Synthesis of 5,5-Bis (p-methoxy-m-bromophenyl)-2-thiohydantoin Derivatives

by

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Abstract

Treatment of 5,5-bis (p-methoxy-m-bromophenyl)-2-thiohydantoin (2a) with methyl iodide in basic alcohol solution gave 5,5-bis (p-methoxy-m-bromophenyl)-2-methythiohydantoin (3a), in 81.0% yield, whose ten new derivatives (3b-3f), (4a-4e) were also prepared in a similar fashion.

Introduction

Diphenylhydantoin has been used as anticonvulsant drug for many years, but it has many side effects1), such as trema, slurred speech, nystagmus and diplopia. If the atom of 2-position of diphenylhydantoin is sulphur instead of oxygen, then the structure is similar to thiopental (A) which is an anesthetic agent. If the nitrogen is alkylated the structure is similar to mephobarbital2) (B) which is an anticonvulsant agent.

A series of N- and S- alkyl derivatives of 5,5-diphenyl-2-thiohydantoin was prepared as possible anticonvulsants3). So the purpose of this study is to synthesize another series of anticonvulsant by modifying the structure of diphenylhydantoin. It is hope that the anticonvulsive effects of the eleven new compounds will be improved and their side effects reduced.

Experimental Section

Chemical Methods and Materials. Melting points were determined on a Büchi SMP-20 apparatus and were not corrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100, 100MHz FT-NMR spectrometer, using TMS as internal standard and solvents as specified. Chemical shifts were reported in δ units. Signals are quoted as s(singlet), d(doublet), t(triplet), br(broad), and m(multiplet). IR spectra (KBr) were recorded on a Perkin-Elmer model 567 IR spectrophotometer. Mass spectra were obtained with a JEOL JMS-D300, at 70 eV, high resolution mass spectrometer. TLC was performed on plastic film coated with silica gel Merck F-254 (EM Laboratories, Inc., Elmstord, N.Y.). The solvent used was ethylacetate. All other reagents were commercial products of the highest purity.

Alkylation of 5,5-bis(p-methoxy-m-bromophenyl)-2-thiohydantoin[3-15] (Scheme I).

5,5-Bis(p-methoxy-m-bromophenyl)-2-methylthiohydantoin (3a)

1.0g (2.07m mole) of 5,5-bis(p-methoxy-m-bromophenyl)-2-thiohydantoin (2a) was dissolved in ethanol containing 1.5ml of 3N sodium hydroxide solution the mixture was stirred, dropped 0.4ml of propyl iodide in and refluxed for 0.5 hour, filtered, then the crystal was recrystallized with ethanol, dried to give 3a 0.83g (yield 81.0%, mp 93-94°C); TLC Rf=0.72; IR (cm^{-1}) 3100 (NH), 1960 (C=O); NMR (DMSO-d_6, δ) 2.6 (s, 3H, -S-CH_3), 3.8(s, 6H, -OCH_3x2), 7.0-7.4 (m, 6H, -C_6H_3x2), 11.4(br, 1H, NH-1).

5,5-Bis(P-methoxy-m-bromophenyl)-2- ethylthiohydantoin (3b)

Derivative (*3b*) was also prepared in a similar fashion as (*3a*) but instead of methy iodide this time ethyl iodide was used and refluxed for 1.5 hr. (yield 79.1%, mp 88-89°C); TLC Rf=0.76; IR(cm^{-1}) 3150 (NH), 1680(CO); NMR (DMSO-d_6, δ) 1.3 (t, J=7.4 Hz, 3H, -s-CH_2-CH_3), 3.2(q, J=7.4Hz, 2H, S-CH_2-CH_3), 3.8 (s, 6H, -OCH_3x2), 7.1-7.4(m, 6H, -C_6H_3x2), 11.3(br, 1H, -NH-1); Ms, m/e (relative intensity) 576 (39, M+4), 514(87, M+2), 512(39, M^+), 497(10, M^+-CH_3), 439 (100, M-CSC_2H_5), 328(11, M^+-CH_3O-C_6H_3–Br), 226(22,CH_3–O–C_6H_3(Br) –CH–CO, 192 (19, 226–OCH_3–H–H), 62 (10, 2-OCH_3)

5.5-Bis(p-methoxy-m-bromophenyl)-2-propylthiohydantoin (3c)

Derivative (*3c*) was also prepared in a similar fashion as (*3a*) but instead of methyl iodide this time propyl lodide was used and refluxed for 1 hr. (yield 75.5%, mp 86-87°C); TLC Rf=0.73; IR(cm^{-1}) 3140 (NH), 1680(CO); NMR (DMSO-d_6, δ) 1.0 (t, J=7.2Hz, 3H, $-CH_2-C\underline{H}_3$), 1.7(m, 2H, $-C\underline{H}_2-CH_3$), 3.3(t, 2H, $-S-C\underline{H}_2-CH_2-$), 3.8(s, 6H, $-OCH_3$x2), 7.1-7.4(m, 6H, $-C_6H_3$x2), 11.2(br, 1H, NH-1).

