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Efficient Synthesis of 5,5-Disubstituted Bis-hydantoins/spirohydantoins and a Tetrakis-analogue: A Drug-like Multi-cyclic Scaffold

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An easy method was developed for the efficient preparation of diversely new 5,5-disubstituted N(3),N'(3)-linkaged bis-hydantoins. At first, using the same methods, some ketones and terephthalaldehyde were converted to several hydantoins, and a new bis-hydantoin, respectively. Then, 1,6-dibromohexane, as a mild reagent, was employed for the alkylation and incorporation of synthesized substrates to produce quantitative yields of the desired bis-hydantoins. A tetrakis-hydantoin including four effective heterocyclic rings was also surprisingly synthesized from 5,5'-(1,4-phenylene)bis(imidazolidine-2,4-dione). The aim of this study is to synthesis of bis- and tetra core-hydantoins, bis-drug-like molecules employing a practical and reliable reaction process that requires slight amount of reagents; a process that is simple, accessible producing remarkable yields from an easy procedure that is cost effective and/or environmentally friendly. The resultant hydantoins potentially have bis- or multi-drugs behaviors in comparison with mono-counterparts, as cited in the literature for similar heterocyclic compounds. Spectral analysis confirmed the structures of the synthesized hydantoins.

Keywords: Spirohydantoin, Bis-hydantoin, Imidazolidine-2,4-dione, N(3),N'(3)-hexamethylene-bis-hydantoin, Antiepileptic, Bis-drug

INTRODUCTION

The discovery of hydantoins and successfully developing novel hydantoins-based drugs for the treatment of epilepsy, convulsion [1-6], tumors [4-12], arrhythmic [3-5], viral [1,3,13], HIV [1,3], microbial [14-16], cancer [5,10,17-22], alzheimer [20], diabetes [4,5], migraine [23] and other conditions/disorders have always caused worldwide interests among chemists. Hydantoin scaffolds are an important structural unit found in agrochemicals [24]. Hydantoins are also precursors to unnatural and natural occurring α-amino acids [3,14,24]. New discoveries of hydantoin derivatives as radio sensitizers and markers of oxidative cell damage in cancer, aging and neurological disorders have also been reported [17,24,25]. Recently, in a promising research on cancer therapy, it was revealed that the substitution of N(3) in some mono-hydantoins enhanced their pharmaceutical activities in treating certain types of tumor cells in a unique manner [4,5]. Bis-drugs are estimated to exhibit double therapeutic behaviors. Following reports (by A.M.Sh. El-Sharief, Z. Moussa) about superior medicinal and pharmacological activities exhibited by some bis-heterocyclic drugs in comparison to mono-heterocyclic counterparts and looking for ways to develop a simple, rapid, convenient and eco-friendly method for the substituted hydantoins has encouraged the exploration of bis-hydantoin as a manifold medicinal agent [26]. Some potential applications of bis-hydantoins as antitumor agents [7], anticancer agents [4,5], DNA binding linkages [27] and antimicrobial agents [15] have been provided in the literature. In the present work, we discuss a one-pot synthetic route for the preparation of some novel N(3),N'(3)-hexamethylene-bis-hydantoins as bis-drugs, using a previously reported spiro- and nonspiro mono-hydantoins [1,3]. A new synthesized bis-hydantoin is also utilized to produce a tetra cyclic hydantoin. This synthetic procedure can be considered as click-chemistry [28].

