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Synthesis of new Hydantoin-3-Acetic acid Derivatives

Chang-Hyun Oh, Yong-Koo Kang, Sang-Woo Park, and Jung-Hyuck Cho*

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131-650

Soon-Kyung Kwon

Department of Pharmacy, Duksung Womens' University, Seoul 140-132.
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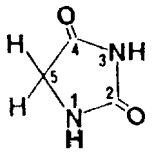
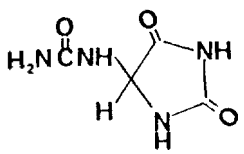
Through the Bucherer-Berg method, new 5-alkylthiomethyl or 5-alkylsulfonylmethylhydantoins were prepared. The reaction of ethyl chloroacetate with these compounds gave 3-acetate and the subsequent hydrolysis with dilute sodium hydroxide resulted in 3-hydantoinacetic acid derivatives. These products are expected to exhibit anti-inflammatory and analgestic activities.

Introduction

Hydantoin (2,4-imidazolidinedione, glycolurea) was first discovered by Bayer in 1861 as a hydrogenation product of allantoin and its derivatives are important intermediates in the synthesis of several amino acids and also used as anticonvulsants or antibacterials.[1-7] In the course of our studies on



hydantoin



allantoin

the development of new pharmaceutically active substances, several hydantoin derivatives were prepared. Of these we report the synthesis of 3-hydantoinacetic acid derivatives with alkylthio or alkylsulfonylmethyl group at the 5-position of hydantoin ring, which are known to exhibit anti-inflammatory and analgestic activities.[8,9]

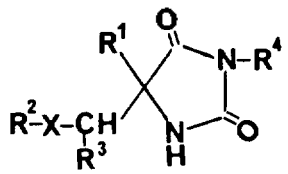
Most of hydantoin derivatives were prepared in good yield through the Bucherer-Berg synthesis, i.e. the reaction of corresponding ketones with 2 mol. equivalent of potassium cyanide and 4 mol. equivalent of ammonium carbonate in 60% aqueous alcohol at 65°C.[5,10-14] Kwon and his co-workers synthesized several 5-aryl-5-alkylthiomethyl-hydantoins and their anti-inflammatory properties were determined in the rat paw oedema test.

Recently they reported the preparation of twenty 5,5-disubstituted 3-hydantoinacetic acid derivatives for developing new anti-inflammatory and analgestic agents.[9] These compounds were screened for the above effects and as a result five of them, e.g. 5-phenyl-5-propylthiomethyl hydantoin-3-acetate showed a significant analgestic activity. Therefore we introduced some other alkylthiomethyl group on the 5-position of hydantoin ring and also chloroacetone, in stead of phenacyl chloride, was utilized to modify the other substituent on that position. We expect the better anti-inflammatory or analgestic effects for this kind of derivatives and the results of screening will be reported later in the separate paper.

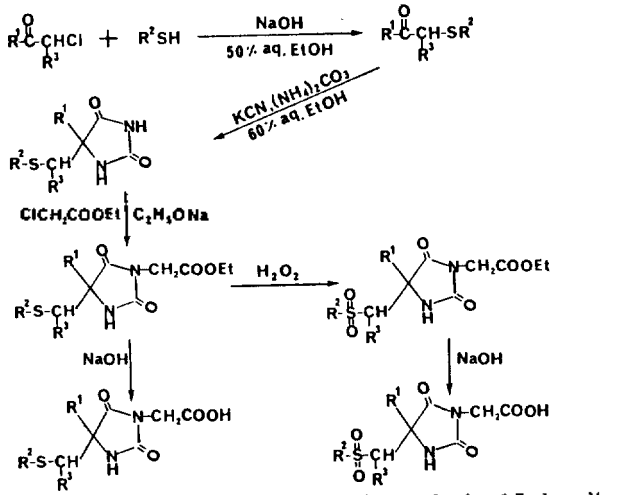
Results and Discussions

By the reaction of phenacyl chloride or chloroacetone with alkyl(or aryl)mercaptan, phenyl(or methyl) alkyl(or aryl) thiomethyl ketones were prepared and they were converted to 5-phenyl(or methyl)-5-alkyl(or aryl)thiomethylhydantoins by Bucherer-Berg synthesis in good yields. The reaction of ethyl chloroacetate with these compounds gave the corres-

