Preparation and Hypoglycemic Activity of Some 3,5-Disubstituted Hydantoins

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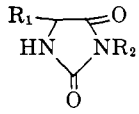
Some new 3,5-disubstituted hydantoins were prepared for testing as hypoglycemic agents. In addition, some L-5-[4(or 5)imidazolylmethyl]hydantoins and L-5-[4(or 5)imidazolylmethyl]thiohydantoins, prepared by reaction of L-histidine methyl ester with various isocyanates, are described and their physical and pharmacological properties discussed. An explanation is offered for the observed increased acidity of these imidazoles over that of other alkylimidazoles. Four new isocyanates were prepared and characterized in the course of this work. Although a modest level of hypoglycemic activity was observed in the rat by the oral route, no activity was found on administration to guinea pigs or dogs.

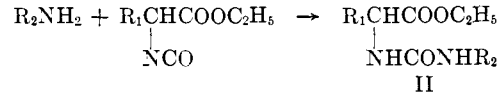
Certain 5,5-disubstituted[1,2] and 3-substituted hydantoins[3,4] are reported to possess a variety of pharmacological activities. Of special interest was the reported[3] hypoglycemic activity found for simple 3-substituted hydantoins. This report prompted the preparation of further simple derivatives of 3,5-disubstituted hydantoins as well as a series of 3-substituted-5-[4(or 5)-imidazolylmethyl]hydantoins.



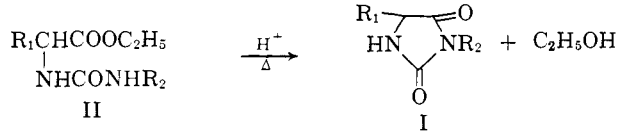
Synthetic procedures differed in those cases where R_1 = alkyl or aralkyl from those where R_1 = 4(or 5)-imidazolylmethyl and will therefore be discussed separately.

(A) 3-Alkyl 5-Substituted Hydantoins.—Reaction of an α-isocyanato ester with an amine to give a hydantoate ester (II) which is then cyclized in acid, offered the simplest, most flexible of the many reported routes[4] to hydantoins. A previously known[5] technique for preparing the required α-isocyanato esters from α-amino esters and phosgene served very well. In two cases optically pure amino esters (L-phenylalanine ethyl ester and L-leucine ethyl ester) were employed as starting materials, while in another series an optically inactive ester was used (DL-alanine ethyl ester) (Table VI, Experimental section).

α-Isocyanato esters reacted with amines in ether solution in most cases in near quantitative yields to give analytically pure hydantoate esters (II) (see Table I).



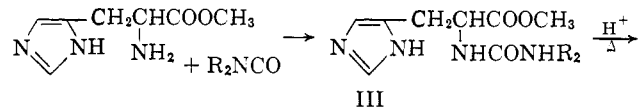
Hydantoins (I) were prepared by cyclization of the hydantoates II in aqueous acid at steam bath temperatures.



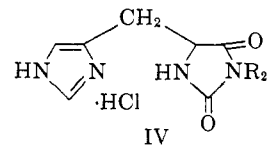
Yields were usually near quantitative and first crops analytically pure. Table II summarizes the data on these 3-substituted 5-alkylhydantoins.

Some compounds of type I were optically active (footnotes to Table II) suggesting that the series of reactions from optically active amino ester to the hydantoins I probably had little effect on the asymmetric carbon atom.

(B) L-5-[4(or 5)Imidazolylmethyl] 3-Substituted Hydantoin Hydrochlorides (IV).—Preparation of L-5-[4(or 5)imidazolylmethyl] 3-substituted hydantoins by the general procedure described before was thought to be impractical, since the required α-isocyanato ester from histidine ethyl ester would not be expected to be stable. Instead, reaction of a series of isocyanates with L-histidine methyl ester was employed.



III



IV

For this sequence, L-histidine methyl ester was prepared from its hydrochloride at low temperature and stored in the freezer for use without further purification. Reactions of this amino ester with a series of isocyanates in chloroform solution gave methyl L-2-[4(or 5)imidazolylmethyl] 5-substituted hydantoates (III) in good yields (Table III). Four new isocyanates (p-trifluoromethylphenyl, hexadecyl, 2,4-dimethoxyphenyl, and n-octyl) prepared and characterized in the course of this work are described in the Experimental section.

