodo-1,3,5-triphenyl pyrazole

(II) (0.01 mol), phenyl hydrazine (0.01 mol) and ethanol (25 mL) were refluxed for 3 h. The reaction mixture was poured into water. The product formed was filtered, washed with water, dried and crystallised from rectified spirit to get (V).

Antimicrobial Activity: The antimicrobial activity of compounds under study was determined by agar well technique. For this purpose agar wells were cut with sterilized cork borer. The plates were heavily seeded with microorganisms. For each microorganism separate sterilized nutrient agar plate was used. The compounds under study were insoluble in water and hence were dissolved in DMSO. Solutions of compounds under study at a concentration of 50 μg/mL were placed in each agar well. These plates were incubated at 37°C for 48 h. After 48 h diameters of zones of inhibition were recorded. Penicillin was used as a standard for comparison.



Scheme-1

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