Synthesis of *bis*-3-Alkyl-5-arylhydantoins and *bis*-3-Alkyl-5-arylthiohydantoins Separated by Two and Four Carbon Atoms

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Synthesis of 1,2- and 1,4-*bis*-thiohydantoins and hydantoins employing ethylenediamine and 1,4-diaminobutane as spacers is described. Compounds containing a two carbon bridge were synthesized by alkylation of ethylenediamine with two equivalents of *N*-*t*-butyl-α-(*p*-toluenesulfonyloxy)phenylacetamide **3**. The phenyl isothiocyanate adduct of **3** cyclized in refluxing toluene to form **1a**. Other isothiocyanate or isocyanate adducts derived from alkylation product **4** required hydrolysis to induce cyclization. Compounds **1b-1f** were obtained in this way. Compounds with a four carbon bridge were obtained by reaction of two equivalents of methyl α-bromophenyl acetate and 1,4-diaminobutane to produce *N,N'-bis*-[(α-phenyl-α-methoxycarbonyl)methyl]butylenediamine **6**. The isothiocyanate or isocyanate adducts from **6** cyclized, without hydrolysis, to form compounds **2a-2e**.

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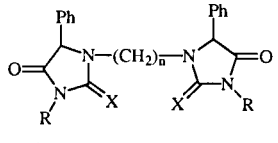
In the course of our studies directed toward the synthesis of biologically active compounds, we had occasion to synthesize *bis*-3-alkyl-5-arylhydantoins and *bis*-3-alkyl-5-arylthiohydantoins separated by 2- and 4-carbon spacers. These compounds are viewed as bivalent ligands as the aryl group of these agents is superimposable on the 5-aryl of phenytoin, a well-known antiseizure agent, and the ethylene and butylene spacers alter the interatomic band distance between the two pharmacophores [1,2].



1 n = 2

a; R = Ph, X = S
b; R = Et, X = S
c; R = Me, X = S
d; R = *i*-Pr, X = S
e; R = Et, X = O
f; R = Me, X = O

2 n = 4

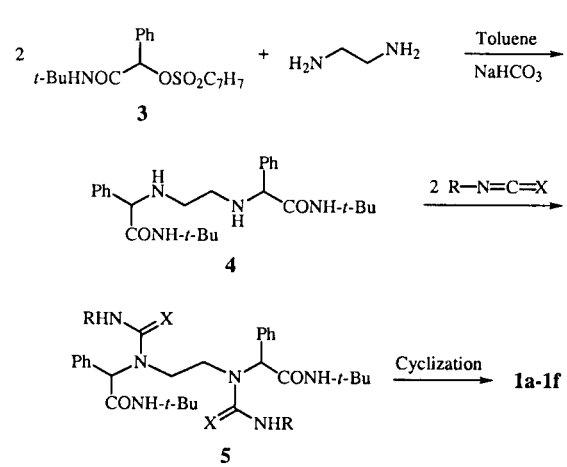
a; R = Me, X = O
b; R = Me, X = S
c; R = Me, X = O
d; R = Et, X = S
e; R = Ph, X = S

The compounds, n = 2, were synthesized as shown in Scheme 1. The compounds, n = 4, were prepared as depicted in Scheme 2.

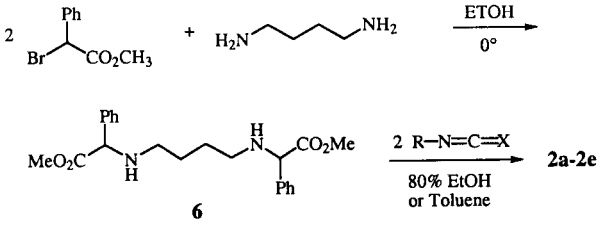
In Scheme 1, the tosylate ester, *N*-*t*-Butyl-α-(*p*-toluenesulfonyloxy)phenylacetamide **3** was prepared from *N*-*t*-butyl-α-hydroxyphenylacetamide [3] and *p*-toluenesulfonyl chloride in pyridine [4]. By use of a 2:1 molar ratio of tosylate ester to ethylenediamine, the ethylenediamine bridge to the pro-pharmacophores **4** was established. The *N*-*t*-butylamide function served to minimize nucleophilic attack at the carbonyl group and facilitate tosylate displacement. Compound **4**, *N,N'*-[(*bis*-α-phenyl-α-*t*-butylaminocarbonyl)methyl]-ethylenediamine, was purified by column chromatography, to give a thick, viscous oily material. The structure was further confirmed as the *bis*-*N*-ethylurea adduct, formed by reaction with 2 equivalents of ethyl isothiocyanate.

