The Carboxylation of Hydantoins[1]

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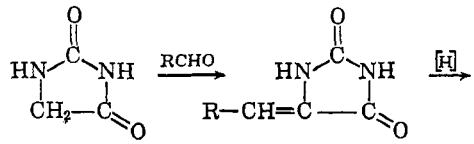
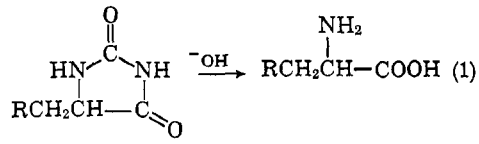
A method has been developed for the carboxylation and alkylation of hydantoins. It has been shown that this method provides a simple route to a number of amino acids in good yield from readily available, stable starting materials.

The hydantoin ring system has been intensively studied during the hundred odd years since it was discovered by Baeyer[2] in 1861 during his work on uric acid. Much of the interest in hydantoin chemistry has largely been centered in two areas, the natural occurrence of hydantoins[3] and synthesis of a variety of compounds for use as pharmaceuticals.[4] However, except for a few isolated but significant cases, no serious attention has been given to chemistry involving the methylene group at the 5-position of the ring. The condensation of aldehydes to form 5-aralkylidinehydantoins (I) and their subsequent reduction was first reported by Wheeler and Hoffman[5] in 1911. This reaction has since been used in the preparation of a



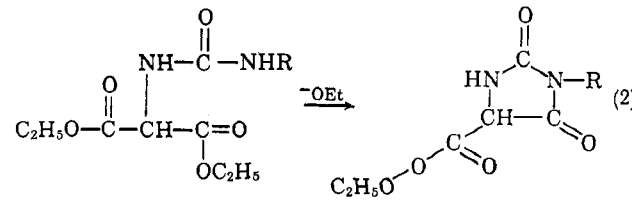
I



large number of amino acids.[3] Condensation with formamidines[6] and bromination[7] are the other two reactions of the methylene group that have received considerable attention.[7]

It has now been found that the methylene group is susceptible to carboxylation with magnesium methyl carbonate (MMC).[8] Hydantoin-5-carboxylic acids have received little attention in spite of the fact that they can be viewed as derivatives of aminomalonic acid and therefore should undergo the typical reactions of substituted aminomalonates. Fischer[9] and Biltz[10a] isolated substituted hydantoin-5-carboxamides as degradation products from purines, and Biltz[10b] isolated 3-methyl-5-carboxyhydantoin. However, no chemistry was examined except that he showed it was readily decarboxylated when heated to 130°. Johnson and Nicolet[11] prepared 5-carbamidohydantoin by ring closure of N-carboethoxyaminomalonamide. They unsuccessfully tried to condense the amide with urea to form uric acid and successfully hydrolyzed the amide as their only attempts at establishing the chemistry of the derivatives of hydantoin-5-carboxylic acids.

A recent paper[12] disclosed a preparation of 5-carboethoxyhydantoins which was carried out *via* an ethoxide-catalyzed ring closure of ureidomalonates (eq. 2). The ready oxidation of the ester was noted,



although no products were definitely characterized. The oxidation was assumed to occur at the 5-position and a compound with the proper analysis for 3-phenyl-5-hydroxy-5-carboethoxyhydantoin was isolated. The authors also pointed out that the remaining proton at the 5-position is readily removed to form a sodium salt of the ester, which in aqueous solution underwent rapid "autosaponification".

Carboxylation of Hydantoin.—A solution of hydantoin and magnesium methyl carbonate in dimethylformamide was heated for 3 hr. at 65°. During this time considerable evolution of gas took place[13] and the reaction mixture finally set up to a clear gel. A portion of the solid was dissolved in methanol in order to examine the ultraviolet spectrum. A new absorption peak at 278 mμ had been produced, and acidification immediately caused the peak to disappear. The alkali metal salts of hydantoin absorb at approximately 220 mμ[14] as does the magnesium salt which was prepared from magnesium methoxide in methanol. While the new absorbance at 278 mμ was probably due to the same type of chelated structure as previously observed in the carboxylation of nitroalkanes[8] and ketones[15] with magnesium methyl carbonate, carboxylation on nitrogen to form an allophanate was also possible. However, reaction of 3-benzylhydantoin with magnesium methyl carbonate showed a similar change in the ultraviolet region, while neither 5,5-dimethylhydantoin or 5-methylhydantoin underwent any spectral change in the 275-mμ region. These facts are consistent with the chelated structure II.