5.5-Bis (p-methoxy-m-bromophenyl)-2-isopropylthiohydantoin (*3d*)

Derivative (*3d*) was also prepared in a similar fashion as (*3a*) but instead of methyl iodide this time isopropyl iodide was used and refluxed for 1.5hr. (yield 80.5%, mp 96-97°C): TLC Rf=0.70; IR(cm^{-1}) 3150(NH), 1670(CO); NMR (DMSO-d_6) 1.3 (d, J=7.3Hz, 6H $(CH_3)_2$), 3.8(s, 6H, $-OCH_3$x2) 4.1(m, 1, CH), 7.1-7.4(m, 6H, C_6H_3x2), 11.2(br, 1H, NH-1).

5.5-Bis (p-methoxy-m-bromophenyl)-2-butylthiohydantoin (*3e*)

Derivative (*3e*) was also prepared in a similar fashion as (*3a*) but instead of methyl iodide this time butyl iodide was used and refluxed for 1.5hr. (yield 70.6%, mp 78-79°C); TLC Rf=0.68; IR(cm^{-1}) 3140(NH), 1680(CO); NMR (DMSO-d_6) 0.9(t, J=7.3Hz, 3H, $-CH_2-CH_3$), 1.2-1.8 (m, 4H, $-(CH_2)_2-$, 3.2(t, J=7.2Hz, 2H-$S-CH_2-CH_2-$), 3.8(s, 6H, $-OCH_3$x2), 7.1-7.4(m, 6H, $-C_6H_3$x2), 11.4 (br, 1H, NH-1).

5.5-Bis(p-methoxy-m-bromophenyl)-2-amylthiohydantoin (*3f*)

Derivative (*3f*) was also prepared in a similar fashion as (*3a*) but instead of methyl iodide this time amyl iodide was used and refluxed for 1 hr. (yield 78.2%, mp 90-91°C); TLC Rf=0.73; IR(cm^{-1}) 3140(NH), 1680(CO): NMR(DMSO-d_6) 0.9(t, J=7.3Hz, 3H, $-CH_2-C\underline{H}_3$) 1.0-1.8(m, 6H, $-(CH_2)_3$), 3.2(t, J=7.2Hz, 2H, $S-C\underline{H}_2-CH_2-$), 3.8(s, 6H, $-OCH_3$x2), 7.1-7.4(m, 6H, $-C_6H_3$-x2), 11.3(br, 1H, NH-1).

5.5-Bis(p-methoxy-m-bromophenyl)-1-methyl-2-methylthiohydantoin (*4a*)

1.0g(2.01 mmole) of 5.5-Bis(p-methoxy-m-bromophenyl)-2-methylthiohydantoin (*3a*) was dissolved in ethanol contain 0.6 ml of 3N sodium hydroxide solution, the mixture was stirred, dropped 0.3ml of methyl iodide in and refluxed below 70°C for 45min., filtered, then the crystal was washed with water and dried to give *4a* 0.80g (yield 77.4%, mp 166-167°C); TLC Rf=0.56; IR (cm^{-1}) 1710(CO); NMR(DMSO-d_6, δ) 2.6(s, 3H, $S-CH_3$), 2.9(s, 3H, $N-CH_3$), 3.8(s, 6H, $C-OCH_3$x2), 7.1-7.4(m, 6H, $-C_6H_3$x2); Ms, m/e (relative intensity) 516(20, M+4), 514(40, M+2), 512(20, M^+), 483(16, $M^+-CH_2-CH_3$), 442(100, 440+2), 440(30, $M^+-CH_2-CSCH_2$), 422(40, $M^+-2-OCH_3-CO$), 212(40, $H_3C-C_6H_3(Br)-CNH$), 62 (4,2-OCH_3).