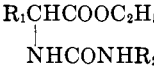
In one experiment designed to prepare methyl L-2-[4(or 5)-imidazolylmethyl]-5-(p-methoxyphenyl)-hydantoate (III, R_2 = p-$CH_3OC_6H_4$), spontaneous cyclization to L-3-(p-methoxyphenyl)-5-[4(or 5)-imidazolylmethyl]-hydantoin occurred during attempted recrystallization of the hydantoate from boiling ethanol–water (see Experimental). Apparently, activation (*i.e.*, increased nucleophilicity) of the 5-nitrogen atom by the p-methoxyphenyl substituent was sufficient to cause cyclization in the absence of acid.

Cyclization of hydantoates (III) by heating in 6 N hydrochloric acid yielded the desired hydantoin hydro-

(1) A. Frost, *J. Mental Sci.*, **85**, 976 (1939).
(2) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 262.
(3) A. Roy, S. Zaidi, and S. Popli, *J. Sci. Ind. Res.* (India), **19** (3), 75 (1960).
(4) See ref. 2, p. 256.
(5) S. Goldschmidt and M. Wick, *Ann.*, **575**, 217 (1952).

TABLE I

ETHYL 2,5-DISUBSTITUTED HYDANTOATES

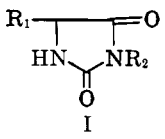


II

R_1	R_2	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	p-ClC_6H_4	81	134–135	$C_{12}H_{15}ClN_2O_3$	53.24	53.18	5.56	5.65	10.35	10.32
CH_3	C_6H_5	86	80.5–81.5	$C_{12}H_{16}N_2O_3$	61.00	61.13	6.83	6.82	11.86	11.88
CH_3	p-$CH_3C_6H_4$	89	125–126.5	$C_{13}H_{18}N_2O_3$	62.38	62.40	7.25	7.27	11.50	11.28
CH_3	$CH_3(CH_2)_7$	100	38.5–40.5	$C_{14}H_{28}N_2O_3$	61.73	62.09	10.37	10.25	10.65	10.75
$(CH_3)_2CHCH_2$	p-ClC_6H_4	91	93–95	$C_{15}H_{21}ClN_2O_3$	57.59	57.67	6.77	6.68	8.96	8.62
$(CH_3)_2CHCH_2$	3,4-$(CH_3O)_2C_6H_3$	93	77–79	$C_{17}H_{26}N_2O_5$	60.33	60.12	7.75	7.58	8.58	8.67
$(CH_3)_2CHCH_2$	p-$CH_3C_6H_4$	98	85–87	$C_{16}H_{24}N_2O_3$	65.72	65.71	8.27	7.97	9.58	10.00
$C_6H_5CH_2$	p-ClC_6H_4	90	144.5–145.5	$C_{18}H_{19}ClN_2O_3$	62.33	62.63	5.52	5.52	8.08	8.08
$C_6H_5CH_2$	3,4-$(CH_3O)_2C_6H_3$	88	111–113	$C_{20}H_{24}N_2O_5$	64.50	64.36	6.50	6.49	7.52	7.47
$C_6H_5CH_2$	p-$CH_3C_6H_4$	94	120–120.5	$C_{17}H_{22}N_2O_3$	69.91	69.79	6.80	6.78	8.58	8.56
$C_6H_5CH_2$	$CH_3(CH_2)_3$	95	96–98	$C_{16}H_{24}N_2O_3$	65.72	65.99	8.27	8.39	9.58	9.98

TABLE II

3,5-DISUBSTITUTED HYDANTOINS



I

R_1	R_2	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[a]	p-ClC_6H_4	96	169.5–170.5	$C_{10}H_9ClN_2O_2$	53.46	53.60	4.04	3.99	12.47	12.42
CH_3[a]	C_6H_5	76	170.5–171.5	$C_{10}H_{10}N_2O_2$	63.14	63.15	5.35	5.19	14.73	15.00
CH_3[a]	p-$CH_3C_6H_4$	86	165.5–166.5	$C_{11}H_{12}N_2O_2$	64.69	64.50	5.92	6.00	13.72	14.08
CH_3[a]	$CH_3(CH_2)_7$	96	72.5–73.5	$C_{12}H_{22}N_2O_2$	63.68	63.57	9.80	9.43	12.39	12.78
$(CH_3)_2CHCH_2$	p-ClC_6H_4[b]	97	189–191	$C_{13}H_{15}ClN_2O_2$	58.53	58.61	5.67	5.70	10.51	10.63
$(CH_3)_2CHCH_2$	3,4-$(CH_3O)_2C_6H_3$	97	178.5–181.5	$C_{15}H_{20}N_2O_4$	61.63	61.89	6.90	6.95	9.59	9.79
$(CH_3)_2CHCH_2$	p-$CH_3C_6H_4$	98	137.5–138.5	$C_{14}H_{18}N_2O_2$	68.27	68.51	7.37	7.29	11.38	11.45
$(CH_3)_2CHCH_2$	$CH_3(CH_2)_7$	80	66.5–67.5	$C_{15}H_{28}N_2O_2$	67.12	67.05	10.51	10.47	10.44	10.68
$C_6H_5CH_2$	p-ClC_6H_4	99	175.5–179.5	$C_{16}H_{13}ClN_2O_2$	63.90	63.66	4.36	4.41	9.32	9.31
$C_6H_5CH_2$	3,4-$(CH_3O)_2C_6H_3$	89	144.5–145.5	$C_{18}H_{18}N_2O_4$	66.24	65.89	5.56	5.41	8.59	8.65
$C_6H_5CH_2$	p-$CH_3C_6H_4$	99	119–121	$C_{17}H_{16}N_2O_2$	72.83	72.60	5.75	5.68	10.00	10.13
$C_6H_5CH_2$	$CH_3(CH_2)_3$[c]	99	137.5–139.5	$C_{14}H_{18}N_2O_2$	68.27	68.66	7.37	7.40	11.37	11.43

