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Synthesis and Antibacterial Activity of Some 4-Substituted-2-phenyl oxazol-5(4H)-one Derivatives

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A series of eight compounds of the class 4-substituted-2-phenyl oxazol-5(4H)-one was synthesized using benzoyl glycine as the starting compound. Condensation of eight different aldehydes was effected by refluxation with benzoyl glycine for different optimum periods in acetic anhydride media in presence of freshly fused sodium acetate. The synthesized compounds were characterized by UV, IR and NMR spectrometric methods. All the synthesized compounds were allowed to undergo antibacterial testing by agar dilution method. Some of the compounds showed appreciable activity on certain organisms.

Key Words: Synthesis, Antibacterial activity, 2-Phenyloxazol-5(4H)-one.

INTRODUCTION

Importance of oxazoles, isoxazoles, oxazolinones, etc. is well established in medicinal chemistry[1, 2]. The present work encompasses the synthesis of certain oxazolinones *via* benzoyl glycine preparation. N-Benzoylglycine was then converted to 2-phenyl oxazol-5-one followed by reaction of the active methylene group of the oxazolone with a number of aldehydes to afford the corresponding benzylidine derivative. These azlactones were isolated, purified by crystallization and their melting points were determined and their structures were confirmed by IR and NMR. Eight such synthesized oxazolones or azlactones were screened for antibacterial activity on some Gram positive and Gram negative microorganisms. During such test six out of eight showed significant activity.

EXPERIMENTAL

The melting points of synthesized compounds were taken in open capillary tubes on a Gallenkamp-5 melting point apparatus and are uncorrected. The IR spectra were recorded in the 4000–400 cm^{-1} range using KBr disks on a Perkin-Elmer 297 spectrophotometer. The ^1H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer in $CDCl_3$.

Preparation of N-benzoylglycine: To a mixture of glycine (0.33 mol) in 10% sodium hydroxide solution in a round bottom flask, benzoyl chloride (0.385 mol) was added in five portions and vigorously shaken for 30 min. The clear solution was cooled and transferred to a beaker containing crushed ice. The

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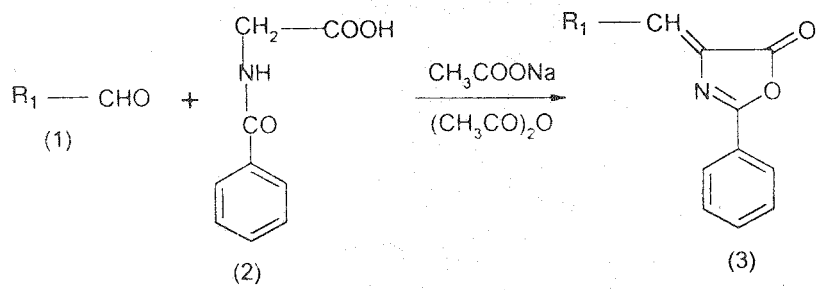
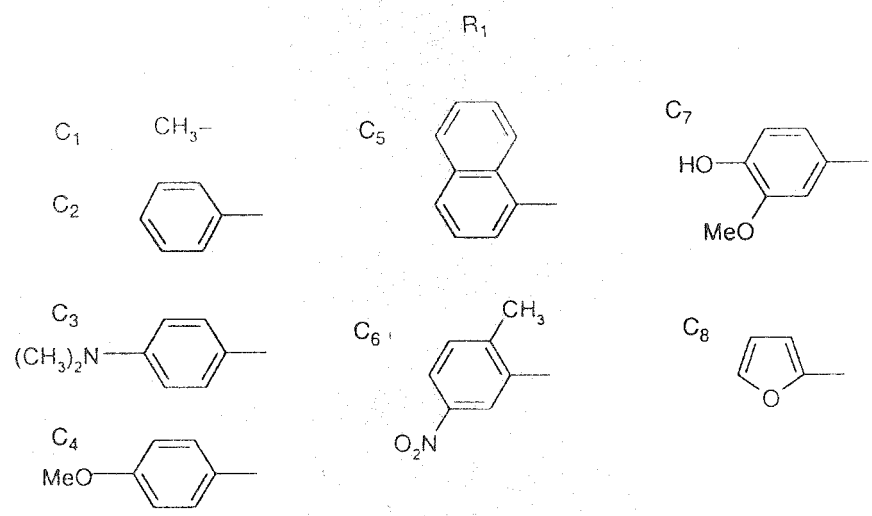
solution was acidified to Congo red with concentrated hydrochloric acid and the white solid of benzoyl glycine thus separated was filtered and washed with cold water. After carbon tetrachloride treatment for the removal of benzoic acid, the compound was recrystallized from hot water; m.p. 187°C.