Reaction of **4** with two equivalents of phenyl isothiocyanate in refluxing toluene resulted in spontaneous cyclization of the *bis*-phenyl isothiocyanate adduct **5** to form **1a**. Thiourea adducts derived from methyl isothiocyanate, ethyl isothiocyanate, and isopropyl isothiocyanate did not undergo cyclization as described for the phenyl isothiocyanate reaction. The adducts derived from these isothiocyanates were cyclized with concentrated hydrochloric acid/glacial acetic acid. It is plausible to conclude that cyclization of the phenyl isothiocyanate adduct proceeds without hydrolysis of the amide function because the phenyl

Scheme 1



Scheme 2



and *t*-butyl group cause congestion that is eased by displacement of *t*-butylamine resulting in cyclization.

In Scheme 2, two equivalents of methyl α-bromophenylacetate was reacted with an equivalent of 1,4-diaminobutane in absolute ethanol. To minimize amide formation, 1,4-diaminobutane dissolved in absolute ethanol was slowly added at 0° to a methyl α-bromophenylacetate solution in absolute ethanol. The reaction product, *N,N'-bis*[(α-phenyl-α-methoxycarbonyl)methyl]butylenediamine **6** was not purified but reacted with 2 equivalents of isothiocyanate or isocyanate. For the isothiocyanate reactions, 80% ethanol was used as the solvent; for the isocyanate reactions, dry toluene in a nitrogen atmosphere was employed. The reaction mixture was heated at 85-90° for 2.5 hours resulting in cyclization and the isolation of compounds **2a-2e.**

Confirmation of structure of all the compounds synthesized was provided by elemental analyses, nmr, ir, and mass spectral data. The ^{13}C nmr are listed in Table 1; ^{1}H nmr are presented in Table 2; physicochemical properties and mass spectral data are given in Table 3.

All the compounds synthesized were pharmacologically evaluated to ascertain if they could prevent seizures in male albino mice induced by maximal electroshock [5]. No anti-seizure activity was found in any of the compounds.

EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by either Quantitative Technologies (Whitehouse, NJ) or Galbraith Laboratories (Knoxville, TN). FT infrared spectrum were recorded using a Nicolet Impact 410 spectrometer. The ^{1}H nmr spectra were recorded on a General Electric QE-300 and Joel FX 90Q at 300 MHz and 90 MHz respectively and are reported in δ values (ppm) relative to TMS. ^{13}C nmr were recorded on a General Electric QE-300 at 75 MHz. Mass spectra were obtained using a ZAB2-SE mass spectrometer.

N-t-Butyl-α-(*p*-toluenesulfonyloxy)phenylacetamide **3**.

N-t-Butyl-α-hydroxyphenylacetamide (37.9 g, 0.18 mole), prepared by a Ritter reaction as described by Anatole and Medete [3] was added to pyridine (60 ml), then cooled in an ice bath to 5°. *p*-Toluenesulfonyl chloride (38.51 g, 0.20 mole) was added in small portions with stirring. The solution was maintained below 20° and stirred for 3 hours, and 250 ml of 3*M* hydrochloric acid was added causing the product to precipitate. The reaction product was filtered, dried at 50°, recrystallized from *t*-butyl alcohol giving 17 g (26%) of **3**, mp 136-138°; ir: 3400, 1670, 1190, 1370 cm^{-1}.

Anal. Calcd. for $C_{19}H_{23}NO_4S$ (361.5): C, 63.13; H, 6.41; N, 3.88; S; 8.87. Found: C, 63.23; H, 6.41; N, 3.79; S; 9.18.

Table 1

^{13}C nmr Spectrum for Compounds **1a-1e**, δ ppm

	Aryl	Ethylene	Benzylic	Thioketone	Carbonyl	Methylene	Methyl	Methine
1a	129 135	43, 61	67	172	182	-	-	-
1b	129- 133	40, 61	68	170	184	38	16	-
1c	128- 133	42	61	173	186	-	30	-
1d	131- 133	39, 62	67	173	184	-	19	50
1e	127- 133	38	63	171 [a]	156[b]	33	13	-

[a] Represents the value of ureido carbonyl. [b] Represents the value of lactam carbonyl.

