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Note

Synthesis of 5-Alkylthio(or sulfonyl)methyl-5-*m*-methoxyphenylhydantoin-3-acetic Acid Derivatives

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For the development of new antiinflammatory and analgesic drugs, new 5-alkylthio (or sulfonyl) methyl-5-*m*-methoxyphenylhydantoin-3-acetic acid derivatives(alkyl; ethyl, propyl, butyl) were prepared. The 5,5-disubstituted hydantoins which were used as starting materials, were prepared according to Bucherer-Berg method. The reaction of ethyl chloroacetate with these compounds gave 3-acetate and the subsequent hydrolysis with dilute sodium hydroxide resulted in hydantoin 3-acetic acid derivatives. Through the same procedure of equivalent hydantoins or the oxidation of 5-alkylthiohydantoin compounds described above, 5-alkylsulfonylmethyl-5-*m*-methoxyphenylhydantoin-3-acetic acid derivatives were also synthesized.

Key words: 5-Alkylthio (or sulfonyl) methyl-5-*m*-methoxyphenylhydantoin-3-acetic acid derivatives, Antiinflammatory, Analgesic

INTRODUCTION

A number of 5,5-disubstituted hydantoins have found important use in medicine as anticonvulsants and hypnotics. The antiepileptic phenytoin can be simply prepared by Bucherer-Bergs reaction. The Bucherer-Bergs synthesis (Ware, 1950), i.e., the reactions of aldehyde and ketones with potassium cyanide (2 mole) and ammonium carbonate (4 mole) in 50% aqueous alcohol at 60-70℃, gives excellent yields of hydantoins.

Long (1946) reported the preparation of 5-alkylthiomethyl- and 5-alkylsulfonyl-5-phenylhydantoin and their anticonvalsant activities. Winstead (1965) reported the preparation of a number of N-3-acetic acid derivatives of 5,5-disubstituted hydantoins and the investigation of their pharmacological behavior. Schulte *et al.* (1978) synthesized 3-aralkylsulfonyl derivatives of 5-aralkyl-5-alkylthio(sulfonyl)methyl hydantoins and 5-aralkyl-5-alkoxylmethyl hydantoins to develop new antiinflammatory agents. Suh *et al.* (1982) synthesized several 5-aryl-5-alkylthio(or sulfonyl) methyl hydantoin-3-acetic acid and their antiinflammatory properties were determined in the rat paw edema test. They reported that the potent antiinflammatory effect was found when the methylcarboxyl group was substituted at the N-3 position. Oh *et al.* (1988) reported the preparation of some other 5-methyl(or phenyl)-5-aralkylthio(or sulfonyl) methylhydantoin-3-acetic acids.

In this study, we introduced *m*-methoxyphenyl group on the 5-position of hydantoin ring in hope of the improved antiinflammatory and analgesic effects.

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MATERIALS AND METHODS

Melting points were determined on a Büchi 535 melting point apparatus and uncorrected. NMR spectra were recorded on a JEOL UNM-PMX 60 SI NMR spectrometer using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1310 IR spectrometer using KBr discs.

General Procedure for Alkylthiomethyl *m*-Methoxyphenyl Ketones

Sodium hydroxide (0.12 mole) was dissolved in 220 ml of water and 96 ml of ethanol and cooled to 0℃. To this solution were added 0.12 mol of alkyl mercaptan and α-bromo-*m*-methoxy acetophenone with stirring. The mixture was refluxed for 4 hrs, cooled and diluted with two-fold volumes of water. The mixture was extracted twice with 60 ml of ether. The fractions of ether extracts were combined and dried over sodium sulfate. After filtration and removal of the ether, the residue gave the ketone as a pale yellow liquid in high yield.

Ethylthiomethyl *m*-methoxyphenyl ketone (1): Yield: 87%; IR (KBr) cm $^{-1}$: 3060(aromatic), 2950(CH),

2860(OCH_3), 1660(C=O); NMR ($CDCl_3$+DMSO-d_6) δ: 1.23(t, 3H, CH_3), 2.56(m, 2H, CH_2), 3.76(s, 2H, CH_2S), 3.83(s, 3H, CH_3O), 6.86-7.53(m, 4H, C_6H_4).