Preparation of eight respective oxazolones: Eight 4-substituted-2-phenyl oxazol-5 (4H) ones were prepared from benzoyl glycine by the following procedure. Benzoyl glycine (0.25 mol) and appropriate aldehyde (0.25 mol) were dissolved in acetic anhydride (0.75 mol) and freshly fused sodium acetate (0.25 mol) was added **(Scheme-1).** The reaction mixture was refluxed for 2 h in a water bath. After cooling to room temperature ethanol was added and kept overnight at 5°C in a refrigerator. Following day the solid was filtered, washed with a little alcohol, dried and finally recrystallized from suitable solvent. The physico-chemical characteristics of the synthesized compounds are given in Table-1.



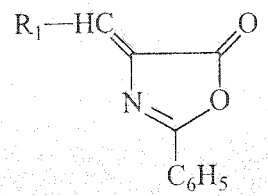


Scheme-1

Antibacterial activity

Determination of minimum inhibitory concentration (MIC) of synthesized compounds (C_1 to C_8)[3, 4] (Table-2). The MIC of C_1 to C_8 was determined by agar dilution method. In this method the drug was added at concentrations of 0 (control), 25, 50, 100, 200 μg/mL in molten nutrient agar and poured in petri dishes. The organisms were grown in peptone water and the overnight culture was spot-inoculated on the nutrient agar plates such that each inoculam contained

TABLE-1
PHYSICO-CHEMICAL CHARACTERISTICS OF THE SYNTHESIZED COMPOUNDS



Compd. No.	Compounds	m.f. (m.w.)	m.p. (°C)	Yield (%)	Substituents R_1	IR (KBr) cm^{-1}, ^1H NMR ($CDCl_3$)
C_1	4-Acetylidene-2-phenyl oxazol-5(4H)one	$C_{11}H_9NO_2$ (187)	161–2	52.42	CH_3—	1762 ν(C═O), 1554 ν(Arom.—CH),1522 ν(—C—P—C); 2.8–2.9 ν(CH_3), 5.2–5.4 ν(CH═C), 6.2–6.3 ν(C_6H_5).
C_2	4-Benzylidene-2-phenyl oxazol-5(4H)one	$C_{16}H_{11}NO_2$ (245)	166–7	97.05	C_6H_5—	1802 ν(C═O), 1567 ν(Arom.—H), 1512 ν(—C—O—C); 6.8–0.9 m 10 H ν(C_6H_5)$_2$, 5.81–5.92 ν(CH═C).
C_3	4-(4′-Dimethyl amino phenyl)-2-phenyl oxazol-5(4H)one	$C_{18}H_{16}NO_2$ (292)	216–7	62.06	*p*—$(CH_3)_2N$—C_6H_5—	1764 ν(C═O), 1602 ν(Arom.—CH), 1366 ν(—$N(CH_3)_2$); 6.6–6.7 ν(C_6H_5) 6.4–6.5 ν(C_6H_4), 5.51–5.67 ν(CH═C), 2.4–2.8—N— ν(CH_3)$_2$
C_4	4-(4′-Methoxy phenyl)-2-phenyl oxazol-5(4H)one	$C_{17}H_{13}NO_3$ (279)	154–5	75.09	*p*—CH_3O—C_6H_5—	1722 ν(C═O) 1627 ν(Arom.—CH), 1052 ν(C—O—C), 6.72–6.75 ν(C_6H_4), 6.24–6.42 ν(C_6H_5), 2.24–2.4 ν(OCH_3)
C_5	4-(Naphthyl)-2-phenyl oxazol-5(4H)one	$C_{20}H_{13}NO_2$ (299)	164–5	51.25	—$C_{10}H_7$	1734 ν(C═O), 1542 ν(Arom.—CH), 7.5–7.6 ν(1-naphthyl), 5.7–5.9 ν(CH═C)
C_6	4-(5′-Nitro-2′-methyl phenyl)-2-phenyl oxazol-5(4H)one	$C_{17}H_{12}N_2O_4$ (308)	198–9	58.68	5-NO_2-2-CH_3—C_6H_4—	1801 ν(C═O), 1513 ν(CH_3), 7.2–7.25 ν(C_6H_3), 5.9–6.2 ν(CH═C), 2.25–2.3 ν(CH_3)
C_7	4-(4′-Hydroxy-3′-methoxy phenyl)-2-phenyl oxazol-5(4H)one	$C_{17}H_{13}NO_4$ (295)	192–3	95.08	4-OH-3-OCH_3—C_6H_4—	1760 ν(C═O), 1622 ν(OCH_3), 1360 ν(OH), 6.8–6.9 ν(OH), 6.31–6.4 ν(C_6H_3), 6.5 –6.63 ν(C_6H_5), 2.2–2.5 ν(OCH_3)
C_8	4-(Furfuryl)-2-phenyl oxazol-5(4H)one	$C_{14}H_{10}NO_3$ (240)	168–9	78.62	C_4H_3O—	1742 ν(C═O), 1612 ν(Arom.—CH), 8.2–8.5 ν(CH═C), 6.7–6.9 ν(2-furfuryl) 6.4–6.5 ν(C_6H_5)

