[CONTRIBUTION FROM THE ORGANIC RESEARCH DIVISION, U. S. VITAMIN & PHARMACEUTICAL CORPORATION]

Hydantoic Acid Esters and Amides

SEYMOUR L. SHAPIRO, IRA M. ROSE, ERIC ROSKIN, AND LOUIS FREEDMAN

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A series of hydantoic acid amides and δ-substituted hydantoic acid esters and amides has been synthesized and examined for pharmacological effects. Selected compounds afforded good anticonvulsant and antiinflammatory activity.

Many investigations of substituted hydantoins have yielded important pharmacological activity,[1] and other workers[2] have evaluated open chain analogs of such physiologically active ring systems. Herein, such analogs of hydantoin (Table) have been examined for pharmacological activity, particularly as anti-inflammatory agents,[3] anticonvulsants,[1] and antibacterial agents.[4]

The reaction of ethyl hydantoate with primary amines proceeded readily in methanol to give the corresponding amides of hydantoic acid (compounds 46–60), and with α,ω-diamines, the diamides[5,6] were obtained (compounds 61–68). While the reaction was readily effected with substituted alkylamines (compounds 48, 58, 59), it was unsuccessful with secondary amines (*N*-methylbenzylamine), or with amines having substituents on the α-carbon atom (*d*-α-methylphenethylamine, α-phenethylamine, isopropylamine, benzhydrylamine).

Bachmann[7] found water was an acceptable solvent using methylamine, but the sterically hindered α-phenethylamine could not be induced to react in methanol, in methanol under sodium methoxide catalysis, or in water. Instead, the reaction with this amine, as well as with *N*-methylbenzylamine, yielded hydantoin.

With the amines successfully employed, ethyl hydantoate is converted and does not cyclize to hydantoin. Alternatively, with steric hindrance in the amine,[8,9] cyclization to hydantoin occurs. It was of interest that the benzylamine failed to give the corresponding amide when acetonitrile was substituted for methanol as the solvent. Aromatic amines such as aniline,[10] did not react, nor did sodium *p*-aminobenzoate.[11]

The reactions of amines with carbethoxymethyl isocyanate[12,13] gave the corresponding ethyl α-substituted hydantoates (compounds 1–17). These were readily isolable crystalline solids except in the instance of the esters from the *N*-methyldialkylaminoalkylamines which were obtained as liquids. In the reaction with dimethylaminopropylamine, a waxy product was obtained which, in the course of purification by distillation, cyclized to 3-dimethylaminopropylhydantoin (I).

The ethyl δ-substituted hydantoates were converted by treatment with ammonia to the hydantoamides (compounds 18–33), and with benzylamine to the corresponding *N*-benzyl δ-substituted hydantoamides (compounds 34–45).

Compound 9 which has an aliphatic and aromatic carbethoxy group gave but a single product with each amine (compounds 26 and 40) with attack presumably involving displacement at the more reactive aliphatic ester site.[14]

(1) (a) J. J. Spurlock, *J. Am. Chem. Soc.*, **75**, 1115 (1953); (b) P. C. Teague, A. R. Ballentine, and G. L. Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953); (c) E. Ware, *Chem. Revs.*, **46**, 403 (1953); (d) R. E. Nitz, W. Persch, and A. Schmidt, *Arzneimittel-Forsch.*, **5**, 357 (1955); (e) C. L. Mitchell, H. H. Keasling, and E. G. Gross, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 122 (1959); (f) W. Perkow, *Arzneimittel-Forsch.*, **10**, 284 (1960); (g) B. Lustig and W. Persch, *Arzneimittel-Forsch.*, **4**, 733 (1954); (h) G. Stille and I. Brunckow, *Arzneimittel-Forsch.*, **4**, 723 (1954).