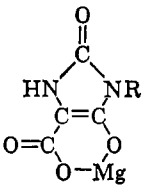
Stiles[15] had previously shown that the products formed on carboxylation of ketones could be easily

(1) A preliminary report of some of this work was published as a Communication to the Editor, *J. Am. Chem. Soc.*, **86**, 961 (1964).
(2) A. Baeyer, *Ann.*, **117**, 178 (1861).
(3) E. Schulze and J. Barbiere, *Ber.*, **14**, 1834 (1881); J. B. Collip and R. Sandin, *Trans. Roy. Soc. Can., Sect. V*, **22**, 185 (1928); J. D. Dutcher, J. R. Johnson, and W. F. Bruce, *J. Am. Chem. Soc.*, **67**, 1736 (1945).
(4) E. Ware, *Chem. Rev.*, 403 (1950).
(5) H. L. Wheeler and G. Hoffman, *Am. Chem. J.*, **45**, 368 (1911).
(6) F. B. Dains, R. Thompson, and W. F. Asendorf, *J. Am. Chem. Soc.*, **44**, 2310 (1922).
(7) S. Gabriel, *Ann.*, **350**, 118 (1906).
(8) H. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, **85**, 616 (1963).
(9) E. Fisher, *Ann.*, **215**, 253 (1882).
(10) (a) H. Biltz, *Ber.*, **43**, 1600 (1910); (b) *ibid.*, **46**, 3407 (1913).
(11) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 355 (1914).
(12) W. Garner and H. Tieckelmann, *J. Org. Chem.*, **29**, 2003 (1964).
(13) Hydantoin is a reasonably strong acid, $pK_a = 7.59 \times 10^{-10}$ [J. K. Wood, *J. Chem. Soc.*, **89**, 1833 (1906)] and thus was expected to decompose approximately 1 equiv. of magnesium methyl carbonate.
(14) R. E. Stuckey, *ibid.*, 331 (1947).
(15) M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

TABLE I

Hydantoin	Yield, %	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
3-Benzyl-5-carbomethoxy	28	134–136	58.06	4.87	11.28	58.40	5.60	12.33
3-α-Naphthyl-5-carboethoxy	35	80–86[a]	64.42	4.73	9.39	65.18	4.77	9.61
3-Phenyl-5-carbomethoxy[b]	72	177–179	56.41	4.30	11.96	56.43	4.42	11.95
3-Phenyl-5-carboethoxy	38	108–110[c]	58.06	4.87	11.28	57.71	4.81	11.42
1-Methyl-3-phenyl-5-carboethoxy	48	95–97						

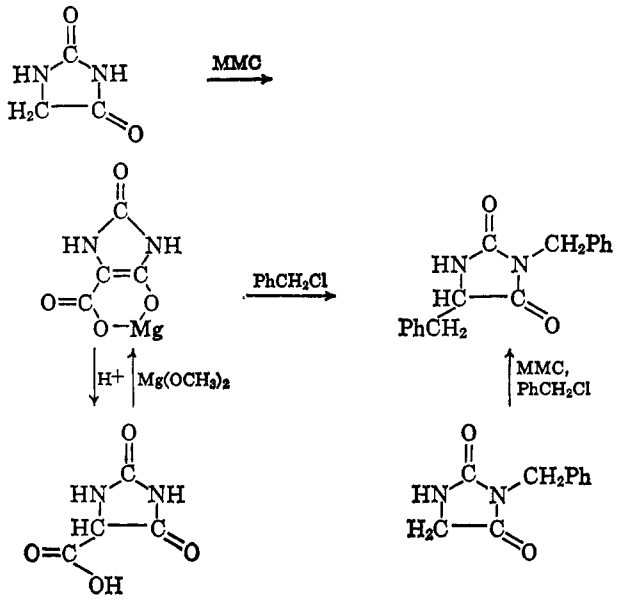
[a] A. H. Cook, *et al.* [*J. Chem. Soc.*, 3789 (1952)] report m.p. 85°. [b] Calcd.: mol. wt., 234. Found: mol. wt., 233. [c] W. Garner, *et al.* [*J. Org. Chem.*, **29**, 2003 (1964)] report m.p. 110°.



II

alkylated. Two similar reactions were carried out using hydantoin and 3-benzylhydantoin. After carboxylation, benzyl chloride was added and in each case a good yield of 3,5-dibenzylhydantoin was obtained. The product was identified by comparison with an authentic sample prepared from β-phenylalanine. These reactions are summarized in Chart I.

CHART I



Preparation of 5-Carboalkoxyhydantoins.—While the results discussed in the preceding section are consistent with the formation of 5-carboxyhydantoins on carboxylation with MMC, no success was had in actual isolation of the free carboxylic acids. Since this probably was due to the ready decarboxylation[10b] of the acids, esterification was employed to avoid this problem.

A solution of 3-benzylhydantoin in MMC was heated for 3 hr. at 70°, the chelate was precipitated by pouring the reaction mixture into ether and adding methanolic hydrogen chloride to the precipitate. A product was isolated which had the correct n.m.r. spectrum for 3-benzyl-5-carbomethoxyhydantoin [in cycles per second downfield from TMS, a methoxy singlet (236), a benzyl singlet (287), a methynyl singlet (308), and an aromatic singlet (440)]; however, considerable difficulty was experienced in obtaining a sharp-melting product from the original glassy material and the analyses were at best borderline.