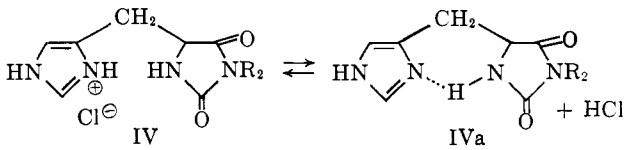
[a] Used DL-alanine ethyl ester hydrochloride as starting material for this series. [b] $[\alpha]^{25}D$ −44.1° (c 1.0, ethanol). [c] $[\alpha]^{23}D$ −64.3° (c 1.0, ethanol).

chlorides (IV) in good to excellent yields (Table IV). Infrared spectra of all hydantoins of type IV exhibited strong carbonyl absorption at or near 5.65 and 5.85 μ, supporting[6] the cyclized structure IV.

Four attempted cyclizations of imidazolylmethyl hydantoates failed to give isolable products. These included III: R_2 = 2-chlorophenyl; R_2 = 2,5-dichlorophenyl; R_2 = 2,4-dimethoxyphenyl; and R_2 = carbethoxymethyl. In the first two cases, steric hindrance of the 5-nitrogen atom by the 2-chloro atom probably prevents cyclization; starting material could always be detected (papergram) in the complex mixtures. Where R_2 = 2,4-dimethoxyphenyl, again the 2-substituent was probably responsible for incomplete cyclization. After 3 hr. reflux in 6 N hydrochloric acid, infrared spectra suggested the presence of the desired hydantoin but this could not be separated from impurities. In the last case, where R_2 = carbethoxymethyl, two cyclization paths are possible for the hydantoate since two ester functions are available for reaction with either the (a) N-5 or (b) N-3 atom. Indeed, papergrams indicated the presence of two compounds, neither of which was starting material; however, no further attempts were made to separate and characterize the mixture.

In three cases where optical rotation was determined, the L-5-[4(or 5)imidazolylmethyl]hydantoins were levorotatory [IV: R_2 = p-ClC_6H_4, $[\alpha]D^{25}$ −55.8° (c 0.7, ethanol); R_2 = $CH_3CH_2CH_2$, $[\alpha]D^{25}$ −44.0° (c 1.0, ethanol); R_2 = C_6H_5, $[\alpha]D^{25}$ −89.1° (c 1.0, ethanol)] suggesting that the series of reactions from L-histidine methyl ester to IV probably had little effect on the asymmetric carbon atom.

Titrations with sodium hydroxide in 1:1 dioxane–water of two compounds of type IV revealed an increased acidity for these compounds (IV: R_2 = $CH_3(CH_2)_3$, pK_a = 5.1, and R_2 = p-ClC_6H_4, pK_a = 5.0) over simple alkylimidazole hydrochlorides [*e.g.*, (4 or 5)-methylimidazole hydrochloride has pK_a 7.5]. One possible explanation for this enhanced acidity may be the favorable steric arrangement of the free base of IV (IVa) which allows strong hydrogen bonding between the imidazole and hydantoin rings.

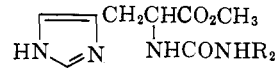


IV IVa

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd. Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 221.