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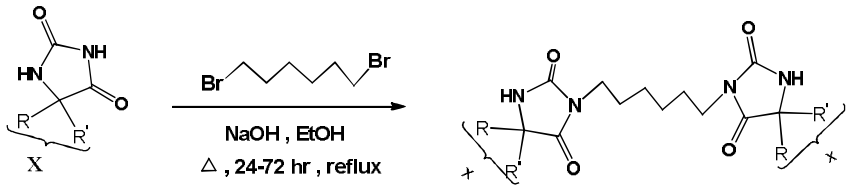


1a-g **2a-g**

a: X (R = Ph, R' = Me)

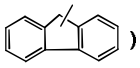
b: X (R = 4- methylphenyl, R' = Me)

c: X (R = 4-chlorophenyl, R' =H)

d: X (R = R' = Ph)

e: X (R, R' = cyclohexyl)

f: X (R, R' = cyclopentyl)

g: X (R, R' = )

Scheme 1. Synthetic route to bis-hydantoins 2a-g

EXPERIMENTAL

General Procedure

High-resolution ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) spectra were obtained *via* a Bruker 500 DRX-Avance NMR spectrometer. The compounds were dissolved in deuterated DMSO as NMR solvent. IR data were obtained with a Shimadzu 470 spectrometer. Mass spectra were recorded using a GC-MS Agilent Technologies QP-5973N MSD instrument. The melting points of crystalline compounds were measured with an electrothermal melting point apparatus which was not adjusted. The purification of crystalline compounds was performed by recrystallization, and in some cases by preparative thin-layer chromatography with silica gel 60 GF_{254}. All chemicals were purchased from Aldrich Chemical Company, Merk or Fluka, and were used as received without further purification.

Synthesis of Bis-hydantoins (2a-g). General Procedure

Salts were obtained in a direct one-pot synthesis: Mono-hydantoin (1a-g), prepared through Bucherer-Bergs reaction, (0.005 mol) was suspended in a solvent mixture of 1.0 M NaOH solution (5 ml) and ethanol (5 ml). The mixture was heated at reflux (60-65 °C) for 15 min after which 1,6-dibromohexane (0.36 ml, 0.0024 mol) was added in a drop wise manner through the top of a reflux condenser to the solution and the reaction was heated for 24-72 h. The mixture was allowed to cool in an ice bath, filtered, washed with water and the products (2a-g) recrystallized from ethanol several times (Scheme 1 and Table 1).

The EtOH 96% was the recrystallization solvent in all cases; except for the recrystallization of bis-hydantoin d, where a mixture of DMSO and EtOH was applied.

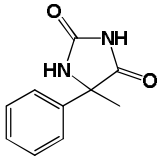
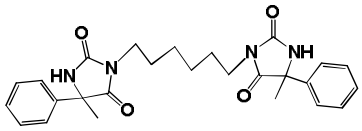
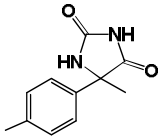
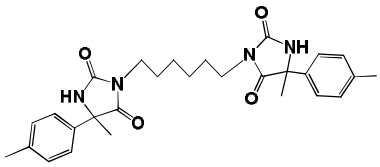
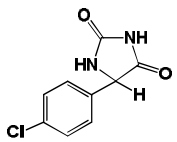
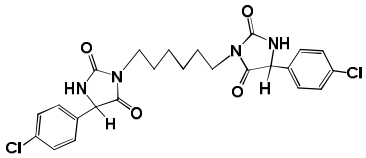
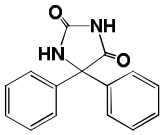
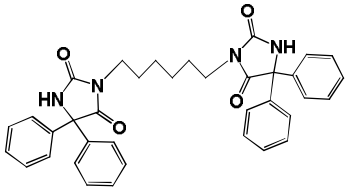
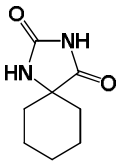
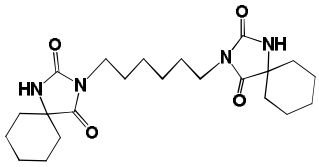
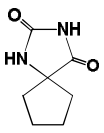
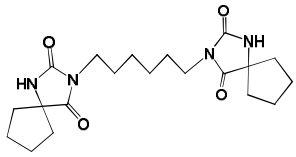
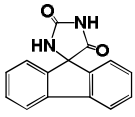
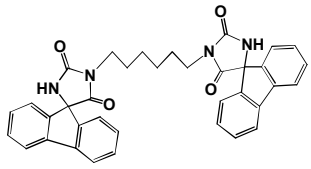
Synthesis of 5,5'-(1,4-Phenylene)bis(imidazolidine-2,4-dione) (3)