Table 1. List of prepared hydantoin Derivatives



compound	R^1	R^2	X	R^3	R^4	yield(%)	m.p(°C)
17	$-C_6H_5$	$-C_2H_5$	-S-	H	H	50	195-196
18	$-C_6H_5$	$-C_3H_7$	-S-	H	H	57	141-142
19	$-C_6H_5$	$-C_4H_9$	-S-	H	H	57	109-110
20	$-C_6H_5$	-t-butyl	-S-	H	H	54	206-208
21	$-C_6H_5$	-iso-butyl	-S-	H	H	51	101-102
22	$-C_6H_5$	$-C_5H_{11}$	-S-	H	H	63	101-102
23	$-C_6H_5$	o-chlorobenzyl	-S-	H	H	49	145-147
24	$-CH_3$	$-C_3H_7$	-S-	H	H	53	117-119
25	$-CH_3$	-t-butyl	-S-	H	H	79	208-210
26	$-CH_3$	-t-amyl	-S-	H	H	67	185-187
27	$-CH_3$	-iso-amyl	-S-	H	H	71	122-124
28	$-CH_3$	phenyl	-S-	H	H	60	—
29	$-CH_3$	o-toluyl	-S-	H	H	81	154-155
30	$-CH_3$	o-chlorobenzyl	-S-	H	H	76	—
31	$-CH_3$	phenyl	-S-	CH_3	H	72	—
32	$-CH_3$	o-chlorobenzyl	-S-	H	74	—	
33	$-C_6H_5$	$-C_2H_5$	-S-	H	$-CH_2COOH$	88	159-160
34	$-C_6H_5$	$-C_3H_7$	-S-	H	$-CH_2COOH$	88	85-86
35	$-C_6H_5$	$-C_4H_9$	$-SO_2-$	H	$-CH_2COOH$	72	101-103
36	$-C_6H_5$	-iso-butyl	$-SO_2-$	H	$-CH_2COOH$	51	101-102
37	$-C_6H_5$	-t-butyl	-S-	H	$-CH_2COOH$	79	206-208
38	$-C_6H_5$	$-C_5H_{11}$	$-SO_2-$	H	$-CH_2COOH$	77	104-105
39	$-C_6H_5$	o-chlorobenzyl	$-SO_2$	H	$-CH_2COOH$	81	185-187
40	$-CH_3$	$-C_3H_7$	-S-	H	$-CH_2COOH$	90	134-136
41	$-CH_3$	-t-butyl	-S-	H	$-CH_2COOH$	88	174-176
42	$-CH_3$	-t-amyl	-S-	H	$-CH_2COOH$	91	172-174
43	$-CH_3$	-iso-amyl	-S-	H	$-CH_2COOH$	84	167-169
44	$-CH_3$	phenyl	-S-	H	$-CH_2COOH$	84	119-121
45	$-CH_3$	o-toluyl	-S-	H	$-CH_2COOH$	85	125-128
46	$-CH_3$	o-chlorobenzyl	-S-	H	$-CH_2COOH$	85	150-152
47	$-CH_3$	o-chlorobenzyl	-S-	CH_3	$-CH_2COOH$	88	167-168
48	$-CH_3$	phenyl	-S-	CH_3	$-CH_2COOH$	81	158-160



Scheme 1. General reaction path for the synthesis of 5-phenyl(or methyl)-5-alkyl(or aryl)thio(or sulfonyl)methylhydantoin-3-acetic acids.

ponding 3-acetates[15-17] and these were hydrolysed with aqueous sodium hydroxide to give 3-hydantoinacetic acid derivatives. 5-phenyl(or methyl)-5-alkyl(or aryl)sulfonylmethylhydantoins were also obtained by H_2O_2 oxidation of corresponding alkyl(or aryl)-thiomethyl compounds. (Scheme 1)

In the Bucherer-Berg synthesis of hydantoins, their yields varied from 50 to 80% depending on the nature of R^1 group, i.e. methyl substituent for R^1 showed higher value than phenyl group. The same behavior was observed for R^2 substituent. Such results could be explained in terms of steric effect. Oxidation yields were in general over 90% and in the hydrolysis reaction better yield was obtained for the alkyl(or aryl)thiomethyl hydantoins than that of alkyl(or aryl)sulfonylmethyl derivatives. The melting points of hydantoin derivatives with more branched substituents for R^2, e.g. tert-butyl, tert-amyl, were, as we anticipated, higer than that of other isomers. In the course of oxidation reactions, the formation of mono-oxidation product, sulfoxide, was not observed. Corresponding mass spectra clearly showed the fact that the ox-

idation proceeded completely to give sulfonyl derivatives.

