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N-Substituted hydantoin derivatives have been synthesized by the condensation of an α-amino acid derivative, a primary amine and diphenyl carbonate. The method has been applied to the synthesis of hydantoin derivatives with two hydroxyl and/or carboxyl groups.

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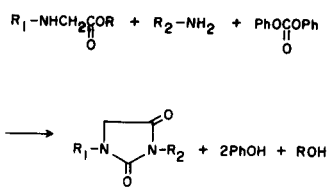
Many synthetic methods of hydantoin (2,4-diketotetrahydroimidazole) derivatives have been reported (1). One of the most typical processes for *N*-substituted hydantoins involves treatment of α-amino acid or its ester with isocyanate initially to form hydantoic acid or hydantoate followed by cyclization (1-3). We wish to report a novel and convenient synthetic method of *N*-substituted hydantoin derivatives. The method is based on a condensation of α-amino acid derivative, primary amine and diphenyl carbonate as shown in the following scheme.



The synthesis was carried out by heating equimolar amount of reactants around 200° in a solvent with high boiling point such as cresol and *N*-methylpyrrolidone. Fourteen hydantoin derivatives having aliphatic and/or aromatic substituents on 1 and/or 3-positions have been synthesized. They are summarized in Table I.

All of them except for VI and VII were synthesized by using ethyl ester of corresponding α-amino acid derivatives. Compounds VI and VII, on the other hand, were derived from *N*-methylglycine (sarcosine).

Use of ethanolamine and ethylenediamine as amine components gave unsuccessful results, since they react with diphenyl carbonate to form stable 2-oxazolidone and 2-imidazolidone, respectively.

L-Phenylalanine ethyl ester showed an exceptional behaviour in the reaction with aniline and diphenyl carbonate in NMP at 180°. 1-Phenoxycarbonyl-3-phenyl-5-benzylhydantoin (X) was isolated in 21% yield. A plausible explanation is that 3-phenyl-5-benzylhydantoin once formed reacts further with diphenyl carbonate to afford X.

It is interesting to note that hydantoin formation takes place predominantly, even though reactions, such as formation of symmetric urea from α-amino acid derivative and/or primary amine, are expected to compete with formation of hydantoic acid or hydantoate, an intermediate prior to ring closure. Possibly, the symmetric ureas once formed will transform to hydantoic acid or hydantoate by disproportionation.

The present method has several advantages over the conventional method. Instead of unstable and toxic isocyanates, the present method employs stable and less toxic diphenyl carbonate which is mass-produced as a raw material for polycarbonate, and inexpensive and widely available primary amines. In addition, the method is applicable to the synthesis of hydantoin derivatives containing functional groups such as carboxyl and hydroxyl groups without any protection of these groups. The conventional method, on the other hand, requires the protection or masking of such reactive groups.

The method mentioned above was applied to the syntheses of a diol, a hydroxy-carboxylic acid and dicarboxylic acids containing hydantoin ring. They are shown in Table II. These compounds are useful especially for thermally stable polymers containing hydantoin ring (4-8), e.g. polyamides, polyesters and polycarbonates.

EXPERIMENTAL

Materials.

All amines, glycine ethyl ester, L-phenylalanine ethyl ester hydrochloride and sarcosine were obtained commercially. The preparation of *N*-(*p*-carboxyphenyl)glycine ethyl ester (9), *N*-phenylglycine ethyl ester (10) and *p,p'*-methylenebis(*N*-phenylglycine ethyl ester) (6) have been reported. *N*-(*m*-Carboxyphenyl)-glycine ethyl ester was prepared from *m*-aminobenzoic acid and ethyl chloroacetate by using calcium carbonate as an acid acceptor. The procedure was nearly the same as that used for the synthesis of *p*-isomer (9). The yield was 64%, m.p. 190-191° (from ethanol).

Anal. Calcd. for $C_{11}H_{13}NO_4$: N, 6.28. Found: N, 6.16.

Hydantoin Derivatives (I-IX and XI-XV).