TABLE III

L-METHYL 2-[4(or 5)IMIDAZOLYLMETHYL] 5-SUBSTITUTED HYDANTOATES

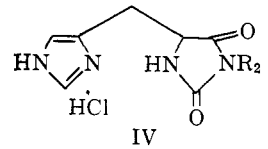


III

R_2	Yield, %	M.p., °C.	Recrystn. solvent	Empirical formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
$CH_3(CH_2)_3$	54	161.5–162.5	$CHCl_3$	$C_{12}H_{20}N_4O_3$	53.71	53.56	7.51	7.25	20.88	20.79
p-ClC_6H_4	90	156.5–157.5	$CHCl_3$–Et_2O	$C_{14}H_{15}ClN_4O_3$	52.10	52.31	4.68	5.02	17.36	16.99
$CH_3(CH_2)_2$	95	151.5–152.5		$C_{11}H_{18}N_4O_3$	51.96	52.00	7.13	7.16	22.08	22.26
C_6H_5	99	138.5–139.5	EtOH	$C_{14}H_{16}N_4O_3$	58.32	58.38	5.59	5.38	19.43	19.41
p-$CH_3C_6H_4$	85	144.5–146.5	EtOH	$C_{15}H_{18}N_4O_3$	59.59	59.58	6.00	6.26	18.53	18.86
2,5-$Cl_2C_6H_3$	83	167.5–169.5		$C_{14}H_{14}Cl_2N_4O_3$	47.07	46.98	3.95	3.86	15.69	15.44
o-ClC_6H_4	3	152.5–153.5	$CHCl_3$–hexane	$C_{14}H_{15}ClN_4O_3$	52.10	52.07	4.68	4.68	17.36	17.30
p-BrC_6H_4	91	165.5–166.5	$CHCl_3$–hexane	$C_{14}H_{15}BrN_4O_3$	45.79	45.81	4.12	4.10	15.26	15.47
C_6H_{11}	87	191–193	EtOH–hexane	$C_{14}H_{22}N_4O_3$	57.12	56.82	7.54	7.34	19.04	19.09
$CH_3(CH_2)_7$	49	120–122	Et_2O–EtOH	$C_{16}H_{28}N_4O_3$	59.23	59.36	8.70	8.64	17.27	17.66
2,4-$(CH_3O)_2C_6H_3$	81	164.5–165.5	EtOH–hexane	$C_{16}H_{20}N_4O_5$	55.17	55.19	5.77	6.02	16.09	16.22
$CH_3(CH_2)_{15}$	87	116–119	EtOH	$C_{24}H_{44}N_4O_3$	66.02	66.17	10.16	10.31		
$-CH_2COOC_2H_5$	73	83–87	Me_2CO–Et_2O	$C_{12}H_{18}N_4O_5$	48.32	48.55	6.08	6.23	18.78	19.10
p-$CF_3C_6H_4$	83	155.5–157.5	EtOH–H_2O	$C_{15}H_{15}F_3N_4O_3$	50.56	50.82	4.24	4.00	15.73	15.81

TABLE IV

L-5-[4(or 5)IMIDAZOLYLMETHYL] 3-SUBSTITUTED HYDANTOIN HYDROCHLORIDES

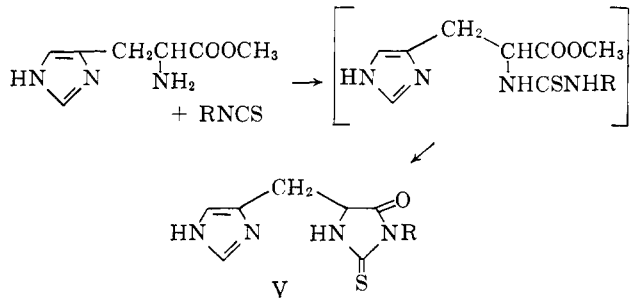


IV

R_2	Yield, %	M.p., °C.	Recrystn. solvent	Empirical formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
$CH_3(CH_2)_3$	96	221–222	EtOH–Et_2O	$C_{11}H_{18}ClN_4O_2$	48.44	48.17	5.91	6.18	20.54	20.55
p-ClC_6H_4	93	285–288	EtOH–Et_2O	$C_{13}H_{14}Cl_2N_4O_2$	47.72	47.56	3.39	3.73	17.13	17.13
$CH_3(CH_2)_2$	84	214–217	EtOH–Et_2O	$C_{10}H_{15}ClN_4O_2$	46.72	46.51	5.45	5.82	21.66	21.35
C_6H_5	84	262.5–264.5	EtOH–Et_2O	$C_{13}H_{13}ClN_4O_2$	53.34	53.27	4.46	4.30	19.14	19.33
p-$CH_3C_6H_4$	74	277.5–278.5	EtOH–Et_2O	$C_{14}H_{15}ClN_4O_2$	54.81	54.56	4.60	4.78	18.27	18.47
p-BrC_6H_4	80	292–294	EtOH	$C_{13}H_{12}BrN_4O_2$	42.01	42.26	2.98	3.09	15.08	15.37
C_6H_{11}	87	271.5–273.5	EtOH–Et_2O	$C_{13}H_{19}ClN_4O_2$	52.26	52.06	6.07	6.35	18.75	18.96
p-$CH_3OC_6H_4$	70	269.5–271.5	EtOH	$C_{14}H_{15}ClN_4O_3$	52.10	52.08	4.68	4.80	17.36	17.31
$CH_3(CH_2)_7$	84	236–238	EtOH	$C_{15}H_{23}ClN_4O_2$	54.78	54.65	7.66	7.44	17.04	17.01
$CH_3(CH_2)_{15}$	90	221–226	EtOH	$C_{23}H_{41}ClN_4O_2$	62.63	63.05	9.37	9.32	12.70	12.58
p-$CF_3C_6H_4$	52	287–289	EtOH	$C_{14}H_{12}ClF_3N_4O_2$	46.61	46.31	3.33	3.33	15.53	15.34