A sample of 3-α-napthylhydantoin was treated in an identical fashion except that ethanol was used in the esterification. This gave a product which appeared to be identical with the 3-α-naphthyl-5-carbethoxyhydantoin obtained by Cook and Hunter[16] from the acid-catalyzed ring closure of N-carboethoxycyanomethyl-N′-α-naphthylurea.

The reaction of phenylisocyanate with glycine and sarcosine was used to prepare 3-phenylhydantoin and 1-methyl-3-phenylhydantoin, respectively. Table I gives the results of the carboxylation and esterification of these hydantoins. In every case, except 3-phenyl-5-carbomethoxyhydantoin, difficulty was experienced in obtaining sharp-melting, well-behaved crystals. Prolonged pumping in high vacuum was required to remove solvents even when crystallization took place without difficulty.

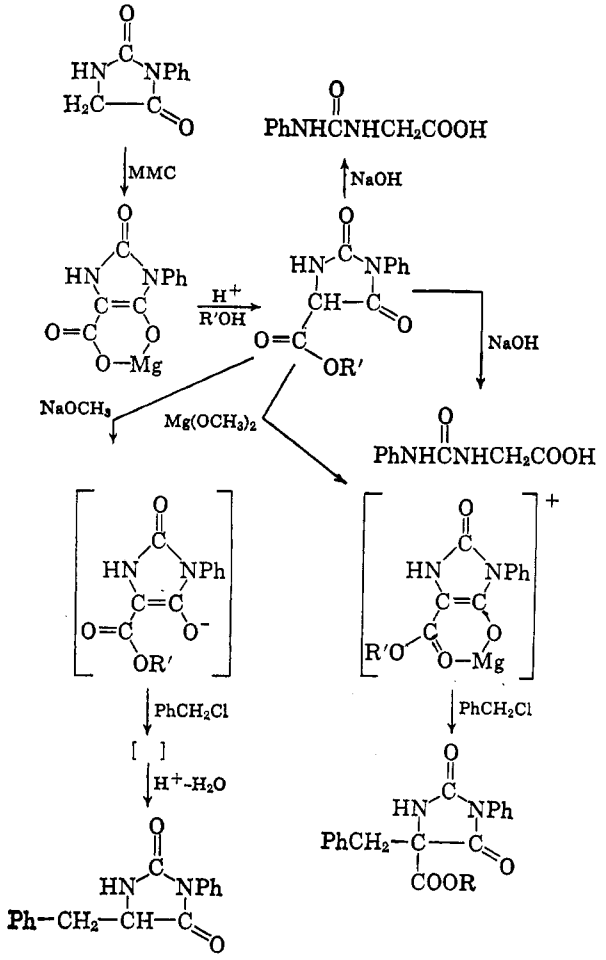
A few of the physical and chemical properties of 3-phenyl-5-carboethoxyhydantoin have been examined. The ionization constant for the remaining proton at the 5-position was found to be $pK_a = 7.78$, six orders of magnitude more acidic than malonic ester.

The sodium salt was prepared by dissolving the ester in anhydrous methanolic sodium methoxide. After reaction with benzyl chloride, an oil was obtained which did not crystallize under any of the conditions tried. Refluxing the oil with aqueous hydrochloric acid gave a 77% yield of 3-phenyl-5-benzylhydantoin. In contrast, the magnesium salt, on reaction with benzyl chloride, gave an easily isolated and crystallized 60% yield of 3-phenyl-5-benzyl-5-carbomethoxyhydantoin. This compound possesses an interesting n.m.r. spectrum in that the asymmetric center at the 5-position of the hydantoin provides a magnetically anisotropic environment for the benzyl methylene protons. These protons are then observed as a cleanly resolved AB quartet.

Garner and Tieckelmann[12] examined the ultraviolet spectrum of the salts of 3-phenyl-5-carboethoxyhydantoin and commented that the spectrum is not stable. Since they were using partially aqueous solution, the disappearance of the absorption peak at 293 mμ was attributed to hydrolysis. The spectrum of the sodium salt was also examined as a part of this work; however, anhydrous methanol–sodium methoxide was used to prepare the salt. As in Garner's case, the peak at 292 mμ faded to one-third of the original intensity apparently even more rapidly, since Garner reports that 48 hr. were required for the complete disappearance of

(16) A. H. Cook and G. D. Hunter, *J. Chem. Soc.*, 3789 (1952).