List of prepared hydantoin derivatives and their yields and also melting points were summarized in Table 1.

Experimental

All ^{1}H-NMR spectra were recorded at 60MHz on Jeol PMX 60SI or 200 MHz Bruker AM 200 spectrometer using TMS as an internal standard. Melting points were measured on a Thomas-Hoover capillary apparatus and were uncorrected. IR spectra were also taken on Perkin-Elmer 1310 spectrometer.

General Procedure for the Synthesis of Ketones(1)-(16). 0.3 equiv. of sodium hydroxide was dissolved in 240 m*l* 50% aqueous ethanol and cooled to 0°C. To this solution was added with stirring 0.3 equiv. of alkyl or aryl mercaptan and same equiv. of phenacyl chloride or chloroacetone.

After refluxing the solution for 90 minutes at room temperature, 500 m*l* water was poured into the solution and was extracted twice with 300 m*l* ethy ether. Ether layer was dried with anhydrous sodium sulfate and the subsequent evaporation gave the ketone as a pale yellow liquid in high yield.

Phenyl ethylthiomethyl ketone(1)
yield: 82%, ^{1}H-NMR: δ ($CDCl_3$); 1.30 (t, 3H, $-CH_3$), 2,50 (q, 2H, $-CH_2-CH_3$), 3.70(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.5 (m, 5H, phenyl)

Phenyl propylthiomethyl ketone(2)
yield: 80%, ^{1}H-NMR: δ($CDCl_3$); 0.95(t, 3H, $C-CH_3$), 1.54 (m, 2H, $-CH_2$), 2.44(t, 2H, CH_2-S), 3.75(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.50(m, 5H, phenyl)

Phenyl butylthiomethyl ketone(3)
yield: 82%, ^{1}H-NMR: δ($CDCl_3$); 0.98(t, 3H, $-C-CH_2$), 2.50 (t, 2H, $S-CH_2$), 3.70(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.50(m, 5H, phenyl)

Phenyl t-butylthiomethyl ketone(4)
yield: 78%, ^{1}H-NMR: δ ($CDCl_3$); 1.35(s, 9H, $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_3$), 3.90(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.90(m, 3H, phenyl), 8.00(m, 2H, phenyl)

Phenyl isobutylthiomethyl ketone(5)
yield: 76%, ^{1}H-NMR: δ($CDCl_3$); 0.95(t, 3H, $-\overset{\overset{CH_3}{|}}{C}-CH_3$), 1.25 (d, 3H, -C-), 3.80(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.35-7.90(m, 5H, phenyl)

Phenyl n-amylthiomethyl ketone(6)
yield: 77%, ^{1}H-NMR: δ($CDCl_3$); 0.95(t, 3H, $-C-CH_3$), 2.70 (t, 2H, $-S-CH_2-$), 3.85(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.35-7.90(m, 5H, phenyl)

Phenyl o-chlorobenzylthiomethyl ketone(7)
yield: 82%, ^{1}H-NMR: δ($CDCl_3$); 3.65(s, 2H, $-S-CH_2$), 3.70(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.40-7.80(m, 9H, phenyl)

Methyl propylthiomethyl ketone(8)
yield: 79%, ^{1}H-NMR: δ($CDCl_3$); 0.98(t, 3H, $-C-CH_3$), 2.25 (s, 3H, $-CH_3$), 2.50(t, 2H, $-S-CH_2-C$), 3.10(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$)

Methyl t-butylthiomethyl ketone(9)
yield: 76%, ^{1}H-NMR: δ ($CDCl_3$); 1.30(s, 9H, $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_3$), 2.30(s, 3H, $-CH_3$), 3.30(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2$)

Methyl t-amylthiomethyl ketone(10)
yield: 75%, ^{1}H-NMR: δ ($CDCl_3$); 1.25(s, 6H, $-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-$), 2.30(s, 3H, $-CH_3$), 3.35(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$)

Methyl isoamylthiomethyl ketone(11)
yield: 73%, ^{1}H-NMR: δ ($CDCl_3$); 1.30(d, 6H, $-C\langle^{CH_3}_{CH_3}$), 2.30(s, 3H, $-CH_3$), 2.50(t, 2H, $S-CH_2-$), 3.30(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$)