The stabilized, hydrogen-bonded form IVa displaces the equilibrium to the right thus increasing the apparent acidity of IV over that to be expected of an alkylimidazole hydrochloride.

(C) L-5-[4(or 5)Imidazolylmethyl] 3-Substituted-2-thiohydantoins (V).—By a procedure similar to that used in preparing IV, L-histidine methyl ester was treated with thioisocyanates in an attempt to prepare thiohydantoates (and thence thiohydantoins by acid cyclization). However, only spontaneous cyclization to the thiohydantoins (V) was observed. Activation of the 5-nitrogen in the thiohydantoate by the neighboring sulfur atom evidently facilitates this cyclization.



V

Analytical data as well as infrared spectra (Table V) support the thiohydantoin structure V since strong absorptions corresponding to the 4-carbonyl are seen at 5.7–5.8 μ (reported[6] 5.6–5.8 μ) and to the 2-thiocarbonyl of the thiourea-like portion of the ring at 8.2–8.8 μ (reported[6] 7.2–8.9 μ).

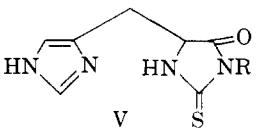
Pharmacological Evaluation.—All of the hydantoins described above were administered orally to rats at 100 mg./kg. and blood glucose levels measured at 2 hr. intervals. Ten control rats were run concurrently with each compound. Blood glucose was determined by a microadaptation of the method of Hoffman[7] using an Auto-Analyzer.

None of the 3,5-disubstituted hydantoins listed in Table II decreased blood glucose levels to any significant degree in the rat. Certain 5-[4(or 5)-imidazolylmethyl]hydantoins, however, showed modest hypoglycemic activity in the rat (Table VII). These blood sugar level reductions could be reproduced in successive experiments. Compound IV, R = 4-chlorophenyl, was also administered to guinea pigs (subcutaneously at 40 mg./kg. and orally at 100 mg./kg.) and dogs (orally.

(7) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

TABLE V

L-5-[4(OR 5)IMIDAZOLYLMETHYL]3-SUBSTITUTED-2-THIOHYDANTOINS



V

R	Infrared absorption, μ	Yield, %	M.p., °C.	Recrystn. solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$CH_3(CH_2)_3$	5.74, 8.85	56	203–205	EtOH–Et_2O	$C_{11}H_{16}N_4OS$	52.35	52.35	6.40	6.34	22.20	22.24
$CH_3(CH_2)_4$	5.72, 8.82	61	142.5–143.5	EtOH–H_2O	$C_{11}H_{22}N_4OS$	57.11	57.12	7.53	7.41	19.03	19.00
C_6H_5	5.70, 8.23	71	203–205	$CHCl_3$–Et_2O	$C_{13}H_{12}N_4OS$	57.33	56.97	4.44	4.51	20.57	20.22
CH_2=$CHCH_2$	5.80, 8.45	59	151.5–152.5	$CHCl_3$–hexane	$C_9H_{11}N_4OS$	51.04	50.61	4.71	5.06	23.81	23.83

TABLE VI

ETHYL α-ISOCYANATO ESTERS

$R_1CHCOOC_2H_5$

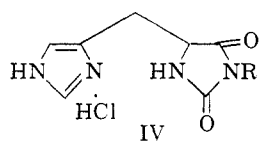
NCO

R_1	Optical isomer	B.p., °C. Reported	B.p., °C. Found	Yield, %
CH_3	DL	69 (11 mm.)	76–77 (24 mm.)	75
$(CH_3)_2CHCH_2$	L	104 (15 mm.)[a]	111 (24 mm.)	85
$C_6H_5CH_2$	L	152 (10 mm.)[a]	106–107 (0.1 mm.)	94

[a] Values for the DL-isomers, ref. 5.