2×10^6 CFU. The plates were incubated at 37°C, examined after 24 h and incubated further for 72 h, if necessary. The lowest concentration of the compounds (C_1 to C_8) in a plate that failed to show any visible macroscopic growth was considered as its MIC. The MIC determination was performed in duplicate for each organism, and the experiment was repeated where necessary.

TABLE-2
ANTIBACTERIAL SCREENING DATA OF THE SYNTHESIZED COMPOUNDS

Bacterial strains tested	Minimum Inhibitory Concentration (μg/mL) of Compounds							
	C1	C2	C3	C4	C5	C6	C7	C8
Staphylococcus aureus ATCC 25923	100	100	100	50	100	50	50	100
S. aureus NCTC 6571	>200	>200	50	50	100	50	50	50
Bacillus pumilus NCTC 8241	100	100	50	50	50	50	50	50
Salmonella typhimurium NCTC 74	>200	>200	100	100	100	100	50	100
Shigella sonnei NCTC 9774	>200	>200	100	100	100	100	50	100
Sh.dysenteriae 7 NCTC 519/66	100	100	100	50	100	100	50	50
Escherichia coli ATCC 25922	>200	>200	100	100	100	100	50	100
Klebsiella pneumoniae 14	>200	>200	100	100	50	100	50	50
Pseudomonas aeruginosa APC 1	>200	>200	100	100	100	100	50	100
Vibrio cholerae ATCC 14033	100	>200	100	50	100	100	100	100

RESULTS AND DISCUSSION

Out of the eight compounds under trial, six compounds (C_3 to C_8) were active against certain organisms even at a 50 g/mL dose level. Thus, C_3 showed activity against two organisms (*S. aureus* NCTC 6571, *B. pumilus* NCTC 8241) while C_4 was active against five organisms (*S. aureus* ATCC 25923, *S. aureus* NCTC 6571, *B. pumilus* NCTC 8241, *Sh. dysenteriae* 7 NCTC 519/66, *V. cholerae* ATCC 14033). Amongst other four compounds, C_5 was active against two, C_6 against three and C_7 against nine organisms while C_8 was active against four organisms. Details are shown in the table. Thus, the C_7 compound was found to be most versatile in its antibacterial activity, which is growth of nine out of ten organisms was prevented.

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