All hydantoin derivatives (I-IX and XI-XV) were synthesized substantially by the same procedure. Data on the solvent for recrystallization, yield, melting and boiling points, elementary and ir analyses are summarized in Tables I and II. Here, a typical preparation is given for 1-phenyl-3-(*p*-methoxyphenyl)hydantoin (V).

A mixture of 3.58 g. (0.02 mole) of *N*-phenylglycine ethyl ester, 2.46 g. (0.02 mole) of *p*-anisidine and 4.28 g. (0.02 mole) of diphenyl carbonate in 10 ml. of cresol was heated gradually with stirring up to 200° over a period of 1 hour. The reaction was continued at the temperature for 3 hours. After partial removal of the solvent and phenol formed, the resulting solution was triturated with ether. The product precipitated was collected by filtration yielding 2.1 g. (35%) of 1-phenyl-3-(*p*-methoxy-

Table I

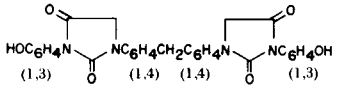
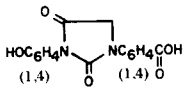
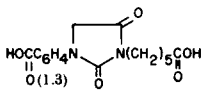
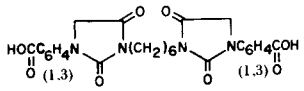
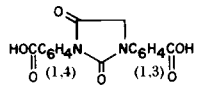
Hydantoin Derivatives (a)

	R_1	R_2	M.p., °C	Yield (b)	Recrystallized from	Formula	Analysis Calcd. (Found) C	H	N	Ir (potassium bromide) cm^{-1}
I	H	C_6H_5	152-153	27	methanol	$C_9H_8N_2O_2$	61.36 (61.04	4.58 4.37	15.90 15.75)	2800-3500 (NH) 1760, 1710 (Hy,c)
II	C_6H_5	n-C_4H_9	75-76	73	aqueous methanol	$C_{13}H_{16}N_2O_2$	67.22 (67.14	6.94 6.63	12.06 11.91)	1755, 1700 (Hy)
III	C_6H_5	4-$CH_3C(=O)C_6H_4$	174-175	----	methanol	$C_{17}H_{14}N_2O_3$	69.40 (69.65	4.80 4.66	9.52 9.57)	1780, 1715 (Hy) 1680 (Ketone)
IV	C_6H_5	4-$C_2H_5OC(=O)C_6H_4$	180-181	53	acetone	$C_{18}H_{16}N_2O_4$	66.65 (66.82	4.97 4.98	8.64 8.68)	1780, 1710 (Hy) 1720 (Ester)
V	C_6H_5	4-$CH_3OC_6H_4$	144-145	35	methanol	$C_{16}H_{14}N_2O_4$	68.07 (67.68	4.99 4.90	9.93 9.75)	1770, 1710 (Hy) 1240 (Ether)
VI	CH_3	C_6H_5	108-109	55	aqueous methanol	$C_{10}H_{10}N_2O_2$	63.15 (63.10	5.30 5.40	14.73 14.76)	1810, 1780, 1720 (Hy)
VII	CH_3	n-C_4H_9	B.p. 86-90 °C/1 mm Hg	41 (d)	---------	$C_8H_{14}N_2O_2$	No analysis (e)			1770, 1710 (Hy)
VIII	3-HOC(=O)C_6H_4	3-$NO_2C_6H_4$	249-250	45	aqueous dioxane	$C_{16}H_{11}N_3O_6$	56.31 (56.33	3.25 3.54	12.31 11.50)	2300-3700, 1700 (COOH), 1780, 1730 (Hy)
IX	4-HOC(=O)C_6H_4	4-ClC_6H_4	300 <	25	acetone	$C_{16}H_{11}N_2O_4Cl$	58.10 (58.24	3.35 3.60	8.47 8.37)	2600-3500, 1680 (COOH), 1780, 1720