CHART II

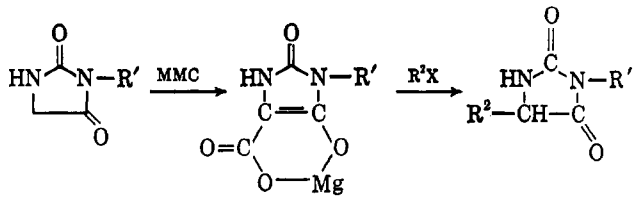


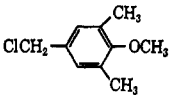
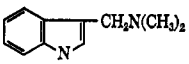
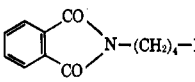
the absorption peak. In our study it seems unlikely that hydrolysis was responsible for decrease in intensity. Again, as in the case of alkylation, the magnesium salt behaved in an entirely different fashion. The absorption maximum was at 301 mμ (ε 2.1 × 10^4) and even after 24 hr. no change had occurred. Hydrolysis in aqueous sodium hydroxide produced α-phenylhydantoic acid (m.p. 192–194°). The reactions are summarized in Chart II. A number of anomalous reactions and rearrangements of the hydantoin-5-carboxylates were observed during the course of the work which will be reported in a forthcoming paper.

Alkylation of the Magnesium Chelate of 5-Carboxyhydantoins.—Stiles[15] has shown that alkyl halides react with the magnesium chelates of β-keto acids prepared from ketones and magnesium methyl carbonate to form alkylated ketones. When a hydantoin is heated with magnesium methyl carbonate, the resulting magnesium chelate can be alkylated without isolation of the initial product.

The hydantoins used in these alkylation experiments were prepared by three different methods. Hydantoin itself was prepared by heating glycolonitrile and ammonium carbonate in dimethylformamide followed by ring closure of the ureidoacetamide by refluxing in aqueous acid. Several of the hydantoins (3-benzyl, 3-decyl, 3-methyl, and 3-ethyl) were prepared by the alkylation of the potassium salt of hydantoin. Reaction of glycine and sarcosine with phenylisocyanate gave 3-phenyl- and 1-methyl-3-phenylhydantoin, respectively. Table II lists the results obtained in alkylating various 3-substituted hydantoins. While hydantoin itself could be alkylated, as discussed above, the use of 3-substituted hydantoins prevented the loss of 1 equiv. of magnesium methyl carbonate by reaction with the acidic imino proton.

TABLE II



R′	R^2X	Yield of hydantoin, %	M.p., °C.	Lit. m.p., °C.
$C_6H_5CH_2$	$C_6H_5CH_2Cl$	99	145–146	
	CH_3I	63	112–114	
	$C_6H_5CHBrCH_3$	56	140–143[a]	
			168–172	
C_6H_5	$C_6H_5CH_2Cl$	90	170–172	170–172[b]
	$(CH_3)_2CHCH_2CH_2Br$	95	117–119	118–119[c]
	$(CH_3)_2CHCH_2Br$	66	126–127	125[d]
	C_6H_5 CH_2CH_2Br	75	117–119	
	$(CH_3)_2CHBr$	40	123–125	124–125[e]
		77	156–158	
	$C_6H_5CH_2SCH_2Cl$	64	150–151	154[f]
		55	173–175	
		53	205–207	202–203[g]
	$NaOOCCH_2CH_2Cl$	56	168–169	
$C_{10}H_{21}$	$C_6H_5CH_2Cl$	62	102–103	

[a] The diasteriomers were separated and analyzed independently. [b] M. Bergmann and D. Delis, *Ann.*, **458**, 89 (1927). [c] Y. Huang, *et al.*, *J. Chinese Chem. Soc.*, **15**, 46 (1947). [d] E. Fisher and M. Skita, *Z. Physik. Chem.*, **33**, 187 (1901). [e] M. Slimmer, *Ber.*, **35**, 403 (1902). [f] L. Crombie and K. C. Hooper, *J. Chem. Soc.*, 3010 (1955). [g] V. I. Maimind, *et al.*, *Zh. Obsch. Khim.*, **28**, 2223 (1958).

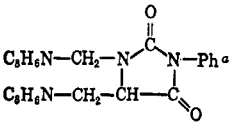
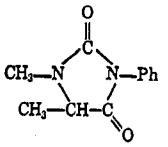
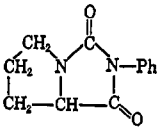
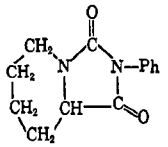
Johnson and Bates[17] commented in their paper on alkylation of the nitrogen at the 1- and 3-position of hydantoin, "the 3-position is the point of attack and the formation of 1- and 1,3-dialkyl derivatives has never been observed." However, during the course of the present work it was found that methyl iodide, when used in excess, reacted with the chelate of 3-phenyl-5-carboxyhydantoin to produce a 68% yield of 1,5-dimethyl-3-phenylhydantoin. The identity of the dimethyl compound was established by carboxylation and methylation of 1-methyl-3-phenylhydantoin. Similarly, when an attempt was made to produce 5-skatyl-3-phenylhydantoin by alkylating the magnesium chelate with gramine methiodide, the principal product isolated was 1,5-diskatyl-3-phenylhydantoin.