Table 2

^{1}H nmr Spectrum of Compounds **1f-2e** [a]

	Aryl	Spacer	Benzylic	Methyl	Ethyl
1f	7.2, 7.6 (m, 10H)	3.6, 3.8 (m, 4H)	4.85(s, 2H)	3.15(s,6H)	-
2a	7.2, 7.35 (m, 10H)	1.2, 2.65, 3.25 (m, 8H)	5.05 (s, 2H)	2.85 (s, 6H)	-
2b	7.18, 7.39 (m, 10H)	1.28, 3.0, 3.81 (m, 8H)	5.28 (s, 2H)	3.08 (s, 6H)	-
2c	7.2, 7.38 (m, 10H)	1.2, 2.65 (m, 8H)	5.05 (s, 2H)	-	1.1, 3.4 (m, 10H)
2d	7.15, 7.40 (m, 10H)	1.2, 3.02, 3.8 (m, 8H)	5.2 (s, 2H)	-	1.05, 3.02 (m, 10H)
2e	7.25, 7.4 (m, 10H)	1.42, 3.05, 3.9 (m, 8H)	5.48 (s, 2H)	-	-

[a] In Dimethyl-d_6 sulfoxide.

Table 3

Bis-Hydantoins/Thiohydantoins Separated by 2 and 4 Carbons, **1a-2e**

	R	X	n	Analysis, % Calcd./Found C	H	N	S	Mo. Wt	M/Z [a]	IR [b] ν cm-1	R S [d]	Mp °C	Yield %
1a	Ph	S	2	68.28	4.66	9.96	11.40	562.7	563.2	1725	*n*-BuOH/ dimethylformamide	320-322	25
				67.34	4.78	9.26	11.39						
1b	Et	S	2	61.77	5.62	12.01	13.74	466.6	467.2	1775	*n*-BuOH/ dimethylformamide	203-204	28
				61.77	5.74	11.86	13.34						
1c	Me	S	2	60.25	5.06	12.78	14.62	438.6	439.2	1725	*n*-BuOH/ dimethylformamide	220-223	36
				59.93	5.19	12.66	14.32						
1d	isPr	S	2	62.78	6.29	11.53	12.87	494.7	495.2	1770	*n*-BuOH/ dimethylformamide	222-225	51
				63.13	6.11	11.33	12.96						
1e	Et	O	2	66.34	6.03	12.90	-	434.5	434	1700, 1775	EtOH	156-157	35
				66.11	6.10	12.69	-						
1f	Me	O	2	65.01	5.46	13.79	-	406.5	406	1700,1775	EtOH	216-219	30
				64.90	5.60	13.70							
2a	Me	O	4 [c]	65.00	6.14	12.63	-	434.5	435.4	1750	EtOH	151-153	30
				65.37	6.17	12.67							
2b	Me	S	4 [c]	60.61	5.72	11.78	13.48	466.6	467.3	1750	*n*-PrOH/ dimethyl sulfoxide	223-226	43
				60.42	5.61	11.61	13.34						
2c	Et	O	4	67.50	6.53	12.11	13.84	462.6	463.4	1700,1775	EtOH	182-184	30
				67.00	6.69	11.94	13.68						
2d	Et	S	4	63.13	6.12	11.13	12.96	497.4	495.2	1750	*n*-PrOH/ dimethyl sulfoxide	230-233	43
				62.81	6.11	11.04	13.09						
2e	Ph	S	4 [c]	68.08	5.21	9.34	10.69	590.7	591.4	1750	EtOH/ dimethyl sulfoxide	265-270d.	31
				68.16	5.16	9.32	11.2						

[a] Values reported for n = 4 compounds are m/z + 1. [b] Nujol mulls. [c] Calculated with 1/2 mole of water. [d] Recrystallization solvent(s).

N,N'-[(*bis*-α-Phenyl-α-*t*-butylaminocarbonyl)methyllethylenediamine **4**.

N-*t*-Butyl-α-(*p*-toluenesulfonyloxy)phenylacetamide **3** (18.0 g, 0.05 mole) and sodium bicarbonate (8.40 g, 0.01 mole) was added to dry toluene (250 ml). To the resultant mixture, ethylenediamine (1.5 g, 25 mmoles) dissolved in dry toluene was added dropwise. The reaction mixture was refluxed for 3 hours, cooled to room temperature, filtered, and washed with 3 x 50 ml of toluene. The mother liquor and washes were combined and washed with 3 x 75 ml of water and dried over magnesium sulfate. The magnesium sulfate was removed by filtration and the solvent removed *in vacuo*. The crude product 10.2 g (93%) was purified using silica gel column chromatography. Petroleum ether:methylene chloride (1:1) then (1:3) and finally (1:9) were used as the eluents. Upon removal of the solvents, 5.2 g (47%) of **4** was obtained as a glass-like material; ir: 3300, 1180, 950, 710 cm^{-1}.