***n*-Propylthiomethyl *m*-methoxyphenyl ketone (2):** Yield: 97%; IR (KBr) cm^{-1}: 3060(aromatic), 2950(CH), 2860(OCH_3), 1665(C=O); NMR ($CDCl_3$+DMSO-d_6) δ: 0.96(t, 3H, CH_3), 1.56(m, 2H, CH_2), 2.51(t, 2H, CH_2), 3.72(s, 2H, CH_2S), 3.82(s, 3H, CH_3O), 6.86-7.53(m, 4H, C_6H_4).

***n*-Butylthiomethyl *m*-methoxyphenyl ketone (3):** Yield: 97%; IR (KBr) cm^{-1}: 3060(aromatic), 2960(CH), 2870(OCH_3), 1660(C=O); NMR ($CDCl_3$+DMSO-d_6) δ: 0.90(t, 3H, CH_3), 1.23(m, 4H, CH_2CH_2), 1.52(t, 2H, CH_2), 3.72(s, 2H, CH_2S), 6.8-7.6(m, 4H, C_6H_4).

General Procedure for 5-Alkylthiomethyl-5-(*m*-methoxypheny)hydantoins

To the ketones (0.11 mol) were added 70% aqueous ethanol, 15 g of potassium cyanide, and 45 g of ammonium carbonate. After refluxing of the mixture for 20 hrs at 55-60℃, the solution was concentrated to its half of original volume and cooled in an ice-water bath. The solution was then acidified with c-HCl. The precipitated solid was filtered and washed with the cold-water. The solid was dissolved again in 100 ml of 5% sodium hydroxide solution. Aquous layer was washed three times with 30 ml of ethyl ether and acidified again with c-HCl. Precipitates was collected through filtration and subsequent recrystallization in dil-ethanol gave white solid.

5-Ethylthiomethyl-5-(*m*-methoxyphenyl)hydantoin (4): Yield: 69%; IR (KBr) cm^{-1}: 3260(NH), 3060(aromatic), 2950(CH), 2860(OCH_3), 1750(C=O), 1715(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 0.95(t, 3H, CH_3), 1.5(q, 2H, CH_2), 3.1(s, 2H, SCH_2C), 3.8(s, 3H, CH_3O), 7.1(m, 4H, C_6H_4), 8.3(s, 1H, NH), 10.5(s, 1H, NH).

5-*n*-Propylthiomethyl-5-(*m*-methoxyphenyl)hydantoin (5): Yield: 90%; IR (KBr) cm^{-1}: 3190(NH), 3040 (aromatic), 2950(CH), 2860(OCH_3), 1760(C=O), 1715 (C=O); NMR($CDCl_3$+DMSO-d_6) δ: 0.97(t, 3H, CH_3), 1.53(m, 2H, CH_2), 2.52(t, 2H, CH_2), 3.13(s, 2H, SCH_2C), 3.85(s, 3H, CH_3O), 7.19(m, 4H, C_6H_4), 8.52(s, 1H, NH), 10.69(s, 1H, NH).

5-*n*-Butylthiomethyl-5-(*m*-methoxyphenyl)hydantoin (6): Yield: 98%; IR(KBr) cm^{-1}: 3240(NH), 3060(aromatic), 2975(CH), 2860(OCH_3), 1740(C=O), 1720(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 1.06(t, 3H, CH_3), 1.39(m, 2H, CH_2), 2.79(t, 2H, CH_2S), 3.36(s, 2H, SCH_2C), 3.73(s, 3H, CH_3O), 7.05(m, 4H, C_6H_4), 8.52(s, 1H, NH), 10.66(s, 1H, NH).

General Precedure for 5-Alkylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoins

Hydantoin prepared above (0.028 mole) was heated with 72 ml of glacial acetic acid, 18 ml of acetic anhydride and 14 ml of 35% hydrogen peroxide for 4 hrs at 70-80℃. This solution was poured into 200 ml of cold water and the precipitated solid was filtered and washed with water. Recrystallization of this precipitates in dil-ethanol gave white crystals.

5-Ethylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin (7): Yield: 91%; IR(KBr) cm^{-1}: 3220,3120(NH), 3020(aromatic), 2925(CH), 2800(OCH_3), 1760(C=O), 1710(C=O), 1390(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 1.23(t, 3H, CH_3), 3.16(m, 2H, CH_2), 3.75(s, 2H, SO_2CH_2C), 3.82(s, 3H, CH_3O), 6.86-7.69(m, 4H, C_6H_4), 9.0(s, 1H, NH), 10.0(s, 1H, NH).

