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Synthesis, Characterization and Antimicrobial Evaluation of Phenylene-1,4-oxy-bis-hydantoins

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ABSTRACT

Phenylene-1, 4-oxy-bis-hydantoins have been synthesized from 5-bromohydantoin and substituted quinol (1,4-dihydroxybenzene) in the presence of K_2CO_3 in dioxane. The structures of newly synthesized compounds have been established on the basis of IR, NMR and Mass spectral data. These compounds were screened for their antibacterial activity against gram +ve and gram – ve bacteria. This phenylene-1, 4-oxy-bis-hydantoins are so far not reported in literature.

Keywords: Hydantoin, bis-hydantoin, quinol, anticonvulsant

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INTRODUCTION

Over a few decades there has been considerable interest in the synthesis and characterization of hydantoin derivatives as an important class of heterocyclic compounds. Hydantoins were originally observed as undesired by-products in the synthesis of peptides[1-2]. Many of hydantoin containing natural and synthetic products exhibit a broad range of biological activity such as antitumour, antiarrhytmic, anticonvulsant and herbicidal etc[3-17]. Hydantoins substituted at C-5 are important medicinal compounds. Epilepsy is a group of chronic neurological disorders whose symptoms result from a brain dysfunction or an abnormal discharge of cerebral neurons. Drug therapy is the major treatment for epilepsy, and among the major drugs used in its treatment are the hydantoins. Among the Phenolic compounds, quinol and its derivatives are widely utilized in the industrial processes including coal-tar production, paper manufacturing, photographic applications and rubber production[18]. They are also employed as monomer inhibitors, antioxidants, agricultural chemicals and the developers in black and white film, lithography, photochemical machining and microfilm. Quinol is known to produce the positive response in the micronucleus and an in vitro test for sister chromosome exchange in human lymphocytes. Therefore, investigation of carcinogenic effect for quinol and its derivatives from cosmetic creams, hair products and pharmaceutical preparations is very important in order to avoid health problems[19].

In view of various biological activities, several bis-hydantoins with quinol moiety have been prepared.

MATERIAL AND METHODS

The chemicals and reagents used in present work were of AR grade and LR grade purchased from SD fine chem. Ltd., and, Loba chem. Ltd. The reaction progress was monitored by TLC technique by using Silica gel, suitable mobile phase of solvent. Iodine chamber and UV lamp were used for visualization of TLC spots. Purification of compounds was achieved by solvent extraction method. The IR spectra were recorded in KBr pellets on FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer in DMSO using tetramethylsilane (TMS) as an internal standard; the chemical shifts were reported in ppm scale. Mass spectra were recorded on JMS-T100LC, Accu TOF Mass spectrometer (DART-MS)**.**The compounds were screened for their antibacterial activities by the agar diffusion method.

EXPERIMENTAL

Synthesis of phenylene-1,4-oxy-bis-hydantoin.(4a)

A mixture of hydantoin (40 mmol, 4g), dioxane (10 ml) and bromine (40 mmol, 2 ml) was vigorously stirred at 100 ^{0} C for 2 hrs. The reaction mixture was then cooled to a room temperature. Another mixture of quinol (20 mmol, 2.2 g) and potassium carbonate (40 mmol, 5.56 g) was then added on to it. The mixture was kept at 100 ^{o}C for 48 hrs with constant stirring. The filtrate was concentrated on a rotary evaporator. The product was subjected to liquid-liquid extraction using ethyl acetate to afford a brown viscous liquid. Similarly, compounds 4b-4g have been prepared.

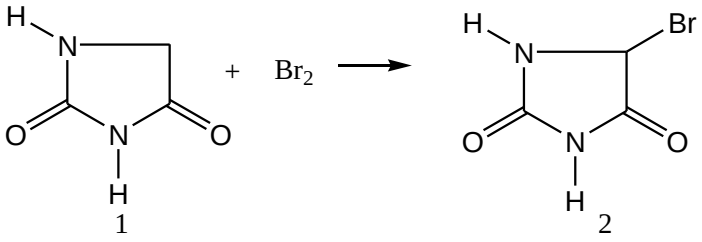
Procedure for antimicrobial activity:

All the operation was carried out under aseptic condition. Standard cultures of Gram-positive Staphylococcus aureus, Bacillus substilis and Gram-negative Escherichia coli, Klebisilla aerogens bacteria were obtained from Department of Microbiology, Dharampeth Science College, Nagpur. Newly prepared compounds were dissolved in dimethyl sulphoxide (DMSO) to prepare stock solution.