It proved possible to take advantage of the double alkylation in the preparation of 1,5-trimethylene-3-phenylhydantoin. This hydantoin was of interest since it could be hydrolyzed to proline. The mag-

(17) T. B. Johnson and J. S. Bates, *J. Am. Chem. Soc.*, **38**, 1087 (1916).

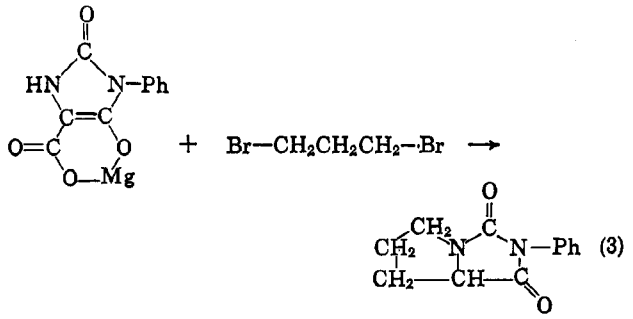
TABLE III

THE ALKYLATION OF THE 1- AND 5-POSITIONS OF 3-PHENYLHYDANTOIN

Alkylating agent	Product	Yield, %	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Gramine methiodide		47	273–275	74.64	5.10	12.89	73.57	5.21	12.93
Methyl iodide		68	145–147[b]	64.69	5.92	13.72	64.92	5.98	13.70
Trimethylene bromide		48	117–119[c]	66.65	5.59	12.95	66.73	5.68	13.08
Tetramethylene bromide		94	159–160	67.81	6.13	12.17	67.39	6.16	11.68

[a] Calcd.: mol. wt., 434.50. Found: mol. wt., 415. [b] E. Friedmann [*Beitr. Chem. Physiol. Path.*, 11, 164 (1906)] reports m.p. 145–146°. [c] E. Fischer [*Ber.*, **34**, 460 (1901)] reports m.p. 118°.

nesium chelate from the reaction of 3-phenylhydantoin with magnesium methyl carbonate was alkylated with trimethylene bromide as shown in eq. 3. Tetramethylene bromide was used in an identical fashion to produce the precursor of pipicolic acid. The products from alkylation with trimethylene and tetramethylene bromide were identical with 3-phenylhydantoins prepared from proline and pipicolic acid, respectively. Results of these experiments are shown in Table III.



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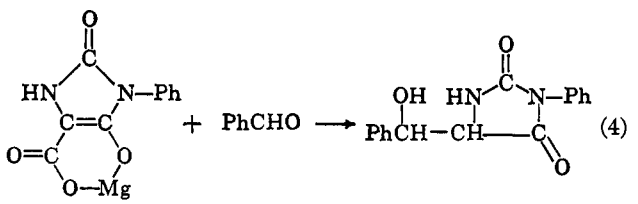
Reaction of the Magnesium Chelate of 5-Carboxyhydantoins with Aldehydes, Anhydrides and Acid Chlorides.—The condensation of aromatic aldehydes with hydantoin constituted the essential part of Wheeler's synthesis of aromatic amino acids.[5] As expected, benzaldehyde easily condenses with the magnesium chelate of the carboxylated hydantoin. In the present case, it was possible to obtain poor yields of each of the diesteriomeric alcohols (eq. 4) by chromatographing the product on silica gel. A 65% yield of 5-benzylidene-3-phenylhydantoin was obtained when the reaction product was dehydrated, in acid, without attempting an isolation of the 5-phenylhydroxymethyl-3-phenylhydantoin.



(4)

Unlike hydantoin, where condensation with aliphatic aldehydes is difficult,[18] the magnesium chelate is easily condensed with heptaldehyde. The product was dehydrated and a 72% yield of 3-phenyl-5-heptylidenehydantoin isolated.

Acid chlorides have also been condensed with the magnesium chelate. Benzoyl chloride gave a 53% yield of 3-phenyl-5-benzoylhydantoin. Ethyl chloroformate reacted at both the 1- and the 5-positions to produce 1,5-di(carboethoxy)-3-phenylhydantoin. In both cases, however, considerable reaction between the acid chloride and the dimethylformamide or magnesium methyl carbonate occurs. This problem was avoided when anhydrides were used instead of acid chlorides. Benzoic anhydride gave an 86% yield of 3-phenyl-5-benzoylhydantoin, and methyl pyrocarbonate[19] a 76% yield of 3-phenyl-5-carbomethoxyhydantoin. The data for these experiments are given in Table IV.