(2) (a) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943); (b) S. D. Upham and O. C. Dermer, *J. Org. Chem.*, **22**, 799 (1957); (c) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

(3) (a) L. A. Cohen and E. M. Fry, *J. Am. Chem. Soc.*, **78**, 5863 (1956); (b) B. K. Forscher and H. C. Cecil, *J. Dental Research*, **36**, 927 (1957).

(4) (a) R. L. Dennis, W. J. Plant, C. G. Skinner, G. L. Sutherland, and W. Shive, *J. Am. Chem. Soc.*, **77**, 2362 (1955); (b) E. Froelich, A. Fruehan, M. Jackman, F. K. Kirchner, E. J. Alexander, and S. Archer, *J. Am. Chem. Soc.*, **76**, 3099 (1954).

(5) C. L. Agre, C. Dinga, and R. Pflaum, *J. Org. Chem.*, **21**, 561 (1956).

(6) O. Stoutland, L. Heglen, and C. L. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(7) W. E. Bachmann and C. E. Maxwell III, *J. Am. Chem. Soc.*, **72**, 2880 (1950).

(8) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).

(9) For similar dependence of steric factors on reactivity in a related series, see E. J. Tarlton, S. Gelblum, M. A. Mosley, and A. F. McKay, *J. Org. Chem.*, **23**, 1973 (1958).

(10) In ref. 7, reaction of aniline with ethyl δ-nitrohydantoate gave ethyl δ-phenylhydantoate, m.p. 109.5–110° (see Table I, compound 8) with no attack at the ester group.

(11) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6322 (1959).

(12) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(13) D. A. Smith and C. C. Unruh, *J. Org. Chem.*, **23**, 301 (1958).

(14) (a) R. L. Herbst, Jr., and M. E. Jacox, *J. Am. Chem. Soc.*, **74**, 3004 (1952); (b) C. C. Price and W. J. Belanger, *J. Am. Chem. Soc.*, **76**, 2682 (1954); (c) B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958); (d) H. M. Humphreys and L. P. Hammett, *J. Am. Chem. Soc.*, **78**, 521 (1956).