5-*n*-Propylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin (8): Yield: 60%; IR(KBr) cm^{-1}: 3260, 3120(NH), 3050(aromatic), 2970(CH), 2860(OCH_3), 1765(C=O), 1730(C=O), 1310(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 1.16(t, 3H, CH_3), 1.79(m, 2H, CH_2), 3.16(m, 2H, CH_2), 3.85(s, 2H, SO_2CH_2C), 4.2(s, 3H, CH_3O), 6.86-7.69(m, 4H, C_6H_4), 8.85(s, 1H, NH).

5-*n*-Butylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin (9): Yield: 67%; IR(KBr) cm^{-1}: 3310, 3290(NH), 3060(aromatic), 2950(CH), 2840(OCH_3), 1725(C=O), 1390(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 0.92(t, 3H, CH_3), 1.32(m, 4H, CH_2CH_2), 2.85(m, 2H, CH_2), 3.69(s, 2H, SO_2CH_2C), 4.06(s, 3H, CH_3O), 6.8-7.6(m, 4H, C_6H_4), 8.86(s, 1H, NH), 10.33(s, 1H, NH).

General precedure for ethyl 5-alkylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetates

To the 188 ml of ethanolic solution of metallic sodium (0.0519 mole) were added 0.0519 mole of hydantoin and the solution was stirred for 30 minutes at room temperature. This solution was refluxed with 0.0519 mole of ethyl chloroacetate for 42 hrs and then cooled to room temperature. Precipitated solid was filtered off. After concentration, the residue was mixed with ether. The organic layer was washed in sequence with water, 5%-NaOH solution and then ice Water. The ether solution was dried with anhydrous sodium sulfate, filtered and evaporated. This residue was cooled to 0℃ and the crude crystal was collected. Recrystallization of this solid from dil-ethanol gave white crystals in moderate yield.

Ethyl 5-ethylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetate (10): Yield: 80%; IR(KBr) cm^{-1}: 3465 (NH), 3060(aromatic), 2960(CH), 2860(OCH_3), 1770(C=O), 1740(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 1.05(t, 3H, CH_3), 1.63(m, 2H, CH_2), 2.08(t, 3H, CH_3), 2.49(m, 2H, $COOCH_2$), 3.49(s, 2H, SCH_2C), 3.75(s, 3H, CH_3O), 4.23(s, 2H, NCH_2CO), 7.3(m, 4H, C_6H_4).

Ethyl 5-*n*-propylthiomethyl-5-(*m*-methoxyphenyl)

hydantoin-3-acetate (11): Yield: 75%; IR(KBr) cm^{-1}: 3320(NH), 3060(aromatic), 2960(CH), 2860(OCH_3), 1770(C=O), 1730(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 1.26 (m, 7H, C_3H_7), 2.08(t, 3H, CH_3), 2.49(m, 2H, $COOCH_2$), 3.49(s, 2H, SCH_2C), 3.75(s, 3H, CH_3O), 4.23(s, 2H, NCH_2CO), 7.39(m, 4H, C_6H_4).

Ethyl 5-*n*-butylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetate (12): Yield: 92%; IR(KBr) cm^{-1}: 3260(NH), 3080(aromatic), 2930(CH), 2860(OCH_3), 1780(C=O), 1750(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 0.89(m, 3H, CH_3), 1.23(m, 4H, CH_2CH_2), 1.5(m, 2H, CH_2), 2.5(m, 5H, CH_2CH_3), 3.03(s, 2H, SCH_2C), 3.75(s, 3H, CH_3O), 4.23(s, 2H, NCH_2CO), 6.86-7.69(m, 4H, C_6H_4).

General Precedure for Ethyl 5-Alkylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetates

Method A: As the N-alkylation of alkylthiomethylhydantoins, the alkylsulfonylmethylhydantoins were treated with sodium ethoxide and ethyl chloroacetate.

Method B: The corresponding alkylthiomethylhydantoin acetic acid esters were oxidated with hydrogen peroxide in glacial acetic acid and acetic anhydride.