TABLE VII

EFFECT ON RAT BLOOD SUGAR OF L-[4(OR 5)IMIDAZOLYLMETHYL]3-SUBSTITUTED HYDANTOINS[a]



IV

R	T_2[b]	T_4	T_6
4-ClC_6H_4	1[c]	2	2
	2	2	2
$CH_3(CH_2)_3$	1	2	1
	1	1	
C_6H_6	2	1	
4-$CH_3C_6H_4$	1	0	
$CH_3(CH_2)_2$	2	1	
4-$(CH_3O)C_6H_4$	2	3	1
	2	1	0
C_6H_{11}	2	1	
$CH_3(CH_2)_7$	0	[d]	
4-BrC_6H_4	2	2	2
4-$CF_3C_6H_4$	1	1	0
$CH_3(CH_2)_{15}$	1	1	1
Chlorpropamide[e]	4	4	

[a] 10 rats per value; 100 mg./kg., oral route. [b] T_2, T_4, and T_6 represent 2, 4, and 6 hr. post administration. [c] Per cent fall in blood sugar from initial values, scored as follows: 0 = 0–5% fall, 1 = 6–15%, 2 = 16–25%, 3 = 26–35%, 4 = 36–45% [d] A modest rise in blood sugar from initial values. [e] Diabinese.®

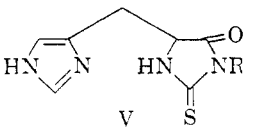
25 mg./kg.) but no significant effect on blood sugar could be observed. Values for a clinically useful hypoglycemic agent, chlorpropamide, are included for reference in Table VII.

Finally, Table VIII presents data on some thiohydantoins prepared as part of this same synthetic program. Again, a compound such as a V, R = $CH_3(CH_2)_6$, was found to be entirely inactive in the guinea pig despite demonstrable modest activity in the rat.

From these data it may be seen that most derivatives of hydantoin studied in the present investigation offer no advantage over the weak activity reported for

TABLE VIII

EFFECT ON RAT BLOOD SUGAR OF 3-SUBSTITUTED-5-[4(OR 5)IMIDAZOLYLMETHYL]THIOHYDANTOINS



V

R	T_2[a]	T_4	T_6
$CH_3(CH_2)_6$	2[b]	3	1
$CH_3(CH_2)_3$	1	1	0
C_6H_5	2	[c]	
CH_2=$CHCH_2$	2	1	

[a] See Table VII, footnotes *a*, *b*, *c*. [b] A rise in blood sugar from initial values.

simple 3-substituted hydantoins[3] and that this moderate level of activity exhibits a species specificity.

Experimental[8]

Ethyl α-Isocyanato Esters (Table VI).—At reflux, a solution of 0.1 mole of appropriate amino ester hydrochloride in 100 ml. dry toluene was stirred vigorously, and a rapid stream of phosgene was introduced over the solution for 2 hr. Removal of the toluene under reduced pressure yielded an oil which was vacuum distilled (Table VI). All of these isocyanates are lachrymators.

Ethyl 2,5-Disubstituted Hydantoates (II).—In an erlenmeyer flask equipped with a dropping funnel, magnetic stirring bar, and protected by a drying tube was dissolved 0.015 mole of an ethyl α-isocyanato ester in 50 ml. of dry ether. To this solution was slowly added a solution of 0.015 mole of amine in 100 ml. ether. After stirring for 0.5 hr., the solvent was evaporated to half volume and cooled. Filtration of the solid and drying under vacuum usually gave analytically pure product (Table I).

Infrared absorptions due to C=O functions in II are found at or near 5.71 and 6.05 μ in all cases.

3-Substituted-5-Alkyl Hydantoins (I). General Procedure.—A solution (or in a very few cases, a suspension) of 0.015 mole of an ethyl 2,5-disubstituted hydantoate (II) in 15 ml. of 6 *N* hydrochloric acid was warmed on the steam bath for 1 hr. Acetone was sometimes added where required to solubilize the hydantoate. If cooling to 0° did not precipitate the product, evaporation of all solvent followed by an ethanol–ether trituration was effective. Almost all products were obtained analytically pure from this procedure (Table II).

In two cases optically pure amino esters (L-phenylalanine ethyl ester and L-leucine ethyl ester) were employed as starting materials, while in another series an optically inactive ester was used (DL-alanine ethyl ester) (Table VI, Experimental).

Infrared absorptions due to carbonyl functions in I are found at or near 5.65 and 5.85 μ in all cases.