TABLE I

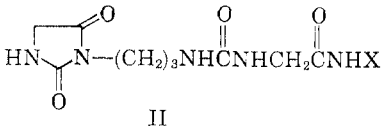
No.	R	M.P.,[b] or B.P., (Mm.)[c]	S[d]	Yield,[e] %	Formula	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					RR_1—N—CO—$NHCH_2COOC_2H_5$[a]						
1[g]	$HOCH_2CH_2$—	74–77	A	83	$C_7H_{14}N_2O_4$	44.2	44.0	7.4	7.1		
2	C_3H_5—[h]	82–83	A	90	$C_8H_{14}N_2O_4$					15.0	15.4
3	i-C_5H_{11}—	77–78	B	78	$C_{10}H_{20}N_2O_3$	55.5	55.8	9.3	9.3	13.0	12.6
4	n-C_7H_{15}—	64–65	A	96	$C_{12}H_{24}N_2O_3$					11.5	11.2
5	[i]	109–114	B	89	$C_{13}H_{22}N_2O_4$	61.4	61.1	8.7	8.8	11.0	10.6
6	$C_6H_5CH_2CHCH_3$—[j]	73–76	B	50	$C_{14}H_{20}N_2O_3$	63.6	63.4	7.6	7.7	10.6	10.5
7	$(C_6H_5)_2CH$—	154–155	C	57	$C_{18}H_{20}N_2O_3$	69.2	69.3	6.5	6.3	9.0	9.5
8[k]	C_6H_5—	111–113	B	74	$C_{11}H_{14}N_2O_3$						
9	p-$C_2H_5OOCC_6H_4$—	139–140	C	81	$C_{14}H_{18}N_2O_5$	57.1	57.1	6.2	6.2		
10	$(CH_3)_2N(CH_2)_2$—[c1]	122–126 (0.10)		76	$C_{10}H_{21}N_3O_3$	51.9	51.8	9.2	9.2	18.2	17.8
11	$(C_2H_5)_2N(CH_2)_2$—[a1]	123 (0.10)		86	$C_{12}H_{25}N_3O_3$	55.6	55.1	9.7	9.9	16.2	16.4
12	$(CH_3)_2N(CH_2)_3$—[a1]	128–130 (0.12)		82	$C_{11}H_{23}N_3O_3$	53.9	53.1	9.5	9.5		
13	[l]	65–66	B	45	$C_{10}H_{19}N_3O_3$	52.4	52.8	8.4	8.4	18.3	18.5
					$C_2H_5OOCCH_2NHCONH$—X—$NHCONHCH_2COOC_2H_5$[m]						
14	—$(CH_2)_3$—	157–159	D	78	$C_{13}H_{24}N_4O_6$	47.0	47.3	7.3	7.4		
15	—$(CH_2)_4$—	169–172	E	85	$C_{16}H_{30}N_4O_6$	48.5	48.5	7.6	7.5	16.2	16.1
16	—$(CH_2)_6$—	170–174	E	91	$C_{16}H_{30}N_4O_6$	51.3	51.7	8.1	8.0	15.0	15.3
17	[n]	207–208	D	79	$C_{14}H_{24}N_4O_6$	48.8	49.3	7.0	7.0	16.3	16.3
					$RR_1NCONHCH_2CONH_2$[a]						
18	$HOCH_2CH_2$—	159–161	E	19	$C_5H_{11}N_3O_3$	37.3	37.8	6.9	6.8	26.1	26.4
19	C_3H_5—[h]	197–198	A	47	$C_6H_{11}N_3O_2$	45.9	46.2	7.1	6.9	26.7	26.4
20	i-C_5H_{11}—	158–161	F	23	$C_8H_{17}N_3O_2$	51.3	51.7	9.2	9.1	22.4	22.6
21	n-C_7H_{15}—	194–195	A	77	$C_{10}H_{21}N_3O_2$	55.8	55.9	9.8	9.5		
22	[t]	118–121	D	47	$C_{11}H_{19}N_3O_2$	58.6	58.8	8.5	8.3	18.7	19.2
23	$C_6H_5CH_2CHCH_3$—[j]	171–173	A	47	$C_{12}H_{17}N_3O_2$	61.3	61.1	7.3	7.5	17.9	17.8
24	$(C_6H_5)_2CH$—	225–229	E	50	$C_{16}H_{17}N_3O_2$	67.8	68.1	6.1	6.2		
25	C_6H_5—	195–197	A	76	$C_9H_{11}N_3O_2$	56.0	56.5	5.7	5.7	21.8	22.1
26	p-$C_2H_5OOCC_6H_4$—	204–205	A	74	$C_{12}H_{15}N_3O_4$	54.3	54.5	5.7	5.8		
27	$(CH_3)_2N(CH_2)_2$—[a1]	97–100	A	94	$C_8H_{18}N_4O_2$	47.5	47.7	9.0	9.2	27.7	28.2
28	$(C_2H_5)_2N(CH_2)_2$—[a1]	84–85	A	83	$C_{10}H_{22}N_4O_2$	52.2	52.2	9.6	10.1	24.3	24.1
29	$(CH_3)_2N(CH_2)_3$—[a1]	95–97	A	97	$C_9H_{20}N_4O_2$	50.0	50.0	9.3	9.2	25.9	25.4
30	[o]	202–204	A	95	$C_7H_{13}N_3O_2$	49.1	49.0	7.7	7.2	24.6	24.4
31	[l]	180–185	A	84	$C_8H_{15}N_4O_2$	48.0	48.2	8.1	7.8	28.0	27.7
					$NH_2COCH_2NHCONH$—X—$NHCONHCH_2CONH_2$[m]						
32	—$(CH_2)_3$—	224–225	F	24	$C_9H_{18}N_6O_4$	39.4	39.4	6.6	7.1	30.6	30.6
33	[n]	228 dec.	F	97	$C_{10}H_{22}N_6O_6$[p]	37.3	38.0	6.9	7.1	26.1	26.7
					$RR_1NCONHCH_2CONHCH_2C_6H_5$[a]						
34	C_3H_5—[h]	186–188	A	38	$C_{13}H_{17}N_3O_2$	63.1	63.0	6.9	7.1	17.0	16.7
35	i-C_5H_{11}—	174–177	C	50	$C_{15}H_{23}N_3O_2$	65.0	65.4	8.4	8.3	15.2	15.4

