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Note

Synthesis of New Hydantoin-3-Ethanethiol Derivatives

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5-sec-Butylthiomethyl-5-alkyl (methyl or phenyl) hydantoins (3-x) were prepared by the reaction of sec-butylthiomethyl alkyl (methyl or phenyl) ketone (1-2), potassium cyanide and ammonium carbonate. 3-(2-Bromoethyl) hydantoins (5-6) were the reaction products of 5-sec-butylthiomethyl-5-alkyl (methyl or phenyl) hydantoin and 1,2-dibromoethane in the presence of potassium hydroxide. Alkylation of **5** and **6** with an excess of alkyl (methyl or ethyl) iodide in THF with sodium hydride as base gave three 1-alkyl (methyl or ethyl)-3-(2-bromoethyl) hydantoins (7-9). Treatment of the 2-bromoethyl group with potassium thioacetate and triethylamine gave three 1-alkyl (methyl or ethyl)-3-(2-acetylthioethyl) hydantoins (10-12). Hydrolysis of the 2-acetylthioethyl group with sodium hydroxide in methanol afforded the three 1-alkyl (methyl or ethyl)-3-(2-mercaptoethyl) hydantoins.

Key words: Synthesis, Hydantoin-3-ethanethiol, Anti-inflammatory activity, Analgesic activity

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 acid (Read, 1922) and are also used as anticonvulsants (Thompson *et al.*, 1925) or antibacterials.

In the course of our studies on the development of new pharmaceutically useful substances, several hydantoin derivatives were prepared. Of these, we reported the synthesis of 3-substituted hydantoin derivatives (Schulte and Kwon, 1978; Oh *et al.*, 1988) with alkylthiomethyl or phenylthiomethyl groups at the 5-position of the hydantoin ring, which are known to exhibit anti-inflammatory and analgesic activities. Therefore we introduced an ethanethiol group on the N-3 position of hydantoin. Most of the hydantoin derivatives were prepared in good yield by the Bucherer-Berg synthesis, i.e., the reaction of the corresponding ketones with 2 mol. equivalents of potassium cyanide and 4mol. equivalents of ammonium carbonate in 60% aqueous alcohol at 65℃.

MATERIALS AND METHODS

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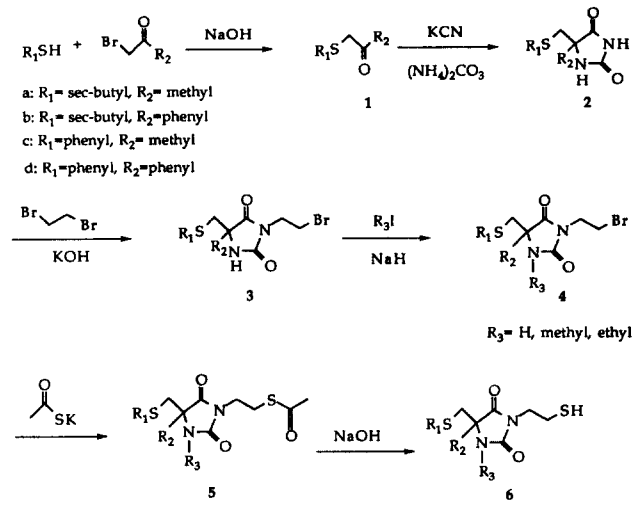

Scheme 1. Synthetic routes to hydantoin 3-ethanethiols

IR spectra(NaCl) were recorded with a Perkin-Elmer 1310 IR spectrometer. ^{1}H NMR spectra were measured on a Varian gemini-300 300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard.

3-(2-Bromoethyl)-5-sec-butylthiomethyl-5-methyl Hydantoin (3a)

A solution of 5-sec-butylthiomethyl-5-methyl hydantoin (**2a**, 10.8 g, 0.05 mol) and KOH (2.8 g, 0.05 mol)

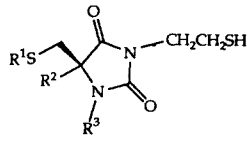

Table I. List of prepared 3-Ethanethiol hydantoin derivatives

Compound	R_1	R_2	R_3
7	sec-butyl	$-CH_3$	H
8	sec-butyl	$-CH_3$	$-CH_3$
9	sec-butyl	$-CH_3$	$-C_2H_5$
10	sec-butyl	$-C_6H_5$	H
11	sec-butyl	$-C_6H_5$	H
12	$-C_6H_5$	$-CH_3$	H
13	$-C_6H_5$	$-CH_3$	$-CH_3$
14	$-C_6H_5$	$-C_6H_5$	H
15	$-C_6H_5$	$-C_6H_5$	$-CH_3$
16	$-C_6H_5$	$-C_6H_5$	$-C_2H_5$

in 95% ethanol was added dropwise over a 6h period to a stirred, refluxing solution of 1,2-dibromoethane (45 g, 0.24 mol) in 95% ethanol. The reaction mixture was dissolved in ethyl acetate. This solution was washed with 5% aq. NaOH solution, and water, and finally dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave a yellow oily residue. 10.5 g (yield 65%)