Hydrolysis of 5-Substituted Hydantoins to Amino Acids.—The barium hydroxide hydrolysis of the 3-phenylhydantoins, to produce free amino acids, was carried out in a number of cases. The method used was essentially that described by Gaudry.[20] A group of examples are given in Table V simply as illustrations of a well-known procedure. In general the yields from the hydrolysis were good except for the preparation of DL-glutamic acid which proceeded at a very slow rate.

(18) T. B. Johnson, *J. Am. Chem. Soc.*, **61**, 2485 (1939).
(19) V. I. Kovalenko, *Zh. Obshch. Khim.*, **22**, 1546 (1952).
(20) R. Gaudry, *Can. J. Res.*, **26B**, 773 (1948).

TABLE IV

REACTION OF 3-PHENYLHYDANTOIN WITH ALDEHYDES, ACID CHLORIDES, AND ANHYDRIDES

Reactant	5-Substituent	Yield, %	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
PhCHO	PhCH(OH)—	10–20	218–220 185–189						
	PhCH=	65	256–257[a]						
$CH_3(CH_2)_5CHO$	$CH_3(CH_2)_5CH$=	72	125–128	70.56	7.40	10.28	70.48	7.41	10.21
PhCCl(=O)	PhC(=O)—	53	198–200						
$(PhC)_2O$ (=O)	PhC(=O)—	86	198–200	68.56	4.32	9.99	68.47	4.50	10.22
$(CH_3OC)_2O$ (=O)	CH_3O—C(=O)—	76	177–179	56.41	4.30	11.96	56.36	4.51	11.95
C_2H_5OCCl (=O)	C_2H_5OC(=O)—	41	94–97	56.25	5.04	8.75	56.08	5.13	8.49

[a] D. R. Seeger and A. MacMillan [*J. Am. Chem. Soc.*, **64**, 1686 (1942)] report m.p. 252–252.5°. [b] 1,5-Disubstituted.

TABLE V

HYDROLYSIS OF 3-PHENYLHYDANTOINS

Amino acid	Hydantoin	Yield, %
DL-Valine	5-Isopropyl	95
DL-Leucine	5-Isobutyl	70
DL-Phenylalanine	5-Benzyl	99
DL-Tryptophan	5-Skatyl	97
DL-Proline	1,5-Trimethylene	94
DL-Lysine hydrochloride	5-(δ-Pthalimidobutyl)	85
DL-S-Benzylcysteine	5-Benzylthiomethyl	84
DL-Glutamic acid	5-Carboxymethyl	30

Experimental Section

The alkylating agents were commercially available materials except for the materials whose preparations are given below. N.m.r. spectra were obtained using a Varian A-60 spectrometer, ultraviolet spectra were from a Perkin-Elmer Ultracord or a Cary Model 14 spectrometer. Magnesium methyl carbonate was prepared as given previously.[8]

Hydantoin.—Hydantoin was both obtained commercially and prepared from glycolonitrile. A solution of 90 ml. of 70% glycolonitrile in 300 ml. of dimethylformamide was slurried with calcium carbonate to remove the acidic impurities in the commercial glycolonitrile. After filtering, 190 g. of ammonium carbonate was added and the reaction mixture was heated to 85° for 90 min. The dimethylformamide was removed and the residue was recrystallized from ethanol–water. The product was largely hydantoic acid amide contaminated with a small amount of nitrile.

Anal. Calcd. for: $C_3H_7N_3O_2$: C, 30.8; N, 35.9; H, 6.0. Found: C, 31.4; H, 6.3; N, 35.2.

Cyclization was effected by refluxing the crude product (m.p. 192–200°) for 12 hr. in 150 ml. of 50% hydrochloric acid (v./v.). Cooling in ice gave 52 g. (m.p. 224–226°) of hydantoin.

Anal. Calcd. for $C_3H_4N_2O_2$: C: 36.00; H, 4.03; N, 27.99. Found: C, 35.88; H, 4.11; N, 28.01.

3-Benzylhydantoin.—A solution of 20 g. of sodium hydroxide in 250 ml. of water and 50 g. of hydantoin were heated to reflux. A total of 110 ml. of benzyl chloride was added to the vigorously stirred solution and heating continued for 20 hr. The reaction mixture was then poured onto 400 g. of ice; the product was filtered off, dried, and recrystallized from benzene, yield 55 g. (58%), m.p. 140–141°, lit.[21] m.p. 141°.

3-Ethylhydantoin.—The potassium salt of hydantoin was prepared by dissolving 50 g. of hydantoin in 1 l. of warm (~60°) ethanol and slowly adding a solution of 30 g. of potassium hydroxide in 250 ml. of alcohol. The potassium hydantoinate precipitated, was filtered off, washed with ethanol, and dried under vacuum at 80°.

A suspension of 14 g. of the salt in 100 ml. of dimethylformamide was prepared. Ethyl bromide (15 g.) was added; the slurry was stirred overnight at room temperature and finally heated to 80° for 1 hr. After cooling to 0°, the potassium bromide was filtered off, the solvent was evaporated under vacuum, and the residue was recrystallized from methanol, yield 6.5 g. (51%), m.p. 100–102°, lit.[22] m.p. 102°.