(a) I was prepared in NMP and II-IX were prepared in cresol. (b) Optimum conditions were not explored. (c) Hydantoin. (d) Contaminated with small amount of cresol used for the solvent, (e) Nmr (deuteriochloroform): δ 0.90 (t, 3H, CH_3CH_2), 1.08-1.70 (m, 4H, $CH_3CH_2CH_2CH_2$), 2.92 (s, 3H, CH_3N), 3.45 (t, 2H, $NCH_2C_3H_7$) and 3.75 ppm (s, 2H, NCH_2CO). Ms: m/e (relative intensity) 170 (M^+ 35) 128 (48), 115 (100), 99 (62) and 42 (62).

Table II

Hydantoin Derivatives with Two OH and/or COOH

Hydantoin Derivatives	M.p., °C	Yield %	Recrystallized from	Formula	Analysis Calcd. (Found) C	H	N	Ir (potassium bromide) cm^{-1}
	237-238	82	NMP/ ethanol	$C_{31}H_{24}N_4O_6$	67.87 (67.92	4.41 4.41	10.21 9.85)	3400 (OH 1770, 1715 (Hy, b)
	300 <	81	NMP/ ethanol	$C_{16}H_{12}N_2O_5$ (c)	61.54 (60.85	3.87 3.92	8.97 8.57)	2000-3600 (COOH) 3400 (OH) 1770, 1710 (Hy)
	208-209	78	ethanol	$C_{16}H_{18}N_2O_6$	57.48 (57.48	5.43 5.29	8.38 8.11)	2300-3500, 1670 (COOH), 1760, 1710 (Hy)
	295	90	NMP/ water	$C_{26}H_{26}N_4O_8$	59.76 (59.81	5.02 5.16	10.72 10.79)	2300-3500, 1680 (COOH), 1770, 1715 (Hy)
	300 <	77	NMP/ ethanol	$C_{17}H_{12}N_2O_6$	60.00 (60.03	3.55 3.54	8.23 8.23)	3600-2100, 1690 (COOH), 1785, 1715 (Hy)

(a) XI-XIV were prepared in cresol and XV in NMP. (b) Hydantoin. (c) A more exact value for carbon could not be obtained.

phenyl)hydantoin (V), m.p. 144-145° (from methanol).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 68.07; H, 4.99; N, 9.93. Found: C, 67.68; H, 4.90; N, 9.75; nmr (deuteriochloroform): 4.40 (s, 2H, CH_2), 3.82 (s, 3H, CH_3) and 6.9-7.8 (m, 9H, aromatic); ir (potassium bromide): 1770, 1710 (C=O of hydantoin), 1240 cm^{-1} (C-O of ether); ms: m/e (relative intensity) 282 (M^+ 76), 149 (62), 134 (19), 105 (100) and 77 (25).

1-Phenoxycarbonyl-3-phenyl-5-benzylhydantoin (X).

L-Phenylalanine ethyl ester hydrochloride (8.6 g., 0.037 mole) was neutralized with aqueous sodium hydroxide. The mixture was extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain L-phenylalanine ethyl ester as an oil. To the residual oil, 3.44 g. (0.037 mole) of aniline and 7.9 g. (0.037 mole) of diphenyl carbonate and 30 ml. of NMP were added. The mixture was heated at 160° for 2.5 hours and 180° for 3 hours. After removal of the solvent, the residual oil was triturated with small amount of methanol to obtain 2.0 g. (21%) of 1-phenoxycarbonyl-3-phenyl-5-benzylhydantoin (X), m.p. 150-151°.

Anal. Calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.27; H, 4.48; N, 7.42; nmr (deuteriochloroform): 3.56 (m, 2H, CH_2), 4.96 (m, 1H, CH) and 6.88-7.60 ppm (m, 15H, aromatic); ir (potassium bromide): 1810, 1750 and 1718 cm^{-1} (C=O); ms: (relative intensity) 386 (M^+ 15), 293 (73), 174 (3), 146 (100), 119 (12), 94 (17), 91 (55) and 77 (35).

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