IR (NaCl): 3200, 2960, 1700, 1400 cm^{-1}

^{1}H-NMR ($CDCl_3$, δ): 0.9 (t, 3H, J=7.4, $\underline{CH_3}CH_2$), 1.2 (d, 3H, J=5.1 $\underline{CH_3}CH$), 1.4 (m, 5H, $-CH_2\overline{CH_3}$), 2.6 (m, 1H, -CHS), 2.8 (s, 2H, $-CH_2S$), 3.5 (t, 2H, J=6.5, $-CH_2$ N), 3.8 (t, 2H, J=6.7, $-CH_2Br$), 7.1 (s, 1H, NH)

1-Methyl-3-(2-bromoethyl)-5-sec-butylthiomethyl-5-methyl Hydantoin (4a)

Alkylating agents, of commercial origin or prepared by known procedures, were dried before use. In this experiment, methyl iodide was redistilled. First, THF was redistilled, it was collected directly in the reaction tube containing the compound (**3a**) (9.7 g, 0.03 mol) previously dried under vacuum. After cooling to 15℃, sodium hydride (1.6 g, 0.04 mol, 60% of immersion) was added, and the mixture was stirred until gas evolution ceased (c. a. 15min). The alkylating agent (methyl iodide, 6.4 g, 0.045 mol) was then added, and stirring was continued for 12h at room temperature. THF was removed under reduced pressure and the residue was extracted with ethyl acetate. Evaporation of the organic solvent gave the crude product, which was purified by column chromatography. Eluent was hexane : ethyl acetate=2 : 1 and a yellow oily product 4.9 g (yield=48.6%) was obtained.

IR (NaCl): 2960, 1750, 1700, 1400 cm^{-1}

1H-NMR ($CDCl_3$, δ): 0.9 (t, 3H,J=7.4, $\underline{CH_3}CH_2$), 1.2 (d, 3H, J=5.3, $\underline{CH_3}CH$), 1.4 (m, 5H, $-CH_2CH_3$), 2.6 (m, 1H, -CHS), 2.8 (s, 2H, $-CH_2S$), 2.9 (s, 3H, N-CH_3), 3.5 (t, 2H, J=6.6, $-CH_2N$), 3.8 (t, 2H, J=6.6, $-CH_2Br$)

1-Methyl-3-(2-acetylthioethyl)-5-sec-butylthiomethyl-5-methyl Hydantoin (5a)

A solution of compound (**4a**) (3.4 g, 0.01 mol), potassium thioacetate (3.42 g, 0.03 mol), triethylamine (1.01 g, 0.01 mol), and acetone and methanol was stirred at 50℃ for 10 hrs. This solution was extracted with ethyl acetate and evaporation of the solvent gave the crude product, which was purified by column chromatography. Eluent was hexane : ethyl acetate=2 : 1, and a light brown oily product 1.73 g (yield=52%) was obtained.

IR (NaCl): 2960, 1760, 1700, 1400

^{1}H-NMR ($CDCl_3$, δ): 0.9 (t, 3H, J=7.4, $\underline{CH_3}CH_2$), 1.2 (d, 3H, J=5.4, $\underline{CH_3}CH$), 1.4 (m, 5H, $-CH_2CH_3$), 2.5 (s, 3H, CH_3CO), 2.6 (m, 1H, -CHS), 2.7 (s, 3H, N-CH_3), 2.8 (s, 2H, $-CH_2S$), 3.2 (t, 2H, J=6.5, CH_2N), 3.4 (t, 2H, J=7.8, $-CH_2S$)

1-Methyl-3-(2-mercaptoethyl)-5-sec-butylthiomethyl-5-methylhydantoin (6)

Compound (**5a**) (1.4 g, 4 mmol) was dissolved in methanol and cooled to 0℃ by ice bath. 1.1 ml of 4*N*-NaOH was added and the solution was stirred at room temperature for 1 hr. Then 1.1 ml of 4*N*-HCl was added, and stirred for 3 min, and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium' sulfate. Evaporation of ethyl acetate gave a yellow oily product, 0.76 g (yield=65.7%).

IR (NaCl cell): 2960, 1700, 1400, 840 cm^{-1}

^{1}H-NMR ($CDCl_3$, δ): 0.9 (t, 3H, J=7.4, $\underline{CH_3}CH_2$), 1.2 (d, 3H, J=5.3, $\underline{CH_3}CH$), 1.4 (m, 5H, $-CH_2\overline{CH_3}$), 2.8 (m, 5H, N-CH_3, S-$\overline{CH_2}$), 2.9 (t, 2H, J=5.8, $\underline{CH_2}SH$), 3.7 (t, 2H, J=5.8, $-CH_2N$)

RESULTS AND DISCUSSION

5-Phenyl(or sec-butyl)-5-methyl(or phenyl)thiomethyl hydantoin was prepared by the Bucherer-Berg synthesis in high yields. The reaction of 1,2-dibromoethane with hydantoin (**2**) in the presence of sodium ethoxide gave compound **3** and Alkylation of N1 was acomplished by alkyl iodide under sodium hydride. The thioacetate was obtained by the reaction with potassium thioacetate in DMF and toluene, and it was hydrolysed with NaOH to give 3-ethanethiol hydantoin (**6**).

Compounds (**7**)~(**16**) were prepared by the same procedure as described for the preparation of 6 and are listed in Table I. We expect the better anti-inflammatory or analgestic effects for this kind of derivatives and the results of screening will be reported later in

a separate paper.

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