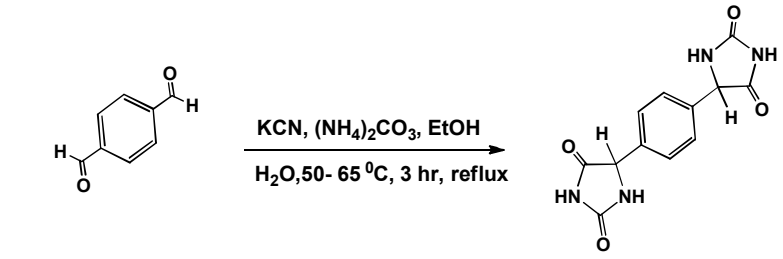
Terephthalaldehyde, as a none α-dicabonyl, was converted to a new bis-hydantoin *via* improving Bucherer-Bergs reaction. Terephthalaldehyde (1.07 g, 8 mmol) was dissolved in 50 ml of a 1:1 (v/v) mixture of ethanol and water in a 100 ml round-bottom vessel while potassium cyanide (2.16 g, 33 mmol) and ammonium carbonate (6.38 g, 66 mmol) were added. The mixture was allowed to reflux at 50-65 °C with stirring for 3 h. The mixture was allowed to cool to room temperature, and after collecting the precipitate, the filtrate was acidified to pH = 2 by drop wise addition of concentrated HCl while stirring. The precipitates were recrystallized from 96% ethanol, and 68% of analytically pure cream-colored powder of bis-hydantoin 3 was collected (Scheme 2).

Synthesis of Macromolecule Tetrakis-hydantoin (4)

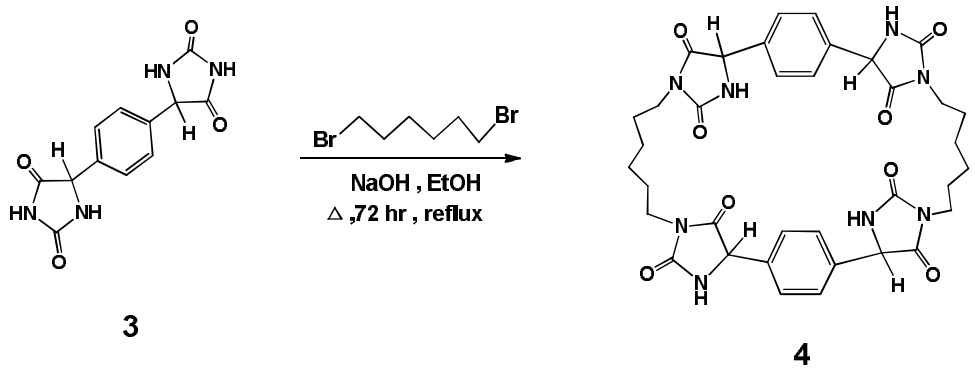
In a variation of this chemistry, stoichiometric amounts

Table 1. Structures of Hydantoins 1a-g and Bis-hydantoins 2a-g

Entry	Substrate (1a-g)	Product (2a-g)	M.p. (°C)	Reaction time (h)	Yield (%)
a			138-140	72	78
b			134-136	72	59
c			198-200	24	62
d			232	72	53
e			202	24	73
f			172	24	88
g			170-172	48	50



Scheme 2. Synthetic route to bis-hydantoin 3



Scheme 3. Synthetic route to macromolecule analogue 4

of bis-hydantoin 3 and dihaloalkane were reacted to yield a novel macrocyclic hydantoin 4 containing four hydantoin moieties, separated by two alkyl and two phenyl linkages. Compound 3 (0.0024 mol) was poured into a mixture of 1.0 M NaOH (5 ml) and ethanol (5 ml). The mixture was heated and allowed to reflux at 60-65 °C for 15 min. Then, 1,6-dibromohexane (0.36 ml, 0.0024 mol) was added drop wise to the solution over the top of the reflux condenser and heated for 72 h. The mixture was allowed to cool in an ice bath, filtered and washed with water. Finally, tetrakis-hydantoin 4 was recrystallized from ethanol several times. In this reaction, some competition between intermolecular and intramolecular linking may cause low yield (Scheme 3). The spectroscopic data for all products are given in the next part.

