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Article

Synthesis, Characterization and Biological Evaluation of 1,3-Bis(5-Hydantoinyloxy) Benzenes

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ABSTRACT

An efficient and straightforward two-step approach toward 1,3-bis(5-hydantoinyloxy)benzenes was developed. A hydantoin is reacted with bromine to produce 5-bromohydantoin, which on reaction with the resorcinol's to produce corresponding 1,3-bis(5-hydantoinyloxy)benzenes in the presence of K_2CO_3 in dioxane. The structures of newly synthesized compounds have been reputable on the basis of their spectral data. Their biological activities against Gram +ve and Gram −ve bacteria are reported.

Key words: Hydantoin, Bis-hydantoin, Anticonvulsant, Resorcinol.

1. INTRODUCTION

Hydantoin (Glycolyurea) is nitrogen-containing five-membered heterocyclic compound containing two nitrogen's at 1 and 3 positions and two carbonyl groups at 2 and 4 positions. Over a few years, there has been significant concern in the synthesis, characterization, and biological evolution of hydration as a vital class of heterocyclic compounds. Hydantoin moiety constitutes an attractive pharmacological scaffolding present in several drugs [1]. Hydantoin and its derivatives displays wide range of biological activities such as anticonvulsant, antidiabetic, antibacterial, antiviral, antifungal, anti-inflammatory, antiarrhythmic, neuroprotective, antihypertensive, analgesic, antiandrogen, or diuretic activities as well as herbicidal or fungicidal properties [2-22]. 5,5-disubstituted Hydantoin derivatives are used in the synthesis of weather-proof high-temperature-stable epoxy resins in the chemical industry. Hydantoin derivative also used in various cosmetics consumer products such as hair sprays cosmetics, photographic film [23]. In this article we wish to report the synthesis, Characterization and biological evolution of substituted 1,3-bis(5-hydantoinyloxy) benzenes against Gram +ve and Gram −ve bacteria.

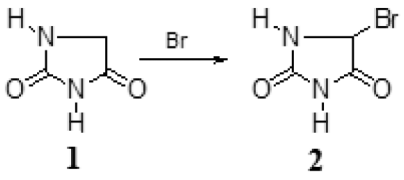
2. EXPERIMENTAL SECTION

2.1. General

The chemicals and reagents used in existing work were of AR, LR grade purchased from Loba chemical and SD fine chemical limited. Melting points of compounds were detected using open capillaries which are uncorrected. The progress of reaction was supervised by the TLC technique using Silica gel and suitable mobile phase of solvent. Iodine chamber and UV lamp were used for visualization of TLC spots. Purification of compounds was achieved by the solvent extraction method. The IR spectra were recorded on FT-IR spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using dimethyl sulphoxide (DMSO) solvent and tetramethylsilane as a reference; the chemical shifts were reported in ppm scale. Mass spectra were recorded on JMS-T100LC, Accu TOF Mass spectrometer (DART-MS). Thermo Finnigan CHN analyzer was employed for the elemental characterization of the products. The newly synthesized compounds were screened for their biological evolution by the agar diffusion method.

2.2. Preparation of 5-Bromohydantoin 2

A mixture of hydantoin **(1)** (40 mmol), dioxane (10 ml), and bromine (40 mmol) was vigorously stirred at 100°C for 2 h. The reaction mixture was cooled and used in the next step.



2.3. Preparation of 1, 3-Bis (5-Hydantoinyloxy) Benzenes 4(a-h)

The mixture of 5-bromohydantoin **2** (40 mmol in 10 ml dioxane), substituted resorcinol **3(a-h)** (20 mmol), and anhydrous potassium carbonate (40 mmol) was kept at 100°C for 48 h with constant stirring. It was filtered. The filtrate was concentrated on a rotary evaporator. It was then poured onto water (50 ml) with stirring. The product was extracted in ethyl acetate (100 ml, liquid-liquid extraction). The brown viscous 1,3-bis(5-hydantoinyloxy)benzenes **4(a-h)** was obtained after evaporation of the solvent [Scheme 1].