5.5-Bis(p-methoxy-m-bromophenyl)-1-ethyl-2-methylthiohydantoin (*4b*)

Derivative (*4b*) was also prepared in a similar fashion as (*4a*) but instead of methyl iodide this time ethyl iodide was used and refluxed for 1.5hr. (yield 75.3%, mp 121-122°C); TLC Rf=0.60; IR(cm^{-1}) 1685(CO); NMR(DMSO-d_6) 1.3(t, J=7.2Hz, 3H, $-CH_2-C\underline{H}_3$), 3.2 (q, J=7.2Hz, 2H, $-C\underline{H}_2-CH_3$), 3.9 (s 6H, $-OCH_3$ x2),7.1-7.4(m, 6H, $-C_6\underline{H}_3$ x2).

5.5-Bis (p-methoxy-m-bromophenyl)-1-propyl-2-methylthiohydantoin (*4c*)

Derivative (*4c*) was also prepared in a similar fashion as (*4a*) but instead of methyl iodide this time propyl iodide was used and refluxed for 1.5hr. (yield 78.1%, mp 154-155°C); TLC Rf-0.58; IR(cm^{-1}), 1680(C=0); NMR(DMSO-d_6, δ) 0.9(t,J=7.2Hz, 3H, $-CH_2-C\underline{H}_3$), 2.6(s, 3H, $S-C\underline{H}_3$), 3.2(t,J=7.1Hz, 2H, $-N-C\underline{H}_2-$), 3.8(s, 6H, $-OC\underline{H}_3$ x2), 7.1-7.4(m, 6H, $-C_6\underline{H}_3$ x2).

5.5-Bis(p-methoxy-m-bromophenyl)-1-butyl-2-methylthiohydantoin (*4d*)

Derivative (*4d*) was also prepared in a similar fashion as (*4a*) but instead of methyl iodide this time butyl iodide was used and refluxed for 1.5hr. (yield 78.1%, mp 154-155°C); TLC Rf=0.58; IR(cm^{-1}) 1680(C=0); NMR(DMSO-d_6, δ) 0.9(t, J=7.2Hz, 3H, $-CH_2-C\underline{H}_3$), 1.4-1.7(m, 4H, $-(CH_2)_2-$), 2.6(s, 3H, $S-C\underline{H}_3$), 3.2(t, J=7.1Hz, 2H, $-N-C\underline{H}_2-$), 3.8(s, 6H, $-OC\underline{H}_3$ x2), 7.1-7.4(m, 6H, $-C_6H_3$ x2).

5.5-Bis(p-methoxy-m-bromophemyl)-1-isoamyl-2-methylthiohydantoin (*4e*)

Derivative (*4e*) was also prepared in a similar fashion as (4a) but instead of methyl iodide this time isoamyl iodide was used and refluxed for 1.5hr. (yield 79.2%, mp 160-162°C); TLC Rf=0.63; IR(cm^{-1}) 1670(C=0); NMR(DMSO-d_6, δ) 0.9(d, J=7.0Hz, 6H, $-(C\underline{H}_3)_2$), 1.4-1.7(m, 3H, $-C\underline{H}_2-C\underline{H}$), 2.6(s, 3H, $S-C\underline{H}_3$), 3.2(t, J=7.2Hz, 2H, $-N-C\underline{H}_2-$), 3.9(s, 6H, $-OC\underline{H}_3$ x2), 7.1-7.4(m, 6H, $-C_6\underline{H}_3$-x2).

Results and Discussion

On synthesis of mono substituted derivatives (*3a-3f*), the amount of 5.5-Bis (p-methoxy-m-bromophenyl)-2-thiohydantoin (2a), sodium hydroxide and alkyl halide reagents must be controlled in the mole ratio of 1:1.1 and the refluxing temperature must be controlled below 70°C. If excess amount of sodium hydroxide or alkyl halide reagents was used, mono and disubstituted mixture were produced, the separation would become difficult.

On synthesis of N-and S-disubstituted derivatives (*4a-4e*), excess amount of sodium hydroxide, double the amount of alkyl halide reagents and longer refluxing time was applied to yield disubstituted compound completely.

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5.5－雙（對甲氧—間溴苯基）－2－硫代乙內醯脲衍生物之合成

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摘要

取5,5－雙（對甲氧—間溴苯基）－2－硫代乙內醯脲（2a），碘化甲烷，氫氧化鈉、乙醇、混合加熱，冷却可得到5,5－雙（對甲氧—間溴苯基）－2－甲基硫代乙內醯脲（3a），產率81.0％，同樣的方法可合成（3b-3f），（4a-4e）10個衍生物。