3,3'-(Hexane-1,6-diyl)bis(5-methyl-5-phenyl-imidazolidine-2,4-dione) (2a). White powder, yield 78%, 0.86 g, m.p.: 138 °C; IR (ν_{max}, cm^{-1}): 1450, 1595, 1705, 1765, 2850-2925 (s), 2975 (w), 3050, 3300; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.07-1.23 (m, 2H), 1.33-1.48 (m, 2H), 1.66 (s, 3H), 3.28-3.31 (m, 1H), 3.45 (t, 1H, J = 6.74 Hz), 7.29-7.34 (m, 1H), 7.38 (t, 2H, J = 7.81 Hz), 7.45 (d, 2H, J = 7.39 Hz), 8.86 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 25.7, 26.3, 28.1, 38.4, 63.5, 126.2, 128.8, 129.4, 140.5, 156.5, 176.2; Exact mass: (M): calcd. for $C_{26}H_{30}N_4O_4$: 462.2267, found: 462.2337.

3,3'-(Hexane-1,6-diyl)bis(5-methyl-5-(*p*-tolyl)-imidazolidine-2,4-dione) (2b). White powder, yield 59%, 0.70 g, m.p.: 134 °C; IR (ν_{max}, cm^{-1}): 1505, 1700, 1770, 2850-2925 (s), 3050 (sh), 3300; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.23 (p, 1H, J = 9.50, 9.17, 6.90 Hz), 1.34 (p, 1H, J = 7.55, 6.40 Hz) 1.42 (p, 1H, J = 6.65, 7.65 Hz), 1.47 (p, 1H, J = 7.28, 5.67 Hz), 1.61-1.63 (s, 3H), 2.26-2.28 (s, 3H), 3.34-3.39 (m, 2H), 7.18 (t, 2H, J = 7.73 Hz), 7.31-7.34 (m, 2H), 8.82-8.83 (s, 1H); Exact mass: (M^+): calcd. for $C_{28}H_{34}N_4O_4$: 490.2580, found: 490.2590.

3,3'-(Hexane-1,6-diyl)bis(5-(4-chlorophenyl)-imidazolidine-2,4-dione) (2c). Cream-colored powder,

yield 62%, 0.75 g, m.p.: 198 °C; IR (ν_{max}, cm^{-1}): 1615, 1700, 1775, 2750, 2850-2925, 3050 (sh), 3325; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.25-1.30 (m, 1H), 1.39 (p, 1H, *J* = 6.86 Hz), 1.71 (p, 1H, *J* = 6.77, 6.55, 11.12 Hz), 1.78 (p, 1H, *J* = 6.39 Hz), 3.44 (t, 1H, *J* = 6.69 Hz), 3.50 (t, 1H, *J* = 6.64 Hz), 7.40 (m, 2H), 7.49 (br s, 1H), 7.56 (d, 1H, *J* = 8.47 Hz), 7.96 (d, 1H, *J* = 8.51 Hz), 9.42-11 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 25.9, 27.5, 27.9, 32.9, 35.8, 38.7, 59.8, 129.4, 130.9, 132.4, 134.8, 138.4, 154.9, 167.9; Exact mass: (M^+): calcd. for $C_{24}H_{24}C_{l2}N_4O_4$: 502.1175, found: 502.1184.