Ethyl 5-ethylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetate (13): Yield: Method A: 68%, Method B: 98%; IR(KBr) cm^{-1}: 3360(NH), 3040(aromatic), 2940(CH), 2820(OCH_3), 1770(C=O), 1750(C=O), 1360(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 1.3(m, 5H, CH_2CH_3), 3.0(t, 3H, CH_3), 3.26(s, 2H, CH_2), 3.75(s, 2H, SO_2CH_2C), 3.92(s, 3H, CH_3O), 4.16(s, 2H, NCH_2CO), 6.75-7.4(m, 4H, C_6H_4), 9.2(s, 1H, NH).

Ethyl 5-*n*-propylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetate (14): Yield: Method A: 47%, Method B: 84%; IR(KBr) cm^{-1}: 3350(NH), 3040(aromatic), 2980(CH), 2870(OCH_3), 1770(C=O), 1755(C=O), 1370(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 0.96(t, 3H, CH_2), 1.25(t, 2H, CH_2), 1.65(m, 3H, CH_3), 1.69(m, 2H, $COOCH_2$), 2.5(m, 3H, CH_2), 3.75(s, 2H, SO_2CH_2C), 3.97(s, 3H, CH_3O), 4.13(s, 2H, NCH_2CO), 6.8-7.5(m, 4H, C_6H_4), 7.66(s, 1H, NH).

Ethyl 5-*n*-butylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetate (15): Yield: Method A: 83%, Method B: 93%; IR(KBr) cm^{-1}: 3330(NH), 3050(aromatic), 2960(CH), 2870(OCH_3), 1775(C=O), 1715(C=O), 1305(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 0.95(m, 3H, CH_3), 1.16(m, 5H, CH_2CH_3), 1.89(m, 4H, CH_2CH_2), 3.39(m, 2H, CH_2), 3.66(s, 2H, SO_2CH_2C), 3.79(s, 3H, CH_3O), 4.14(s, 2H, NCH_2CO), 6.86-7.53(m, 4H, C_6H_4).

General Precedure for 5-Alkylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic Acids

To the 15.4 ml of absolute ethanol were added 0.0077 mole of the ethyl 5,5-disubstituted hydantoin-3-acetate. To this solution were added 0.0077 mole of sodium hydroxide dissolved in a minimum of water. The mixture was refluxed with stirring until saponification was completed, approximately 30 hrs. The sodium 5,5-disubstituted hydantoin-3-acetate began to precipitate out of solution shortly after refluxing was started. The sodium salt was filtered, washed with a small amount of absolute ethanol or petroleum ether, and dried. The salt was dissolved in a small amount of water, the aqueous solution was filtered and acidified with 5%-HCl solution. The acidified solution was thoroughly cooled, the precipitated solid was collected by filtration. Recrystallization of this solid from dilethanol gave pale yellow crystals in high yield.

5-Ethylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (16): Yield: 90%; IR(KBr) cm^{-1}: 3270(NH), 3035(aromatic), 2940(CH), 2840(OCH_3), 2940-2100(acid bag), 1755(C=O), 1710(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 1.06 (t, 3H, CH_3), 2.5(m, 2H, CH_2), 3.01(s, 2H, SCH_2C), 3.66(s, 3H, CH_3O), 4.01(s, 2H, NCH_2CO), 6.8-7.6(m, 4H, C_6H_4), 8.82(s, 1H, COOH).

5-*n*-Propylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (17): Yield: 81%; IR(KBr) cm^{-1}: 3240(NH), 3050(aromatic), 2955(CH), 2860(OCH_3), 3100-2200(acid bag), 1715(C=O), 1655(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 0.82 (t, 3H, CH_3), 1.46(m, 2H, CH_2), 2.46(t, 2H, CH_2), 3.13(s, 2H, SCH_2C), 3.69(s, 3H, CH_3O), 4.1(s, 2H, NCH_2CO), 6.8-7.6(m, 4H, C_6H_4), 8.92(s, 1H, COOH).

5-*n*-Butylthiomethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (18): Yield: 77%; IR(KBr) cm^{-1}: 3440,3400(NH), 3020(aromatic), 2970(CH), 2880(OCH_3), 3000-2500(acid bag), 1750(C=O), 1710(C=O); NMR($CDCl_3$+DMSO-d_6) δ: 0.92(m, 3H, CH_3), 1.3(m, 4H, CH_2CH_2), 2.59(s, 2H, CH_2S), 3.21(s, 2H, SCH_2C), 3.66(s, 3H, CH_3O), 3.91(s, 2H, NCH_2CO), 6.8-7.6(m, 4H, C_6H_4), 10.1(s, 1H, COOH).