Methyl phenylthiomethyl ketone(12)
yield: 79%, ^{1}H-NMR: δ ($CDCl_3$); 1.25(s, 3H, $-CH_3$), 3.65 (s, 2H, $-CH_2-S$), 7.30(m, 5H, phenyl)

Methyl o-toluylthiomethyl ketone(13)
yield: 86%, ^{1}H-NMR: δ ($CDCl_3$); 2.15(s, 3H $=\langle^{CH_3}_{CH_3}$), 2.30(s, 3H, $-CH_3$), 3.55(s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.05(m, 4H, phenyl)

Methyl o-chlorobenzylthiomethyl ketone(14)
yield: 78%, ^{1}H-NMR: δ ($CDCl_3$); 2.30(s, 3H, $-CH_3$), 3.55 (s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 4.05(s, 2H, $-S-CH_2-$), 7.15(m, 4H, phenyl)

Methyl 1-phenylthio)ethyl ketone(15)
yield: 80%, ^{1}H-NMR: δ ($CDCl_3$); 2.30(s, 3H, $-CH_3$), 3.40 (s, 2H, $-\overset{\overset{O}{\|}}{C}-CH_2-$), 7.05(m, 5H, phenyl)

Methyl 1-(o-chlorobenzylthio)ethyl ketone(16)
yield: 81%, ^{1}H-NMR: δ ($CDCl_3$); 1.50(d, 3H, $-\overset{\overset{O}{\|}}{C}-S-$), 2.30 (s, 3H, $-CH_3$), 4.05(s, 2H, $-S-CH_2-$), 7.15(m, 4H, phenyl)

General Procedure for the Synthesis of Hydantoins (17)-(32). To the ketones obtained above (0.2 equiv) was added 60% aqueous ethanol, 18 gram of potassium cyanide, and 70 gram of ammonium carbonate. After refluxing the mixture for 15 hours at 65°C, the whole solution was concentrated to its 1/2 volume and cooled in an ice-water bath.

Then the solution was acidified with 10% d-HCl and the precipitated solid was dissolved again, in 200 m*l* of 5% sodium hydroxide solution. Aqueous layer was washed three times with 100 m*l* ethyl ether and acidified again with 10% d-HCl. Precipitates were collected through filtration and subsequent recrystallization in 50% aq. ethanol gave white solid in moderate yield.

5-phenyl-5-ethylthiomethylhydantoin(17)
yield: 55% (Lit[9]., 50%), m.p.: 195-196°C, ^{1}H-NMR: δ(DMSO-d_6); 1.48(t, 3H, $-CH_3$), 2.85(q, 2H, $-CH_2-S$), 3.40(d, 2H, $-S-CH_2-$), 7.81(m, 5H, phenyl), 9.10(s, 1H, N^1-H), 11.24(s, 1H, N^3-H)

5-phenyl-5-propylthiomethylhydantoin(18)
yield: 60% (Lit[9]., 57%), m.p.: 141-142°C, ^{1}H-NMR: δ(DMSO-d_6); 1.24(t, 3H, $-C-CH_3$), 1.88(m, 2H, $-CH_2-C-$), 3.51(d, 2H, $S-CH_2-$), 7.87(m, 5H,

phenyl), 8.98(s, 1H, N^1-H), 11.24(s, 1H, N^3-H)

5-phenyl-5-butylthiomethylhydantoin(19)

yield: 60% (Lit[9]., 57%), m.p.: 109-110°C, ^{1}H-NMR: δ(DMSO-d_6); 1.26(t, 3H, -C-CH_3), 2.94(t, 2H, -CH_2-S-), 3.54(d, 2H, S-CH_2—), 7.88(m, 5H, phenyl), 9.00(s, 1H, N^1-H), 11.23(s, 1H, N^1-H)

5-phenyl-5-t-butylthiomethylhydantoin(20)

yield: 54%, m.p.: 206-208°C, ^{1}H-NMR: δ(DMSO-d_6); 1.45(S, 9H, -C(CH_3)$_3$), 3.15(d, 2H, -S-CH_2), 7.60(m, 5H, phenyl), 8.50(s, 1H, N^1-H), 10.65(s, 1H, N^3-H)

5-phenyl-5-isobutylthiomethylhydantoin(21)

yield: 51%, m.p.: 101-102°C, ^{1}H-NMR: δ (DMSO-d_6); 1.20(t, 3H, -C-CH_3), 1.45(d, 3H, -C(-)-CH_3), 3.10(d, 2H, -S-CH_2), 7.45(m, 5H, phenyl), 8.70(s, 1H, N^1-H), 10.90(s, 1H, N^3-H)