3,3'-(Hexane-1,6-diyl)bis(5,5-diphenylimidazolidine-2, 4-dione) (2d). White powder, yield 53%, 0.75 g, m.p.: 232 °C; IR (ν_{max}, cm^{-1}): 1490, 1700, 1770, 2850-2925, 3050 (w), 3275; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.18 (p, 2H, *J* = 6.75, 7.28 Hz), 1.24 (p, 2H, *J* = 6.52, 8.36, 7.49 Hz), 1.33 (p, 2H, *J* = 6.45, 6.93 Hz), 1.51 (p, 2H, *J* = 7.23 Hz), 3.31-3.35 (m, 2H), 3.42 (t, 2H, *J* = 7.17 Hz), 7.32-7.41 (m, 20H), 9.28 (s, 1H), 9.59 (s, 1H); Exact mass: (M^+): calcd. for $C_{36}H_{34}N_4O_4$: 586.2580, found: 586.2575.

3,3'-(Hexane-1,6-diyl)bis(1,3-diazaspiro[4.5]decane-2,4-dione) (2e). White needles, yield 73%, 0.73 g, mp 202 °C; IR (ν_{max}, cm^{-1}): 1600, 1699, 1768, 2850-2910, 3070, 3300; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.19 (p, 2H, *J* = 3.36 Hz), 1.21-1.27 (m, 3H), 1.37 (p, 1H, *J* = 7.57, 7.66 Hz), 1.43-1.51 (m, 8H), 1.53-1.57 (br m, 3H), 1.62-1.65 (m, 6H), 1.76 (p, 1H, *J* = 7.56, 7.2 Hz), 3.27-3.30 (m, 1H), 3.49 (t, 1H, *J* = 7.73 Hz), 8.63 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 21.7, 25.3, 25.9, 26.4, 28.2, 32.9, 34.1, 35.8, 38.1, 61.6, 156.7, 177.7; Exact mass: (M^+): calcd. for $C_{22}H_{34}N_4O_4$: 418.2580, found: 418.2586.

2e Stereoisomer. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.19 (p, 2H), 1.22-1.29 (br, p, 2H, *J* = 7.22, 8.84, 11.73 Hz), 1.43-1.48 (m, 4H), 1.51-1.57 (br, m, 3H), 1.61-1.65 (m, 4H), 3.27-3.29 (m, 2H), 8.63 (s, 1H).

3,3'-(Hexane-1,6-diyl)bis(1,3-diazaspiro[4.4]nonane-2,4-dione) (2f). White needles, yield 88%, 0.82 g, m.p.: 172 °C; IR (ν_{max}, cm^{-1}): 1450, 1700, 1772, 2860-2930, 3100, 3290; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.20 (p, 2H), 1.46 (p, 2H, *J* = 6.28, 6.61 Hz), 1.65-1.73 (m, 6H), 1.90 (p, 2H, *J* = 6.51, 4.76, 7.20 Hz), 3.29 (m, 2H), 8.41 (s, 1H); Exact mass: (M^+): calcd. for $C_{20}H_{30}N_4O_4$: 390.2267, found: 390.2274.

3,3'-(Hexane-1,6-diyl)bis([spiro(fluorene-9,5'-imidazolidine)-2',4'-dione]) (2g). White powder, yield 50%, 0.68 g, m.p.: 170 °C; IR (ν_{max}, cm^{-1}): 1600, 1698, 1710, 1765, 2850-2925, 3020, 3210; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.31 (p, 3H, *J* = 7.81, 8.29, 7.19 Hz), 1.44 (p, 2H, *J* = 7.49, 7.93, 7.20 Hz), 1.61 (p, 2H, *J* = 7.15, 7.47, 7.36 Hz), 1.80 (p, 1H, *J* = 7.47, 7.10 Hz), 3.47-3.53 (m, 4H), 7.34-7.40 (m, 4H), 7.49 (t, 2H, *J* = 7.38, 1.18 Hz), 7.90 (d, 2H, *J* = 7.53 Hz), 8.88 (s, 1H); Exact mass: (M^+): calcd. for $C_{36}H_{30}N_4O_4$: 582.2267, found: 582.2259.