TABLE I (*Continued*)

No.	R	M.P.,[b] or B.P., (Mm.)[c]	S[d]	Yield,[e] %	Formula	Analyses, %[f] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
36	*n*-C_7H_{15}—	160–162	A	34	$C_{17}H_{27}N_3O_2$					13.8	14.0
37	[t]	178–179	D	47	$C_{18}H_{25}N_3O_2$	68.5	68.4	8.0	7.8	13.3	13.6
38	$(C_6H_5)_2CH$—	225–230	E	42	$C_{12}H_{23}N_3O_2$	74.0	74.6	6.2	6.1	11.3	11.1
39	C_6H_5—	210–211	A	71	$C_{16}H_{17}N_3O_2$	67.8	68.3	6.1	6.5	14.8	15.1
40	*p*-$C_2H_5OOCC_6H_4$—	211–212	G	31	$C_{19}H_{21}N_3O_4$	64.2	64.0	6.0	6.1		
41	$(CH_3)_2N(CH_2)_2$—[a1]	93	H	32	$C_{15}H_{24}N_4O_2$	61.6	61.6	8.3	8.2	19.2	19.5
42	$(CH_3)_2N(CH_2)_3$—	136–137	C	34	$C_{15}H_{24}N_4O_2$	61.6	61.2	8.3	8.2	19.2	19.5
43	[o]	145–150	C	35	$C_{14}H_{19}N_3O_2$					16.1	16.2
44	[l]	180–183	A	51	$C_{15}H_{22}N_4O_2$	62.0	62.4	7.6	7.6	19.3	19.4
45	[q]	197–203	E	58	$C_{24}H_{30}N_6O_4$	61.8	61.2	6.5	6.6	18.0	17.3
					$NH_2CONHCH_2CONHR$						
46[r]	H	198–200	A	79							
47[s]	CH_3—	181–183	E	76							
48	$HOCH_2CH_2$—	133–134	I	63	$C_5H_{11}N_3O_3$	37.3	37.3	6.9	6.6	26.1	26.0
49	C_3H_5—[h]	177–178	I	33	$C_6H_{11}N_3O_3$	45.9	45.9	7.1	7.1	26.7	26.8
50	*i*-C_5H_{11}—	201–202	J	35	$C_8H_{17}N_3O_2$	51.3	51.4	9.2	9.3	22.4	22.3
51	*n*-C_5H_{11}—	183–185	J	57	$C_8H_{17}N_3O_2$	51.3	51.0	9.2	9.1	22.4	22.5
52	*n*-C_7H_{15}—	182–185	J	63	$C_{10}H_{21}N_3O_2$					19.5	19.2
53	[i]	209–211	J	61	$C_{11}H_{19}N_3O_2$	58.6	58.3	8.6	8.1		
54	[l]	175–177	J	22	$C_8H_{11}N_3O_3$	48.7	48.8	5.6	5.7		
55	$C_6H_5CH_2$—	198–200	J	36	$C_{10}H_{13}N_3O_2$	58.0	58.2	6.3	6.7	20.3	20.0
56	*p*-$ClC_6H_4CH_2$—	197–198	F	58	$C_{10}H_{12}ClN_3O_2$	49.7	50.0	5.0	5.4	17.4	17.4
57	$C_6H_5CH_2CH_2$—	175–177	J	49	$C_{11}H_{15}N_3O_2$	59.7	60.0	6.8	6.6	19.0	18.6
58	$(C_2H_5)_2N(CH_2)_2$—	145–147	D	58	$C_9H_{20}N_4O_2$	50.0	50.1	9.3	8.9	25.9	26.3
59	$(CH_3)_2N(CH_2)_3$—	163–167	D	47	$C_8H_{18}N_4O_2$	47.5	47.6	9.0	8.9	27.7	27.4
60	[u]	205–206	D	57	$C_9H_{21}IN_4O_2$	31.4	31.4	6.2	6.0		
					$NH_2CONHCH_2CONH—X—NHCOCH_2NHCONH_2$[m]						
61	—$(CH_2)_2$—	233–234	G	62	$C_8H_{16}N_6O_4$	36.9	36.8	6.2	6.1	32.3	32.4
62	—$(CH_2)_3$—	226–228	G	68	$C_9H_{18}N_6O_4$	39.4	39.3	6.6	6.5		
63	—$(CH_2)_4$—	242–244	G	45	$C_{10}H_{20}N_6O_4$	41.7	41.8	7.0	7.1		
64	—$(CH_2)_5$—	246	G	49	$C_{11}H_{22}N_6O_4$	43.7	43.4	7.3	6.7	27.8	27.9
65	—$(CH_2)_6$	221–222	G	50	$C_{12}H_{24}N_6O_4$	45.6	45.8	7.7	7.7	26.6	26.6
66	—$(CH_2)_7$—	230	G	35	$C_{13}H_{26}N_6O_4$	47.3	47.2	7.9	7.8	25.4	25.3
67	*m*-$CH_2C_6H_4CH_2$—	220–222	G	45	$C_{14}H_{20}N_6O_4$	50.0	49.8	6.0	6.0	25.0	25.0
68	—$(CH_2)_3NCH_3(CH_2)_3$—	182–183	G	49	$C_{13}H_{27}N_7O_4$	45.2	44.9	7.9	7.9	28.4	27.9