5-phenyl-5-amylthiomethylhydantoin(22)

yield: 65% (Lit[9]., 63%), m.p.: 101-102°C, ^{1}H-NMR: δ(DMSO-d_6); 0.90(t, 3H, -C-CH_3), 1.45(m, 6H, -CH_2-CH_2-CH_2), 3.15(d, 2H, -S-CH_2), 7.50(m, 5H, phenyl), 8.60(s, 1H, N^1-H)

5-phenyl-6-(o-chlorobenzyl)thiomethylhydantoin(23)

yield: 49%, m. p.: 145-147°C, ^{1}H-NMR:δ(DMSO-d_6); 3.20(d, 2H, S-CH_2), 4.00(s, 2h, -CH_2-S-), 7.45(m, 9H, phenyl), 8.75(s, 1H, N^1-H), 10.85(s, 1H, N^3-H)

5-methyl-5-propylthiomethylhydantoin(24)

yield: 53%, m.p.: 117-119°C, ^{1}H-NMR: δ (DMSO-d_6); 1.30(s, 3H, -CH_3), 2.75(s, 2H, -S-CH_2), 7.80(s, 1H, N^1-H), 10.70(s, 1H, N^3-H)

5-methyl-5-t-butylthiomethylhydantoin(25)

yield: 79%, m.p.: 208-210°C, ^{1}H-NMR: δ (DMSO-d_6); 1.25(s, 9H, C(CH_3)$_3$), 1.30(s, 3h, -CH_3), 2.80(s, 2h, -S-CH_2), 2.80(s, 2H, -S-CH_2), 7.80(s, 1H, N^1-H), 10.50(s, 1H, N^3-H)

5-methyl-5-t-amylthiomethylhydantoin(26)

yield: 67%, m.p.: 185-187°C, ^{1}H-NMR: δ (DMSO-d_6); 0.95(t, 3H, -CH_3), 1.25(s, 6H, -C(-)-CH_3), 1.35(s, 3H, -CH_3), 2.70(s, 2H, S-CH_2), 7.75(s, 1H, N^1-H), 10.60(s, 1H, N^3-H)

5-methyl-5-isoamylthiomethylhydantoin(27)

yield: 71%, m.p.: 122-124°C, ^{1}H-NMR: δ (DMSO-d_6); 0,98(d, 6H, -C(CH_3)$_2$), 1.35(s, 3H, -CH_3), 2.50(t, 2H, -CH_2-S), 2.75(s, 2H, S-CH_2), 7.85(s, 1H, N^1-H), 10.65(s, 1H, N^3-H)

5-methyl-5-phenylthiomethylhydantoin(28)

yield: 60%, ^{1}H-NMR: δ (DMSO-d_6); 1.30(s, 3h, -CH_3), 2.70(s, 2H, S-CH_2), 7.30(m, 5H, phenyl), 7.85(s, 1H, N^1-H), 10.70(s, 1H, N^3-H)

5-methyl-5-(o-toluyl)thiomethylhydantoin(29)

yield: 81%, m.p.: 154-155°C, ^{1}H-NMR: δ (DMSO-d_6); 1.40(s, 3H, -CH_3), 2.40(s, 3H, =<$_{CH_3}$), 3.15(s, 2H, S-CH_2), 7.35(m, 4H, phenyl), 7.75(s, 1H, N^1-H), 10.55(s, 1H, N^3-H)

5-methyl-5-(o-chlorobenzyl)thiomethylhydantoin(30)

yield: 76%, ^{1}H-NMR: δ (DMSO-d_6); 1.40(s, 3h, -CH_3), 3.15(s, 2H, S-CH_2), 4.00(s, 2h, -CH_2-S), 7.35(m, 4H, phenyl), 7.75(s, 1H, N^1-H), 10.55(s, 1h, N^3-H)

5-methyl-5-(1-phenylthio)ethylhydantoin(31)

yield: 72%, ^{1}H-NMR: δ (DMSO-d_6); 1.40(s, 3h, -CH_3), 1.55(d, 3H, -C(-)-S-), 4.05(s, 2H, -CH_2-S), 7.35(m, 5H, phenyl), 7.85(s, 1H, N^1-H), 10.50(s, 1H, N^3-H)