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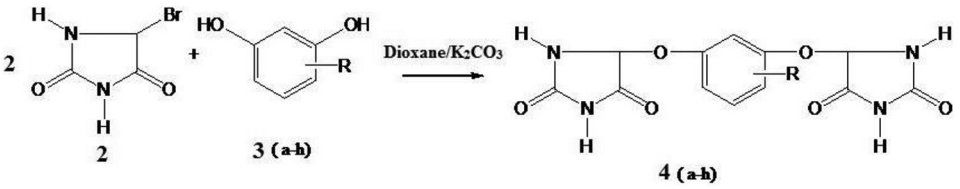

Scheme 1: R = (a) −H, (b) −Cl, (c) −Br, (d) −I, (e) −F, (f) $-NO_2$, (g) $-NH_2$, (h) $-CH_3$.

3. RESULTS AND DISCUSSION

3.1. Chemistry

FT IR Spectra (S1): 1,3-bis(5-hydantoinyloxy)benzene (**4a)** shows bands at 1760 and 1720 cm^{-}1 due to carbonyl group (−C=O) stretching vibrations. A broad peak near at 3456 and 3180 cm^{-}1 was observed due to N-H groups of hydantoin ring. Besides these, band at 1140 cm^{-}1 due to the C-O-C stretch indicates ether linkage. ^{1}H NMR spectra (S2) of 4a showed characteristic singlet near δ10.62 ppm and δ7.98 ppm due to N-H protons. Active methylene protons appeared as singlet near at δ6.42 ppm was observed and aromatic protons as multiplet around δ6.80–7.50 ppm. Molecular ion peak (S3) at m/z 329 $[M+Na]^+$ also lend credence to the structure. All compounds **4(a-h)** gave satisfactory elemental analysis.

Other 1,3-bis(5-hydantoinyloxy)benzenes **4(b-h)** have been prepared by following the above procedure.

3.1.1. 1,3-Bis(5-hydantoinyloxy)-4-chlorobenzene (4b)
IR (KBr): 1764, 1722, 3460, 3185, 1168 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ10.68 (s, 2H, NH), 7.96 (s, 2H, NH), 6.76–7.58 (m, 3H, Ar-H), 6.44 (s, 2H, CH). MS m/z = 363 $[M+Na]^+$. Anal. Calcd for $C_{12}H_9ClN_4O_6$ (%): C, 42.31; H, 2.66; N, 16.54. Found (%): C, 42.43; H, 2.59; N, 16.52.

3.1.2. 1,3-Bis(5-hydantoinyloxy)-5-bromobenzene (4C)
IR (KBr): 1762, 1718, 3462, 3182, 1140 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ10.70 (s, 2H, NH), 7.96 (s, 2H, NH), 6.72–7.45 (m, 3H, Ar-H), 6.40 (s, 2H, CH). MS m/z = 407 $[M+Na]^+$. Anal. Calcd for $C_{12}H_9BrN_4O_6$ (%): C, 37.42; H, 2.36; N, 14.55. Found (%): C, 37.53; H, 2.38; N, 14.38.

3.1.3. 1,3-Bis(5-hydantoinyloxy)-5-iodobenzene (4d)
IR (KBr): 1760, 1715, 3459, 3180, 1145 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): δ10.65 (s, 2H, NH), 7.92 (s, 2H, NH), 6.71–7.32 (m, 3H, Ar-H), 6.36 (s, 2H, CH). MS m/z = 455 $[M+Na]^+$. Anal. Calcd for $C_{12}H_9IN_4O_6$ (%): C, 33.35; H, 2.10; N, 12.97. Found (%): C, 33.43; H, 2.15; N, 12.86.