5,5'-(1,4-Phenylene)bis(imidazolidine-2,4-dione) (3). Cream powder, yield 68%, 1.48 g, m.p.: 295 °$C_{dec.}$. IR (ν_{max}, cm^{-1}): 1515, 1700, 1780, 2755, 3000, 3200, 3300; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 5.17 (s, 1H), 7.35 (s, 2H), 8.40 (s, 1H), 10.79 (s,); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 40.4 (DMSO), 61.8, 127.9, 136.9, 158.3, 174.9;); Exact mass: (M^+): calcd. for $C_{12}H_{10}N_4O_4$: 274.0702, found: 274.0708.

Macromolecule tetrakis-hydantoin (4). white powder, yield 32%, 0.37 g, m.p.: > 200 °$C_{dec.}$; IR (ν_{max}, cm^{-1}): 1510, 1695, 1775, 2850-2925 (s), 3100 (sh), 3300; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 1.06-1.65 (m, 16H), 2.74 (br, s, 1H), 3.00 (br, s, 3H), 3.41 (4H, br), 4.27 (br, s, 1H), 5.19 (br, d, 1H), 7.40 (br, m, 3H), 7.55-7.65 (br, s, 2H), 7.86-7.93 (br, m, 5H), 8.65-9.03 (br, s, 1H), 9.46-9.58 (br, 3H); Exact mass: (M^+): calcd. for $C_{36}H_{40}N_8O_8$: 712.2969, found: 712.2977.

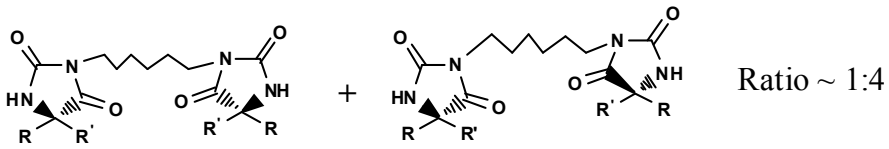
ADDITIONAL INFORMATION

Additional information are provided separately as a supplementary file.

RESULTS AND DISCUSSION

The structures of synthesized bis-hydantoins were elucidated by using M.P., IR, Mass spectra, ^{1}H NMR and ^{13}C NMR techniques. They showed bis-structures in comparison to the parent hydantoins. The acidic *N*(3)H group in hydantoin distinguished by a N(3) chemoselective alkylation in an alkaline milieu, leads to a double alkylation reaction in this process [5,27,29].

In ^{1}H NMR evaluations of bis-hydantoins, some valuable results such as disappearance of N(3) protons, downfield shift of N(1) protons and appearance of aliphatic methylene groups were achieved [30]. Additionally, shifting



2a: R = Ph, R' = Me
2b: R = 4-methylphenyl, R' = Me
2c: R = 4-chlorophenyl, R' = H

Fig. 1. Diastereoisomeric ratios of 2a-c.

of the carbonyl stretching band to lower wavelengths, disappearance of the N(3)H signal at 3200 cm^{-1} and appearance of CH_2 alkyl chain stretching bands at 2850-2930 cm^{-1} confirmed the structures of the resulting bis-hydantoins in IR spectra.

Spectral evaluations also showed some expected symmetry in the structure of new bis-hydantoins. For example, the ^1H NMR spectrum of 2a indicated the presence of 8 signals, corresponding to 30 protons and the ^{13}C NMR spectrum contained 11 signals representing 26 carbon atoms; 4C=O, 4C, 10CH, $6CH_2$ and $2CH_3$ groups. Compounds 2a-c, with two asymmetric carbon atoms in their structures (C_5 of the hydantoin ring) were obtained as mixtures of diastereoisomers (Fig. 1). This was ascertained by monitoring the total integrals of both NH signals in 2a-c and two methyl signals in each isomer of 2b. The compound 2e with no asymmetric center, resulting from two sets of ^1H NMR spectra, after further purification and recrystallization was precipitated as two separable solids conceptualized as a mixture of two conformational stereoisomers due to a subtle conformational phenomenon (ratio 1:2 according to the average integrated signals for NH and cyclohexane protons).

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