5-methyl-5-[1-(o-chlorobenzylthio)]ethylhydantoin(32)

yield: 74%, ^{1}H-NMR: δ (DMSO-d_6); 1.35(s, 3H, -CH_3), 1.55(d, 3H, -C(-)-S-), 3.95(s, 2H, CH_2-S), 7.40(m, 4H, phenyl), 7.80(s, 1H, N^1-H), 10.60(s, 1H, N^3-H)

General Procedure for the Synthesis of 5-Phenyl(or alkyl)-5-alkyl(or aryl)-thiomethyl-hydantoin-3-acetic Acid. To the 400 m*l* ethanolic solution of metallic sodium (0.1 equiv) was added 0.1 equiv of hydantoin and the solution was stirred for 0.5 hour at room temperature. This solution was refluxed with 0.11 equiv of ethyl chloroacetate for 30 hours and then cooled again to room temperature. Precipitated solid was filtered off. After the concentration, the solution was mixed with ethyl ether. Organic layer was washed thoroughly with water, 5% d-NaOH and then water. Etheral solution was dried with anhydrous sodium sulfate and evaporated to produce ester as an oily substance. This hydantoin-3-acetic acid ethyl ester was hydrolysed with sodium hydroxide in 90% aq. ethanol to give the corresponding acid in high yield.

General Procedure for the Synthesis of 5-Phenyl-5-alkyl(or aryl)-sulfonylmethyl-hydantoin-3-acetic Acid Derivatives. 0.02 mole equiv of 5-Phenyl(or alkyl)-thiomethylhydantoin-3-acetic acid derivatives was heated with 20 m*l* acetic acid, 10 m*l* acetic anhydride, and 10 m*l* of 35% hydrogen peroxide for an hour at 70-80°C.

This solution was poured into 100 m*l* cold water and the precipitated solid was filtered. Recrystallzation of this precipitates in aq. ethanol gave white crystal in high yield.

5-phenyl-5-ethylthiomethylhydantoin-3-acetic acid(33)

yield: 90% (Lit[9]., 88%), m.p.: 159-160°C, ^{1}H-NMR: δ(DMSO-d_6); 1.18(t, 3H, -CH_3), 2.55(q, 2H, -CH_2-S), 3.25(d, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.50(m, 5H, phenyl), 9.05(s, 1H, N^1-H)

5-phenyl-5-propylthiomethylhydantoin-3-acetic acid(34)

yield: 90% (Lit[9]., 88%), m.p.: 85-86°C, ^{1}H-NMR: δ(DMSO-d_6); 0.95(t, 3H, -CH_3), 24.5(t, 2H, CH_2-S), 3.15(s, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.45(m, 5H, phenyl), 8.85(s, 1H, N^1-H)

5-phenyl-5-butylsulfonylmethylhydantoin-3-acetic acid(35)

yield: 75% (Lit[9]., 72%), m.p.: 101-103°C, ^{1}H-NMR: δ(DMSO-d_6); 1.25(t, 3H, -CH_3), 3.50(t, 2H, -CH_2-S(=O)=O-), 4.40(s, 2H, -S(=O)=O-CH_2), 4.45(s, 2H, N-CH_2), 7.90 (m, 5H, phenyl), 9.65(s, 1H, N^1-H)

5-phenyl-5-isobutylsulfonylmethylhydantoin-3-acetic acid (36)

yield: 51%, m.p.: 101-102°C, ^{1}H-NMR: δ (DMSO-d_6); 0.95(t, 3H, -CH_3), 3.95(d, 2H, S(=O)=O-CH_2), 4.25(s, 2H,

N-CH_2), 7.60(m, 5H, phenyl), 9.10(s, 1H, N^1-H)

5-phenyl-5-t-butylthiomethylhydantoin-3-acetic acid(37)

yield: 79%, m.p.: 206-208°C, ^{1}H-NMR: δ (DMSO-d_6); 1.30(s, 9H, $-C(CH_3)_3$), 3.28(s, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.60(m, 5H, phenyl)

5-phenyl-5-amylsulfonylmethylhydantoin-3-acetic acid(38)

yield: 80% (Lit[9]., 99%), m.p.: 104-105°C, ^{1}H-NMR: δ(DMSO-d_6); 1.25(t, 3H, $-CH_3$), 3.51(t, 2H, $-CH_2-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$), 4.40(s, 2H, $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_2-$), 4.45(s, 2H, N-$CH_2$-), 7.90 (m, 5H, phenyl), 9.65(s, 1H, N^1-H)