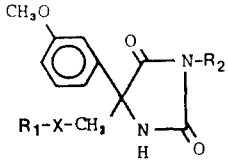
General Precedure for 5-Alkylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic Acids

Method A: As the hydrolysis of alkylthiomethylhydantoin acetic acid esters, the alkylsulfonylmethylhydantoin acetic acid esters were hydrolyzed with sodium hydroxide.

Method B: The corresponding alkylthiomethylhydantoin acetic acids were oxidated with hydrogen peroxide in glacial acetic acid and acetic anhydride.

5-Ethylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (19): Yield: Method A: 81%, Method B: 49%; IR(KBr) cm^{-1}: 3500(NH), 3050(aromatic), 2970(CH), 2830(OCH_3), 2900-2100(acid bag), 1750(C=O), 1720(C=O), 1395(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 1.19(t, 3H, CH_3), 2.97(m, 2H, CH_2), 3.72(s, 2H, SO_2CH_2C), 4.0(s, 3H, CH_3O), 4.75(s, 2H, NCH_2CO), 7.19(m, 4H,

Table I. Prepared hydantoin derivatives



No.	R_1	R_2	X	Formular	M.P. ℃	Yield(%) (method B)
4	Ethyl	H	-S-	$C_{13}H_{16}N_2O_3S$	174-176	69
5	Propyl	H	-S-	$C_{14}H_{18}N_2O_3S$	93- 94	90
6	Butyl	H	-S-	$C_{15}H_{20}N_2O_3S$	106-108	98
7	Ethyl	H	$-SO_2-$	$C_{13}H_{16}N_2O_5S$	176-179	91
8	Propyl	H	$-SO_2-$	$C_{14}H_{18}N_2O_5S$	165-169	60
9	Butyl	H	$-SO_2-$	$C_{15}H_{20}N_2O_5S$	194-197	67
10	Ethyl	$CH_2COOC_2H_5$	-S-	$C_{17}H_{22}N_2O_5S$	75- 76	80
11	Propyl	$CH_2COOC_2H_5$	-S-	$C_{18}H_{24}N_2O_5S$	62- 65	75
12	Butyl	$CH_2COOC_2H_5$	-S-	$C_{19}H_{26}N_2O_5S$	100-104	92
13	Ethyl	$CH_2COOC_2H_5$	$-SO_2-$	$C_{17}H_{22}N_2O_7S$	117-119	68, 98(B)
14	Propyl	$CH_2COOC_2H_5$	$-SO_2-$	$C_{18}H_{24}N_2O_7S$	114-116	47, 84(B)
15	Butyl	$CH_2COOC_2H_5$	$-SO_2-$	$C_{19}H_{26}N_2O_7S$	112-113	83, 93(B)
16	Ethyl	CH_2COOH	-S-	$C_{15}H_{18}N_2O_5S$	113-114	90
17	Propyl	CH_2COOH	-S-	$C_{16}H_{20}N_2O_5S$	119-121	81
18	Butyl	CH_2COOH	-S-	$C_{17}H_{22}N_2O_5S$	162-165	77
19	Ethyl	CH_2COOH	$-SO_2-$	$C_{15}H_{18}N_2O_7S$	93- 95	81, 49(B)
20	Propyl	CH_2COOH	$-SO_2-$	$C_{16}H_{20}N_2O_7S$	100-103	50, 71(B)
21	Butyl	CH_2COOH	$-SO_2-$	$C_{17}H_{22}N_2O_7S$	155-158	23, 59(B)

C_6H_4), 9.16(s, 1H, COOH).

5-*n*-Propylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (20): Yield: Method A: 50%, Method B: 71%; IR(KBr) cm^{-1}: 3540, 3460(NH), 2985 (CH), 2860(OCH_3), 3000-2500(acid bag), 1770(C=O), 1720(C=O), 1320(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 1.0 (t, 3H, CH_3), 1.75(m, 2H, CH_2), 2.99(m, 2H, CH_2), 3.75 (m, 2H, CH_2), 3.89(s, 2H, SO_2CH_2C), 4.17(s, 3H, CH_3O), 4.2(s, 2H, NCH_2CO), 6.8-7.6(m, 4H, C_6H_4), 9.1(s, 1H, COOH).

