Reactivity of Dithiocarbamic Esters: Methods for the Preparation of 3,5-Substituted 2-Thiohydantoins

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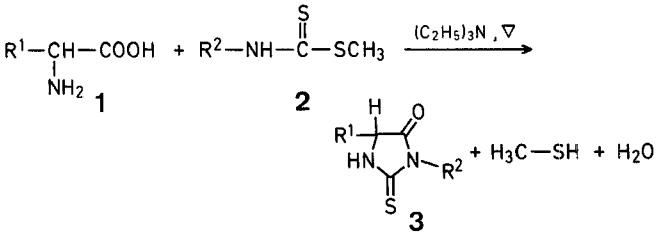
The chemistry of hydantoin derivatives has lately become an area of particular interest because of the anticonvulsant[1,2] and generally immunostimulant[3] properties of these compounds. A number of syntheses of hydantoin derivatives and their sulfur analogs[4] have been performed. *N,O*- and *N,S*-dialkylation of hydantoins and 2-thiohydantoins leads to bicyclic derivatives of imidazooxazoles and imidazothiazoles[5–8] which are potential central nervous system antitumor agents.

Derivatives of 3,5-substituted-2-thiohydantoins have been employed to determine the amino acid sequence in gradual peptide chain degradation[9,10]. These compounds are usually prepared by reaction of an amino acid[11] or amino acid ester[12] with an isothiocyanate. We report here a one-step synthesis of 3-mono- and 3,5-disubstituted 2-thiohydantoins **(3)** from α-amino acids **(1)** and dithiocarbamic esters **(2)**.



It should be mentioned that the formation of thiourea derivatives (compounds **3** are acylthioureas) from alkyl or aryl dithiocarbamates and primary amines has been reported[13] but that our studies[14] have shown that this reaction is not generally applicable; whereas it takes place between methyl *N*-*t*-butyldithiocarbamate and *t*-butylamine it does not proceed between the same dithiocarbamic ester and aniline.

The substituted 2-thiohydantoins may also be prepared from amines, carbon disulfide, base and α-amino acids **(1)** by a one-pot two-stage procedure without isolation of the intermediate dithiocarbamic esters **(2)** (Method B). Further, the synthesis of compounds **3** as depicted in the scheme can also be performed with amino acid esters in place of the free amino acids **1** (Method C).

3,5-Disubstituted 2-thiohydantoins (e.g. **3f**) may also be obtained by heating *N*-(alkylthiothiocarbonyl)-amino acids (e.g. **4**) with primary amines (e.g., aniline) without solvent or in ethanolic solution (Method D).

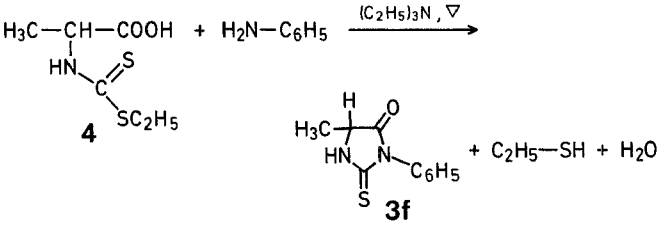


Table. 2-Thiohydantoins **(3)** prepared

3	R^1 (Derivative of amino acid)	R^2	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or m.p. [°C] reported[17]	M.S. (70 eV) *m/e* (rel. intensity, %)
a	H (Gly)	*i*-C_3H_7	83[c]	132–134°	$C_6H_{10}N_2OS$ (158.1)	158 (M^+, 34); 130 (24); 101 (53); 100 (9); 86 (10); 72 (16); 60 (24); 58 (88); 44 (100)
b	H (Gly)	C_6H_5	92	242–244°	245–248°	192 (M^+, 100); 163 (8); 135 (28); 119 (15); 77 (23)
c	CH_3 (Ala)	*i*-C_3H_7	90[c]	115–117°	$C_7H_{12}N_2OS$ (172.1)	172 (M^+, 100); 144 (17); 131 (6); 129 (8); 101 (14); 100 (8); 80 (15); 58 (15)
d	CH_3 (Ala)	*t*-C_4H_9	78[c]	144–146°	$C_8H_{14}N_2OS$ (186.1)	186 (M^+, 1); 158 (12); 131 (19); 115 (33); 100 (8); 86 (28); 69 (12); 58 (85); 57 (89); 44 (80); 41 (100)
e	CH_3 (Ala)	*n*-C_6H_{13}	92	oil	$C_{10}H_{18}N_2OS$ (214.1)	214 (M^+, 15); 181 (100); 144 (19); 131 (52); 86 (17); 158 (98)
f	CH_3 (Ala)	C_6H_5	97	186–187°	185°	206 (M^+, 100); 177 (14); 135 (55); 120 (11); 87 (15); 77 (29)
g	*i*-C_4H_9 (Leu)	*i*-C_3H_7	91	oil	$C_{10}H_{12}N_2OS$ (214.1)	214 (M^+, 82); 181 (12); 171 (7); 160 (32); 149 (38); 116 (11); 102 (14); 101 (10); 100 (12); 86 (44); 60 (35); 58 (100)
h	*i*-C_4H_9 (Leu-	*n*-C_6H_{13}	81[d]	90–92°	$C_{13}H_{24}N_2OS$ (256.1)	256 (M^+, 11); 223 (100); 213 (7); 199 (10); 195 (7); 173 (21); 143 (6); 30 (16); 128 (10); 116 (9); 86 (15); 69 (6); 55 (10)
i	*i*-C_4H_9 (Leu)	C_6H_5	80	182–184°	178°	248 (M^+, 100); 219 (16); 205 (27); 192 (50); 135 (63); 77 (25)
j	C_6H_5—CH_2— (Phe)	*i*-C_3H_7	76[e]	110–112°	$C_{14}H_{18}N_2OS$ (262.1)	262 (M^+, 19); 229 (21); 207 (3); 171 (8); 139 (3); 120 (8); 104 (18); 91 (100); 77 (3); 57 (6)
k	C_6H_5—CH_2— (Phe)	*t*-C_4H_9	91[c]	143–145°	$C_{14}H_{18}N_2OS$ (262.1)	262 (M^+, 9); 229 (16); 207 (2); 171 (16); 120 (9); 115 (10); 104 (15); 91 (100); 77 (7); 58 (26); 57 (30)
l	C_6H_5—CH_2— (Phe)	*n*-C_6H_{13}	86[c]	101–102°	$C_{16}H_{22}N_2OS$ (230.2)	290 (M^+, 2); 257 (54); 223 (16); 207 (5); 199 (7); 167 (5); 120 (12); 104 (17); 91 (100); 77 (4)
m	C_6H_5—CH_2— (Phe)	C_6H_5	88	187–189°	187°	282 (M^+, 59); 249 (14); 191 (8); 181 (31); 135 (14); 131 (18); 91 (100); 77 (22)
n	[N]—$(CH_2)_3$— (Pro)	C_6H_5	78	177–179°	179°	232 (M^+, 100); 203 (8); 135 (76); 77 (24); 60 (30)