5-phenyl-5-(o-chlorobenzyl)sulfonylmethylhydantoin 3-acetic acid(39)

yield: 81%, m.p.: 185-187°C, ^{1}H-NMR: δ(DMSO-d_6); 3.40(s, 2H, $\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-CH_2$), 4.40(s, 2H, N-$CH_2$-), 4.45(s, 2H, $-CH_2$-S), 8.15(m, 9H, phenyl), 9.05(s, 1H, N^1-H)

5-methyl-5-propylthiomethylhydantoin-3-acetic acid(40)

yield: 90%, m.p.: 134-136°C, ^{1}H-NMR: δ(DMSO-d_6); 1.30(s, 3H, $-CH_3$), 2.50(t, 2H, $-CH_2$-S), 2.85(s, 2H, -S-CH_2, 4.00(s, 2H, N-CH_2-), 8.30(s, 1H, N^1-H)

5-methyl-5-t-butylthiomethylhydantoin-3-acetic acid(41)

yield: 88%, m.p.: 174-176°C, ^{1}H-NMR: δ(DMSO-d_6); 1.20(s, 9H, $-C(CH_3)_3$), 1.30(s, 3H, $-CH_3$), 2.90(s, 2H, -S-CH_2), 4.05(s, 2H, N-CH_2-), 8.30(s, 1H, N^1-H)

5-methyl-5-t-amylthiomethylhydantoin-3-acetic acid(42)

yield: 91%, m.p.: 172p174°C, ^{1}H-NMR: δ(DMSO-d_6); 1.25(s, 6H, $-C(CH_3)_2-$), 1.35(s, 3H, $-CH_3$), 2.85(s, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.90(s, 1H, N^1-H)

5-methyl-5-isoamylthiomethylhydantoin-3-acetic acid(43)

yield: 84%, m.p.: 167-169°C, ^{1}H-NMR: δ(DMSO-d_6); 1.00(d, 6H, $-C(CH_3)_2$), 1.35(s, 3H, $-CH_3$), 2.00(t, 2H, $-CH_2$-S), 2.85(s, 2H, -S-CH_2), 4.15(s, 2H, N-CH_2-), 7.85(s, 1H, N^1-H)

5-methyl-5-phenylthiomethylhydantoin-3-acetic acid(44)

yield: 84%, m.p.: 119-121°C, ^{1}H-NMR: δ(DMSO-d_6); 1.30(s, 3H, $-CH_3$), 3.40(s, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.35(m, 5H, phenyl), 8.45(s, 1H, N^1-H)

5-methyl-5-(o-toluyl)thiomethylhydantoin 3-acetic acid(45)

yield: 85%, m.p.: 125-12°C, ^{1}H-NMR: δ(DMSO-d_6); 1.35 (s, 3H, $-CH_3$), 2.30(s, 3H, $=\langle_{CH_3}$), 7.30(s, 2H, S-CH_2, 4.40(s, 2H, N-CH_2-), 7.35(m, 4H, phenyl), 8.45(s, 1H, N^1-H)

5-methyl-5-(o-chlorobenzyl)thiomethylhydantoin-3-acetic acid(46)

yield: 85%, m.p.: 150-152°C, ^{1}H-NMR: δ (DMSO-d_6); 1.35(s, 3H, $-CH_3$), 3.25(s, 2H, S-CH_2), 4.05(s, 2H, $-CH_2$-S), 4.10(s, 2H, N-CH_2-), 7.45(m, 4H, phenyl), 7.85(s, 1H, N^1-H)

5-methyl-5-[1-(o-chlorobenzyl)]ethylhydantoin-3-acetic acid(47)

yield: 88%, m.p.: 167-168°C, ^{1}H-NMR: δ(DMSO-d_6); 1.35(s, 3H, $-CH_3$), 3.80(s, 2H, S-CH_2), 4.10(s, 2H, N-CH_2-), 7.50(m, 4H, phenyl), 7.90(s, 1H, N^1-H)

5-methyl-5-(1-phenylthio)ethylhydantoin-3-acetic acid(48)

yield: 81%, m.p.: 158-160°C, ^{1}H-NMR: (DMSO-d_6); 1.40(s, 3H, $-CH_3$), 4.10(s, 2H, N-CH_2-), 7.40(m, 5H, phenyl), 7.90(s, 1H, N^1-H)

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