L-Histidine Methyl Ester.—This material was prepared from L-histidine methyl ester dihydrochloride by the method of Merri-

(8) Melting points were taken in open capillary tubes in a Thomas-Hoover Uni-Melt apparatus and are corrected. Infrared spectra were measured in potassium bromide pellets. Optical rotations were measured in a 1-dm. tube.

field and Woolley.[9] The liquid product slowly crystallized in the cold (91% yield) and was used without purification in the next step. The solid appears to be unchanged after 3 months in the freezer.

Methyl L-2-[4(or 5)-Imidazolylmethyl] 5-Substituted Hydantoates (III).—A solution of 0.02 mole of histidine methyl ester (free base) in 25 ml. of chloroform (predried over calcium chloride) was prepared at 0° in a flask protected by a drying tube. From a dropping funnel was slowly introduced 0.02 mole of an isocyanate. After stirring at room temperature for 0.5 hr. a solid usually precipitated. In the absence of a precipitate, evaporation of solvent under vacuum left a solid residue. Filtration and recrystallization gave analytically pure material (Table III).

Attempted Synthesis of Methyl L-2-[4(or 5)Imidazolylmethyl]-5-(*p*-methoxyphenyl) Hydantoate.—Reaction of *p*-methoxyphenylisocyanate with histidine methyl ester free base as described above yielded 3.9 g. of solid, m.p. 123–127°. Several attempts to prepare an analytical sample of this material by recrystallizing from ethanol–water gradually raised the m.p. to 213–214°. This material analyzed not for the hydantoate but **for L-5-[4(or 5)imidazolylmethyl]-3-(*p*-methoxyphenyl)hydantoin.**

Anal. Calcd. $C_{14}H_{14}N_4O_3$: C, 58.66; H, 4.93; N, 19.57. Found: C, 58.65; H, 4.93; N, 19.39.

A hydrochloride salt was prepared in methanol solution, m.p. 269.5–271.5° (Table IV).

Isocyanates.—Most of the required isocyanates are commercially available and were used as received. Those prepared for the first time are:

(a) ***n*-Octylisocyanate.**—Phosgene was rapidly passed over a solution of 19.49 g. (0.118 mole) of *n*-octylamine hydrochloride in 200 ml. of refluxing dry toluene. After 2 hr., removal of solvent followed by vacuum distillation yielded a colorless liquid, 13.7 g. (75%), b.p. 100° (26 mm.), n_D^{25} 1.4292.

A derivative was prepared by combining some *n*-octylisocyanate with an equimolar amount of *p*-chloroaniline in dry chloroform solution for 0.5 hr. to yield a white solid, **1-(*p*-chlorophenyl)-3-(*n*-octyl)urea;** m.p. 130–131° after recrystallization from hot chloroform.

Anal. Calcd. for $C_{15}H_{23}ClN_2O$: C, 63.70; H, 8.20; N, 9.91. Found: C, 63.39; H, 8.23; N, 9.87.

(b) **Hexadecylisocyanate.**—Phosgene was passed over a solution of 40 g. (0.144 mole) of hexadecylamine hydrochloride in 500 ml. of refluxing dry toluene for 8 hr. Vacuum distillation yielded a colorless oil, 30.9 g. (80%), b.p. 180–183° (8 mm.), n_D^{25} 1.4479.

Reaction of some hexadecylisocyanate with an equimolar amount of *p*-chloroaniline in dry chloroform solution for 0.5 hr. followed by cooling to 0° gave a white solid derivative, **1-(*p*-chlorophenyl)-2-hexadecylurea;** m.p. 123–124° after recrystallization from hot chloroform.

Anal. Calcd. for $C_{23}H_{39}ClN_2O$: C, 69.94; H, 9.95; N, 7.35. Found: C, 70.11; H, 10.01; N, 7.40.

(c) ***p*-Trifluoromethylphenylisocyanate.**—A rapid stream of phosgene was passed into a mixture of 26.4 g. (0.134 mole) of *p*-aminobenzotrifluoride hydrochloride (m.p. 217–220°) in 500 ml. of dry toluene for 3 hr. After 1.5 hr. all of the solid was in solution. Distillation of the toluene yielded a gelatinous material which on vacuum distillation yielded a colorless oil, 10.6 g. (42%), b.p. 53° (8 mm.), n_D^{25} 1.4695. Some unreacted starting amine salt was recovered from the undistillable pot residue.

Reaction of some *p*-trifluoromethylphenylisocyanate with an equimolar amount of *p*-chloroaniline in dry chloroform gave **1-(*p*-chlorophenyl)-3-(*p*-trifluoromethylphenyl)urea,** m.p. 257.5–258.5°.