[a] Yield of recrystallized product where indicated.
[b] The N analyses were in satisfactory agreement with the calculated values: N, ±0.26.
[c] Recrystallized from ethyl acetate/hexane.
[d] Recrystallized from ethanol.
[e] Recrystallized from acetic acid/water.

The mass-spectral data of products **3** were found to be in accord with literature data[15].

The dithiocarbamic esters **2** were prepared according to Ref.[16,17]. Melting points are uncorrected. Mass spectra were obtained on a Varian MAT 711 mass spectrometer at 70 eV, using a direct insertion probe. All 2-thiohydantoins **3** prepared were racemic.

3,5-Disubstituted 2-Thiohydantoins (3, 3,5-Disubstituted 4-Oxo-2-thioxoimidazolidines); Typical Procedures:

Method A, from α-Amino Acids **(1)** and Methyl Dithiocarbamates **(2)** (General Scheme):

5-Benzyl-3-phenyl-2-thiohydantoin **(3m):** A mixture of DL-phenylalanine (1.65 g, 10 mmol), methyl *N*-phenyldithiocarbamate (1.83 g, 10 mmol), triethylamine (1.4 ml, 10 mmol), and ethanol (30 ml) is heated at reflux temperature for 5 h. The condenser outlet is connected to a wash bottle containing aqueous mercury(II) chloride (to trap the methanethiol evolved). The reaction is complete when the evolution of methanethiol has ceased. The solvent is evaporated under reduced pressure, ethyl acetate (30 ml) is added, and the solution is washed with 1 normal hydrochloric acid (10 ml) and water (2 × 10 ml) to obtain a neutral solution. The organic layer is dried with magnesium sulfate, the solvent is evaporated under reduced pressure, and the residual product is recrystallized from ethanol; yield: 2.48 g (88%); m.p. 187–189 °C.

Method B, One-Pot Synthesis from Amine, Carbon Disulfide, and α-Amino Acid:

5-Methyl-3-phenyl-2-thiohydantoin **(3f):** A mixture of aniline (0.92 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol), carbon disulfide (0.66 ml, 11 mmol), and ethanol (30 ml) is stirred for 2 h at room temperature. Then, methyl iodide (0.62 ml, 10 mmol) is added and stirring is continued for 1 h. DL-Alanine (0.891 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) are then added and the mixture is heated at reflux temperature for 5 h. Work-up is as in Method A; yield: 1.5 g (73%); m.p. 185–187 °C.

Method C, from α-Amino Acid Esters and Methyl Dithiocarbamates **(2):**

3-Phenyl-2-thiohydantoin **(3b):** A mixture of glycine ethyl ester hydrochloride (1.39 g, 10 mmol), triethylamine (1.4 ml, 10 mmol), methyl *N*-phenyldithiocarbamate (1.83 g, 10 mmol), and ethanol (30 ml) is heated at reflux temperature for 5 h. Work-up is as in Method A; yield: 1.78 g (93%); m.p. 242–244 °C.

Method D, from *N*-(Alkylthiothiocarbonyl)-α-amino Acids (e.g. **4**) and Amines:

5-Methyl-3-phenyl-2-thiohydantoin **(3f):**

[Using Triethylamine as Additional Base]: A mixture of *N*-(ethylthiothiocarbonyl)-DL-alanine[17] **(4;** 1.97 g, 10 mmol), aniline (0.92 ml, 10 mmol), triethylamine (1.4 ml, 10 mmol), and ethanol (30 ml) is heated at reflux temperature for 5 h. Work-up is as in Method A; yield: 1.98 g (96%); m.p. 186–187 °C.

[Using Excess Aniline]: A mixture of *N*-(ethylthiothiocarbonyl)-DL-alanine **(4;** 1.97 g, 10 mmol) and aniline (1.94 g, 20 mmol) is heated to gentle reflux. After 15 min, the mixture is cooled to 20 °C, ethyl acetate (30 ml) is added, and the organic solution worked up as in Method A; yield: 1.86 g (90%); m.p. 185–187 °C.

This work was supported by the Polish Academy of Sciences.

Received: September 6, 1982
(Revised form: December 10, 1982)

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