The stock cultures of bacteria were revived by inoculating in broth media (peptone-6 g, NaCl-6 g and Yeast extract 3g, Dextrose-1g, Agar 15 g in 1000 ml of distilled water) and grown at 37° C for 18 hours. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 hour old cultures (100ul, 10^{-4} cfu) and spread evenly on the plate. After 20 minutes, the wells were filled with the solution of compounds at different concentrations. The control wells with Gentamycin were also prepared. All the plates were incubated at 37 °C for 24 hours and diameter of inhibition zones were measured in mm on antibiotic zone reader in various axis and average reading was considered.

RESULTS AND DISCUSSION

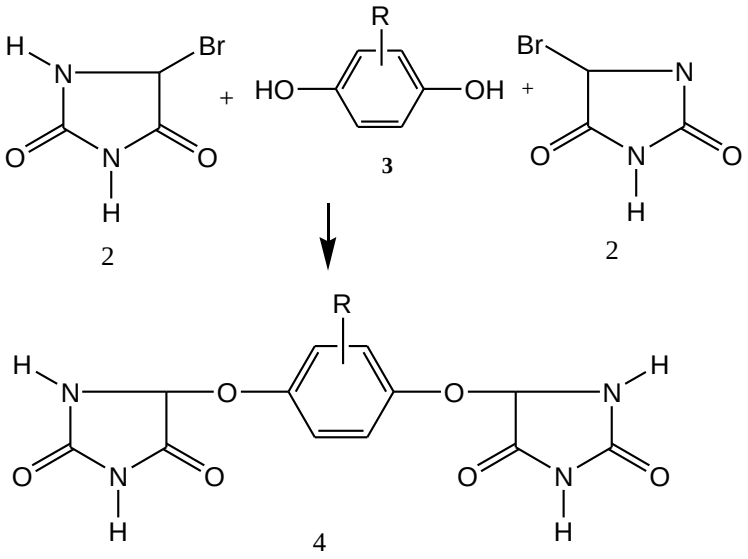
Initial efforts were directed toward the preparation of 5-bromohydantoin, which was obtained by bromination of hydantoin [20] (Scheme-1):



1 2

Phenylene-1,4-oxy-bis-hydantoins was synthesized by interaction between 5-bromohydantoin and substituted quinol by using K_2CO_3 in dioxane . On completion of the reaction the salts were removed and the filtrate was concentrated on a rotary evaporator to give a brown liquid. The

crude product was subjected to liquid-liquid extraction using ethyl acetate to afford a brown viscous liquid (Scheme-2):



Where , R= H,Cl.Br,I,F,NO_2,NH_2

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Table 1:-Physicochemical parameters of Phenylene-1,4-oxy-bis-hydantoin

Sr.No	Compounds	R	M.F	Yield %
1	4a	H	$C_{12}H_{10}N_4O_6$	67.01
2	4b	Cl	$C_{12}H_9N_4O_6Cl$	61.66
3	4c	Br	$C_{12}H_9N_4O_6Br$	66.22
4	4d	I	$C_{12}H_9N_4O_6I$	70.82
5	4e	F	$C_{12}H_9N_4O_6F$	60.20
6	4f	NO_2	$C_{12}H_9N_5O_8$	70.95
7	4g	NH_2	$C_{12}H_{11}N_5O_6$	60.30

Antimicrobial Activity

The synthesized bis-hydantoins 4a-4g have been screened for antimicrobial activity against Gram-positive Staphylococcus aureus, Bacillus substilis and Gram-negative Escherichia coli, Klebisilla aerogens bacteria by agar diffusion method at a concentration 1 mg/l in dimethyl sulphoxide (DMSO) by using the standard drug Gentamycin for bacteria. It was observed that all compounds 4a-4g have exhibited considerable antimicrobial activities.