5-*n*-Butylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoin-3-acetic acid (21): Yield: Method A: 23%, Method B: 59%; IR(KBr) cm^{-1}: 3260,3040(NH), 2945(CH), 2860(OCH_3), 3000-2500(acid bag), 1770(C=O), 1720 (C=O), 1320(SO_2); NMR($CDCl_3$+DMSO-d_6) δ: 0.95(m, 3H, CH_3), 1.51(m, 4H, CH_2CH_2), 3.01(s, 2H, CH_2), 3.79 (s, 2H, SO_2CH_2C), 4.08(s, 3H, CH_3O), 4.13(s, 2H, NCH_2 CO), 6.8-7.6(m, 4H, C_6H_4), 9.3(s, 1H, COOH).

RESULTS AND DISCUSSION

Alkylthiomethylketones were prepared through the reaction of α-bromo-*m*-methoxyacetophenone with alkylmercaptan and converted to 5-alkylthiomethyl-5-(*m*-methoxyphenyl)hydantoins by Bucherer-Berg synthetic method. The reaction of ethyl chloroacetate with these hydantoins gave the corresponding 3-acetates and these products were hydrolysed with aqueous sodium hydroxide to produce hydantoin-3-acetic acid derivatives. 5-Alkylsulfonylmethyl-5-(*m*-methoxyphenyl)hydantoins were also obtained by the oxidation of corresponding alkylthiomethyl compounds with hydrogen peroxide in glacial acetic acid and acetic anhydride.

In the Bucherer-Berg synthesis of hydantoins, their yields varied from 69 to 98% depending on the nature of 5-disubstituents, such results could be explained in terms of steric effect. In the hydrolysis reaction greater yield was obtained for the alkylthiomethylhydantoins than that of alkylsulfonylmethyl derivatives. In the course of oxidation reactions, the formation of mono-oxidation product, sulfoxide, was not observed in our study. Their yields and melting points of prepared hydantoin derivatives are listed in Table I.

Identification of the final products was confirmed by m.p, IR and NMR spectra. Distinctive IR absorption bands of SO_2 were appeared between 1395-1305 cm^{-1}. The hydrogen signals of NMR spectra surrounding SO_2 group were shifted to the lower field than those of alkylthiomethylhydantoins.

Conversion of the ketones to the corresponding hydantoins was accomplished by the method of Bucherer. The yield of the products was good and the mercaptan odor was eliminated by recrystallization. Hydantoins, when unsubstituted in the N-3 position, usually have higher melting point than that with alkyl substi-

tuent on the nitrogen atom. Among two acidic hydrogens on the hydantoin ring, N-3 proton is more acidic due to the presence of two adjacent carbonyl functional groups. Thus, hydantoins were alkylated in the N-3 position prior to N-1 position by treatment with alkylhalides in alkaline condition.

The alkylsulfonylmethylhydantoin derivatives were also synthesized through the same procedure as described for the preparation of alkylthio derivatives or through the oxidation of corresponding alkylthiomethylhydantoins. The products obtained by the two methods were identical as evidence by the IR and NMR spectra. Though the two methods were adapted for the synthesis of the alkylsulfonylmethylhydantoins, the yield of the oxidation method was greater than that containing the akylation of akylsulfonyl hydantoins of N-alkylation or hydrolysis.

REFERENCES CITED

Long, L. M., 5-R-Thiomethyl and 5-R-Sulfonylmethyl-5-phenylhydantoins. *J. Am. Chem. Soc.*, 68, 2159-2161 (1946).

Oh, C. H., Kang, Y. K., Park, S. W., Cho, J. H., Kwon, S. K., Synthesis of new hydantoin-3-acetic acid derivatives. *Bull. Korean Chem. Soc.*, 9(4), 231-235 (19 88).

Schulte, K. E., V. von Wiessenborn and Kwon, S. K., Hydantoin-Dervate als potentiell entzündunghemmende Substanzen. *Eur. J. Med. Chem.*, 13(1), 25 (1978).

Suh, J. J., Kwon, S. K., Synthesis of hydantoin-3-acetic acid derivatives, *The Fed of Asian Pharm. Assoc., Proceedings*, August, Seoul, Korea, 289-297 (1982).

Ware, E., The chemistry of the hydantoins. *Chem. Reviews*, 46, 403-470(1950).

Winstead, M. B., Hamel, C. R., Substitution in the hydantoin ring II. N-3-acetic acid derivatives. *J. Med. Chem.*, 8, 120-122(1965).