Anal. Calcd. for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 46.91; H, 6.25; N, 21.78.

3-Decylhydantoin.—The solution was prepared as given for 3-ethylhydantoin except that *n*-decyl bromide was used. The product was crystallized from ethanol–water, yield 62%, m.p. 95–97°.

5-Benzylhydantoin.—A solution of 16.5 g. of β-phenylalanine and 8.1 g. of potassium cyanate in 30 ml. of water was refluxed for 1 hr. Hydrochloric acid, 15 ml., was added and the reaction mixture was refluxed for an additional 10 min. Cooling in an ice bath gave crystals which were filtered off and recrystallized from benzene–ethanol. A yield of 13 g. (68.5%), m.p. 192–193°, lit.[20] m.p. 189–190°, was obtained.

5-Methylhydantoin.—5-Methylhydantoin was prepared exactly as 5-benzylhydantoin, except alanine was used in place of β-phenylalanine. A yield of 7 g. (61.5%), m.p. 150–152°, lit.[21] m.p. 149–151°, was obtained.

3,5-Dibenzylhydantoin.—A sample of 5-benzylhydantoin (3.8 g.) was added to a solution of 0.8 g. of sodium hydroxide in 20 ml. of 50% aqueous ethanol. Benzyl chloride (2.0 ml.) was added and the reaction mixture was refluxed for 4 hr. After cooling, the product separated and was recrystallized from benzene, m.p. 144–146°.

3-Benzyl-5-methylhydantoin.—This compound was prepared in the same fashion as 3,5-dibenzylhydantoin, and had m.p. 108–110°.

3-Phenylhydantoin.—Glycine, 75 g., was dissolved in 400 ml. of water containing 68 g. of potassium hydroxide. After solution was complete, 132 g. of phenylisocyanate was added to the rapidly stirred solution. The addition required about 4 hr. After standing overnight, the diphenylurea was filtered off, and the filtrate was acidified to precipitate the phenylhydantoic acid. The phenylhydantoic acid was filtered off, dried a short time in air, and cyclized by refluxing for 1 hr. with 200 ml. of water and 200 ml. of concentrated hydrochloric acid. The product crystallized on cooling and was recrystallized from ethanol–water. The yield was 125 g. (72%), m.p. 156–158°, lit.[23] m.p. 154–155°.

1-Methyl-3-phenylhydantoin.—1-Methyl-3-phenylhydantoin was prepared on a 0.1-mole scale, as described for 3-phenylhydantoin, except that sarcosine was substituted for the glycine. The yield was 17.3 g. (91%), m.p. 109–110°, lit.[24] m.p. 108–110°.

3-Phenyl-5-benzylhydantoin.—3-Phenyl-5-benzylhydantoin was prepared from β-phenylalanine and phenylisocyanate as described for 3-phenylhydantoin. A yield of 24 g. (90%), m.p. 172–174°, lit.[25] m.p. 173–174°, was obtained from a 0.1-mole preparation.

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N-(N'-Phenylcarbamyl)tryptophan.—Tryptophan (4.08 g.) was dissolved in 50 ml. of potassium hydroxide (1.5 g.) solution. Phenylisocyanate (2.0 ml.) was added; the mixture was vigorously stirred overnight, filtered, and acidified. The product was recrystallized from methanol–water, m.p. 198–200°.

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.81; H, 5.29; N, 12.98. Found: C, 66.68; H, 5.41; N, 12.79.

3-Phenyl-5-skatylhydantoin.—A slurry of 2 g. of N-(N'-phenylcarbamyl)tryptophan and 30 ml. of 30% hydrochloric acid (v./v.) was refluxed for 1 hr. and cooled to 0°, and the product was filtered off. Recrystallization from chloroform–hexane gave an 88% (1.7 g.) yield of the hydantoin, m.p. 173–176°.

3-Phenyl-5-(benzylthiomethyl)hydantoin.—L-(+)-Cysteine hydrochloride (15.8 g.) and 16 g. of sodium hydroxide were dissolved in 50 ml. of water. When solution was complete the temperature was 85° and 12 ml. of benzyl chloride was added. The reaction was sufficiently exothermic to cause boiling. After the temperature had spontaneously dropped to 40°, 12 ml. of phenylisocyanate was added; the reaction mixture was stirred for 3 hr. and filtered to remove the diphenylurea. Acidification precipitated the hydantoic acid which was added to a mixture of water (70 ml.) and hydrochloric acid (30 ml.). Sufficient ethanol was added at the boiling point of the mixture to produce a homogeneous solution; heating was continued for 1 hr. after which it was cooled to room temperature. The reaction mixture was poured onto 250 g. of ice to precipitate the product. A portion of the solid was recrystallized from ethanol, m.p. 117–119°, lit.[26] m.p. 118–119.5°. The remainder was racemized by dissolving in hot ethanol, adding 2 ml. of 1 *N* sodium methoxide and stirring for approximately 2 min. After acidification and cooling, the racemic product crystallized, m.p. 149–151°.