Characterization Data

1) **phenylene-1,4-oxy-bis-hydantoin (4a)**

   MS: m/z: 306 .^{1}H-NMR: δ 10.20 (s, 2H, NH) , δ 6.12 (s,2H,NH) , δ 6.6-6.8 (s, 4H,Ar-H), δ 6.2(s,2H,CH), IR (KBr, cm^{-1}): 3452 ,3195 ,1720,1768 .

2) **2- chlorophenylene-1,4-oxy-bis-hydantoin (4b)**

MS: m/z: 341 .^{1}H-NMR: δ 10.34 (s, 2H, NH) , δ 6.24 (s,2H,NH) , δ 6.5-6.7 (m, 3H,Ar-H), δ 6.32(s,2H,CH), IR (KBr, cm^{-1}): 3448 ,3186 ,1715,1760.

3) **3-bromophenylene-1,4-oxy-bis-hydantoin (4c)**

MS: m/z: 385 .^{1}H-NMR: 10.42 (s, 2H, NH) , δ 6.34 (s,2H,NH) , δ 6.55-6.85 (m, 3H,Ar-H), δ 6.4(s,2H,CH), IR (KBr, cm^{-1}): 3446 ,3182 ,1712, 1756.

4) **2-iodophenylene-1,4-oxy-bis-hydantoin (4d)**

MS: m/z: 432 .^{1}H-NMR: 10.56 (s, 2H, NH) , δ 6.43 (s,2H,NH) , δ 6.45-7.15 (m, 3H,Ar-H), δ 6.25(s,2H,CH), IR (KBr, cm^{-1}): 3446 ,3178 ,1712,1754.

5) **2-florophenylene-1,4-oxy-bis-hydantoin (4e)**

MS: m/z: 324 .^{1}H-NMR: 10.60 (s, 2H, NH) , δ 6.45 (s,2H,NH) , δ 6.35-6.75 (m, 3H,Ar-H), δ 6.34(s,2H,CH), IR (KBr, cm^{-1}): 3440 ,3174 ,1718,1765.

6) **3-nitrophenylene-1,4-oxy-bis-hydantoin (4f)**

MS: m/z: 351 .^{1}H-NMR: 10.56 (s, 2H, NH) , δ 6.42 (s,2H,NH) , δ 6.92-7.59 (m, 3H,Ar-H), δ 6.56(s,2H,CH), IR (KBr, cm^{-1}): 3438 ,3185 ,1710,1745.

7) **3-aminophenylene-1,4-oxy-bis-hydantoin (4g)**

MS: m/z: 321 .^{1}H-NMR: 10.34 (s, 2H, NH) , δ 6.2 (s,2H,NH) , δ 6.02-6.45 (m, 3H,Ar-H), δ 6.45(s,2H,CH), IR (KBr, cm^{-1}): 3446 ,3178 ,1712,1754.

Table 2:-Antimicrobial activities of Phenylene-1,4-oxy-bis-hydantoins (4a-g)

Compound	Antibacterial Activity (mm)			
	Gram-positive		Gram-negative	
	Staphylococcus aureus	Bacillus	Escherichia coli	Klebisilla aerogens
4a	23	17	19	15
4b	21	15	17	16
4c	20	17	21	17
4d	14	16	20	15
4e	15	19	18	19
4f	14	18	19	17
4g	12	13	17	12
Standard	34	32	35	31

CONCLUSION

The new derivatives of phenylene-1,4-oxy-bis-hydantoin were synthesized in moderate to excellent yields using 5-bromohydantoin and substituted quinol as starting materials and characterized by IR, ^{1}H-NMR and mass spectral analysis. The presented synthetic procedure is convenient and simple to prepare bis-hydantoins. The screening results indicate that the

compounds 4a-4g was found to be active against both Gram-positive and Gram-negative bacteria.

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