Anal. Calcd. $C_{26}H_{38}N_4O_2$ (438.6): C, 71.20; H, 9.73; N, 12.78. Found: C, 70.47; H, 8.69; N, 12.64.

N,N'-bis-[α-Phenyl-α-*t*-butylaminocarbonyl)methyl]-*N,N'-bis*-(ethylaminothiocarbonyl)ethylenediamine **5**, R = Et, X = S.

Ethyl isothiocyanate (1.48 g, 20.8 mmoles) dissolved in dry toluene was added dropwise to a stirred solution of *N,N'*-[(*bis*-α-phenyl-α-*t*-butylaminocarbonyl)methyl]ethylenediamine **4** (4.6 g, 10.4 mmoles) dissolved in toluene (80 ml). The reaction mixture was heated at 80° for 2 hours. A fine white precipitate began to form and the reaction mixture was refluxed for 1.5 hours. Upon cooling overnight, a precipitate formed and 1.43 g (33%) of white solid, mp 256-257° after recrystallization from ethyl acetate/ethanol was obtained. When the filtrate was allowed to stand over the weekend, an additional 0.85 g (20%) of **5**, (R = Et, X = S) was collected; ir 3375, 3455, 1660, 1030 cm^{-1}; ^{13}nmr: aryl 128 δ, ethylene 36 δ, benzylic 60 δ, carbonyl 172 δ, and 159 δ, methylene 42 δ, methyl 18 δ, *t*-butyl 29 δ, methine 52 δ; ms: 581.6, 508.5, 155.1 119 (m/z).

Anal. Calcd. $C_{32}H_{48}N_6O_4$ (580.8): C, 66.18; H, 8.33; N, 14.47. Found: C, 66.29; H, 8.45; N, 14.21.

1,2-*bis*-(3,5-Diphenylimidazolidine-2-thion-4-on-yl)ethane **1a**.

N,N'-[(*bis*-α-Phenyl-α-*t*-butylaminocarbonyl)methyl]ethylenediamine **4** (1.45 g, 3.3 mmoles) was dissolved in 80% ethanol (15 ml) and phenyl isothiocyanate (0.97 g, 7.2 mmoles) was added all at once. The solution was heated at 80° for two hours and then allowed to cool. The reaction mixture was concentrated *in vacuo*, the residue rubbed with a mixture of acetone/ethanol and cooled in the refrigerator. Upon cooling, a crystalline material **1a** was collected by filtration. It was recrystallized from a suitable solvent. Tables 1 and 3.

Scheme 1. Preparation of Compounds **1b-1f**.

N,N'-[(*bis*-α-phenyl-α-*t*-butylaminocarbonyl)methyl]-ethylenediamine **4** (7.30 mmoles) was dissolved in 95% ethanol, and isothiocyanate (14.60 mmoles) was slowly added to the solution. The reaction mixture was stirred and heated to 80° for 2 hours. The reaction mixture was concentrated *in vacuo*, and concentrated hydrochloric acid (31 ml) and glacial acetic acid (60 ml) added to the residue. The mixture was refluxed with stirring for 2 hours. The product precipitated on cooling, or was obtained

by concentration of the reaction mixture *in vacuo*. It was recrystallized from a suitable solvent. Tables 1 and 3 [6].

Scheme 2. Preparation of Compounds **2a-2e**.

Methyl α-bromophenylacetate (20 mmoles) and sodium bicarbonate (30 mmoles) were added to absolute ethanol (250 ml). The mixture was cooled with magnetic stirring to 0° in an ice-water bath. 1,4-Diaminobutane (10 mmoles), dissolved in absolute ethanol (50 ml) was added dropwise to the cooled suspension. Once the addition was complete, about 2 hours, the reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo*, 100 ml of water was added to the residue, and methylene chloride (4 x 25 ml) was used to extract the aqueous suspension. The methylene chloride extract was dried over magnesium sulfate, the drying agent removed by filtration and the filtrate concentrated *in vacuo* to give residue. The oily residue was dissolved in 100 ml of 80% ethanol, and isothiocyanate (0.02 moles) was added all at once and the reaction mixture was heated at 85-90° for 2.5 hours, then allowed to stand overnight with stirring at room temperature. A white precipitate formed; it was recrystallized from an appropriate solvent. Tables 2 and 3 [6].

Acknowledgements.

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[6] Dry toluene and a nitrogen atmosphere was the solvent employed in the reactions that used isocyanates.