Anal. Calcd. for $C_{14}H_{10}ClF_3N_2O$: C. 53.43; H, 3.20; N, 8.90. Found: C, 53.09; H, 3.22; N, 8.95.

(d) **2,4-Dimethoxyphenylisocyanate.**—Preparation of this isocyanate required four steps from 2,4-dimethoxybenzoic acid (Eastman Organic). The latter acid (50 g. (0.27 mole)) was converted to its methyl ester using methanol (300 ml.) and concentrated hydrochloric acid (3 ml.) in refluxing chloroform (250 ml.). After 24 hr., all solvent was evaporated, the crude ester dissolved in chloroform, washed successively with water, 5% sodium bicarbonate, and water, and the chloroform solution dried over sodium sulfate. Evaporation of solvent gave a pale brown oil (39 g.) which was immediately combined with 19 g. of 95% hydrazine and heated on the steam bath for 5 hr. Cooling produced a solid which was filtered and washed with some cold methanol yielding 29.3 g. (81%) of **2,4-dimethoxybenzhydrazide,** m.p. 110–113°. Derivatization was accomplished by refluxing some of the hydrazide in acetone solution followed by cooling to 0° yielding **N^1-(2,4-dimethoxybenzoyl)-N^2-isopropylidenehydrazine,** m.p. 188–190°.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.86. Found: C, 61.22; H, 6.73; N, 11.71.

Slow addition of a solution of 10.59 g. (0.15 mole) sodium nitrite in 60 ml. of water to a cold solution of 29 g. (0.148 mole) of 2,4-dimethoxybenzhydrazide in 750 ml. of *N* hydrochloric acid gave an immediate white precipitate. Heavy solid formation forced the addition of another 250 ml. of *N* hydrochloric acid. After stirring for 0.5 hr., filtration and drying yielded a white solid, **2,4-dimethoxybenzoylazide,** 26.6 g. (87%), m.p. 70.5–71.5° dec. (gas evolution). An analytical sample could not be prepared from this unstable material.

The crude 2,4-dimethoxybenzoylazide was dissolved in 150 ml. of dry benzene in a system protected from moisture. Gradually raising the temperature to reflux caused vigorous nitrogen evolution. After 0.5 hr. of reflux, solvent was distilled at atmospheric pressure and the residue distilled under vacuum to give **2,4-dimethoxyphenylisocyanate,** a colorless liquid, 15.7 g. (71%), b.p. 140° (11 mm.), which solidified in the cooled receiver (m.p. 30–31°).

A derivative was prepared by reacting 2,4-dimethoxyphenylisocyanate with an equimolar amount of *p*-chloroaniline in dry chloroform solution. Cooling to 0° and filtering yielded a white solid, **1-(*p*-chlorophenyl)-3-(2,4-dimethoxyphenyl)urea,** m.p. 187–189°.

Anal. Calcd. for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.49; H, 4.85; N, 9.17.

L-5-[4(or 5)Imidazolylmethyl] 3-Substituted Hydantoin Hydrochlorides (IV).—A solution of 12.59 g. (0.039 mole) of methyl L-α-imidazolylmethyl-5-(*p*-chlorophenyl)hydrantoate, 75 ml. of acetone, and 75 ml. of 6 *N* hydrochloric acid was heated on the steam bath for 1 hr. Addition of 75 ml. of water and cooling to 0° yielded, in two crops, a white solid, L-5-imidazolylmethyl-3-(*p*-chlorophenyl)hydantoin hydrochloride, 10.5 g. (83%), m.p. 293–294°.

In cases where addition of water did not precipitate solid, all solvent was evaporated under reduced pressure and the residual solid recrystallized (see Table IV).

L-5-[4(or 5)Imidazolylmethyl] 3-Substituted 2-Thiohydantoins (V).—A general procedure for the preparation of V from commercially available isothiocyanates is illustrated. To a solution of 4.5 g. (0.027 mole) of L-histidine methyl ester (free base) in 50 ml. of chloroform at 0° was slowly added a solution of 3.1 g. (0.027 mole) of *n*-butylisothiocyanate in 20 ml. of chloroform. After stirring 0.5 hr. at room temperature, evaporation of half of the solvent under reduced pressure yielded a white solid, L-5-[4(or 5)-imidazolylmethyl]-3-(*n*-butyl)-2-thiohydantoin, 4.1 g. (61%), m.p. 203–2 05°.

Table V lists the physical properties of these thiohydantoins.

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(9) R. B. Merrifield and D. W. Woolley, *J. Am. Chem. Soc.*, **78**, 4646 (1956).