Chloromethyl Benzyl Sulfide.—The sulfide was prepared by chloromethylation of benzyl mercaptan[27] and had b.p. 121–123° (10 mm.).

N-(4-Bromobutyl)phthalimide was prepared by the direct reaction of tetramethylene bromide and potassium phthalimide, m.p. 79–80°, lit.[28] m.p. 79.5–80°.

General Procedure for the Alkylation of N-3-Substituted Hydantoins.—A 2 *M* solution of magnesium methyl carbonate (50 ml.) was saturated with carbon dioxide at 80° by passing a slow stream of gas over the stirred reagent for approximately 1 hr. The carbon dioxide was replaced by a slow nitrogen stream, and 0.05 mole of the appropriate hydantoin was added. After 1.5 hr. at 80° a total of 0.055 mole of alkylating agent was added. In most instances all of the alkylating agent was added at one time. However, in the cases of methyl iodide, benzyl chloride, and α-phenethylbromide, the reaction was so vigorous that the halide was added by drops.

The reaction mixture was heated to 110° for 5 hr. or to reflux if the alkylating agent was low boiling. The temperature was raised slowly to 110° as the alkylating agent was consumed. It was cooled and poured, with vigorous stirring, into 25 ml. of concentrated hydrochloric acid and 100 g. of ice. The product separated and crystallized in a short time. Yields were highest if the hydrolysis mixture was allowed to stand at 5° overnight to complete the crystallization.

Alkylation of Hydantoin.—Hydantoin was benzylated by the procedure for N-3-substituted hydantoins, except 0.12 mole (15.2 g.) of benzyl chloride was used. Hydrolysis and recrystallization gave 17.6 g. (93%) of 3,5-dibenzylhydantoin, m.p. 145–146°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.91; N, 10.03.

3-Benzyl-5-methylhydantoin.—3-Benzylhydantoin was methylated according to the general procedure, except that the hydrolysis mixture was evaporated almost to dryness under vacuum and extracted with hot benzene. The benzene was evaporated, and recrystallization from benzene–hexane gave 12.9 g. (63%) of product, m.p. 112–114°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.56; H, 6.03; N, 14.10.

3-Phenyl-5-carbomethoxyhydantoin.—3-Phenylhydantoin (140 g.) was added to 500 ml. of 2 *M* magnesium methyl carbonate solution and there action mixture was heated at 100° for 3 hr. It was cooled and the chelate was precipitated by pouring the mixture (with vigorous stirring) into 2.5 l. of diethyl ether. After decanting the ether, 2 l. of cold methanol (−50°) containing 200 g. of anhydrous hydrogen chloride was added to the solid.[29] The solution was allowed to warm spontaneously to room temperature and stirred overnight. A substantial fraction of product had crystallized by morning; it was filtered off, and the filtrate was cooled to −10° for 2 hr. to complete the crystallization. Recrystallization of the combined crops from ethanol–dimethylformaide gave a 72% (133 g.) yield of 3-phenyl-5-carbomethoxyhydantoin, m.p. 177–179°.

Alkylation of 3-Phenyl-5-carbomethoxyhydantion. Magnesium Salt.—A solution of 5.85 g. (0.025 mole) of 3-phenyl-5-carbomethoxyhydantoin and 0.025 mole of magnesium methoxide in 50 ml. of methanol was prepared. After a few minutes a thick slurry was formed to which was added 3 ml. of benzyl chloride. After refluxing overnight the mixture was poured into ice and hydrochloric acid. The solid which was filtered off was composed of two materials, one methanol soluble. The methanol-soluble material was recrystallized from benzene–hexane: m.p. 118–120°. The n.m.r. spectrum in trifloroacetic acid (cycles per second downfield from TMS) showed a methoxyl singlet (229 c.p.s.), two different aromatic groups (centered at 442 c.p.s.), and a quartet (267, 283, 295, and 310 c.p.s.) due to a benzyl methylene group on an asymmetric center confirming the structure of 3-phenyl-5-benzyl-5-carbomethoxyhydantoin.

Sodium Salt.—The above experiment was repeated except that 0.05 mole of sodium methoxide was substituted for the magnesium methoxide. Examination of the crude product did not show the benzyl quartet and several crystallization attempts met with failure. Refluxing the crude product with hydrochloric acid gave a 77% yield of 3-phenyl-5-benzylhydantoin.

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(29) The solid precipitate is extremely hygroscopic; therefore the addition of the methanol must be completed as rapidly as possible without excessive heating. The addition of solid carbon dioxide has been found advantageous in controlling the temperature.