3.1.4. 1,3-Bis(5-hydantoinyloxy)-4-fluorobenzene (4e)
IR (KBr): 1763, 1718, 3465, 3183, 1148 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6): δ10.80 (s, 2H, NH), 9.94 (s, 2H, NH), 6.87–7.75 (m, 3H, Ar-H), 6.52 (s, 2H, CH). MS m/z = 347 $[M+Na]^+$. Anal. Calcd for $C_{12}H_9FN_4O_6$ (%): C, 44.45; H, 2.80; N, 17.28. Found (%): C, 44.54; H, 2.84; N, 17.18.

3.1.5. 1,3-Bis(5-hydantoinyloxy)-5-nitrobenzene (4f)
IR (KBr): 1762, 1716, 3463, 3181, 1150 cm^{-1}. ^{1}H NMR (400MHz, DMSO-d6): δ10.88 (s, 2H, NH), 9.94 (s, 2H, NH), 6.94–7.95 (m, 3H, Ar-H), 6.54 (s, 2H, CH). MS m/z = 374 $[M+Na]^+$. Anal. Calcd for $C_{12}H_9N_5O_8$ (%): C, 41.04; H, 2.58; N, 19.94. Found (%): C, 41.10; H, 2.63; N, 19.86.

3.1.6. 1,3-Bis(5-hydantoinyloxy)-5-aminobenzene (4g)
IR (KBr): 1754, 1710, 3452, 3174, 1132 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): δ10.32 (s, 2H, NH), 7.74 (s, 2H, NH), 6.62–7.26 (m, 3H, Ar-H), 6.34 (s, 2H, CH), 4.12 (s, 2H, $-NH_2$). MS m/z = 344 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{11}N_5O_6$ (%): C, 44.87; H, 3.45; N, 21.80. Found (%): C, 44.94; H, 3.56; N, 21.68%.

Table 1: Antimicrobial activity of 1,3-bis(5-hydantoinyloxy) benzenes 4(a-h)

Compd[aA].	Zone of Inhibition[b] (mm)			
	Gram-positive		Gram-negative	
	S. aureus	*B. subtilis*	*E. coli*	*K. aerogenes*
4a	20	15	19	16
4b	23	21	26	24
4c	20	23	18	17
4d	19	21	23	19
4e	27	23	28	21
4f	20	21	18	17
4g	20	18	19	21
4h	18	21	18	18
Std.	34	32	35	31

[a]Concentration of test compounds and standard 100 µg/ml, [b]Average zone of inhibition in mm, *S. aureus: Staphylococcus aureus, B. subtilis: Bacillus subtilis, E. coli: Escherichia coli, K. aerogens: Klebsiella aerogenes. Std.: Gentamycin.*

3.1.7. 1,3-Bis(5-hydantoinyloxy)-4-methylbenzene (4h)
IR (KBr): 1760, 1715, 3468, 3184, 1142 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d6): δ10.42 (s, 2H, NH), 7.78 (s, 2H, NH), 6.52–7.28 (m, 3H, Ar-H), 6.27 (s, 2H, CH), 4.12 (s, 2H, $-NH_2$), 2.32 (s, 3H, $-CH_3$). MS m/z = 343 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{12}N_4O_6$ (%): C, 48.75; H, 3.78; N, 17.49. Found (%): C, 48.85; H, 3.83; N, 17.40.

3.2. Antimicrobial Activity

1,3-Bis(5-hydantoinyloxy)benzenes **4(a-h)** have been screened 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 DMSO using the standard drug Gentamycin. It was observed that all compounds **4(a-h)** have exhibited considerable antimicrobial activities.

4. CONCLUSION

In this article, the new 1,3-bis(5-hydantoinyloxy)benzenes have been synthesized, characterized by spectroscopic techniques, and screened against Gram-positive *S. aureus, B. substilis,* and Gram-negative *E. coli, K. aerogens* bacteria for their biological evolution. They have shown significant bacterial activities.

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