[a] R_1 is hydrogen unless otherwise shown; [a1] R_1 = CH_3. [b] Melting points were determined on a Fisher-Johns melting point block and are not corrected. [c] Compound no. (n_D^{20}) — 10(1.4715); 11(1.4694); 12(1.4704). [d] S = recrystallizing solvent; A = crystallized from reaction mixture; B = ethyl acetate—hexane; C = ethyl acetate; D = ethyl acetate—ethanol; E = ethanol; F = water; G = ethanol-water; H = ethyl acetate–ether; I = ethyl acetate–methanol; J = butanol–ethyl acetate. [e] Yields are indicated for analytically pure product. [f] Analyses by Weiler and Strauss, Oxford, England. [g] Reported, A. C. Smith, Jr., and C. C. Unruh, *J. Org. Chem.*, **22**, 442 (1957). [h] C_3H_5 = allyl. [i] R = 2,5-endo-methylenecyclohexylmethyl—. [j] Derived from *d*-α-methylphenethylamine. [k] Reported, W. Siefkin, *Ann.*, **562**, 75 (1949), m.p. 111°. [l] RR_1N derived from *N*-methylpiperazine. [m] X shown under R column as —$(CH_2)_n$—. [n] HN—X—NH replaced by derivative from piperazine. [o] RR_1N is pyrrolidyl; compound obtained from corresponding ethyl ester, m.p. 112–113°. [p] Analyses calculated for dihydrate. [q] Compound is bis-*N*-benzyl derivative of compound 33. [r] Reported, Beilstein IV, p. 362, m.p. 204°. [s] Reported, W. E. Bachmann and C. E. Maxwell, III, *J. Am. Chem. Soc.*, **72**, 2880 (1950), m.p. 180–180.5°. [t] R = furfuryl. [u] Methiodide of compound 59.

Ammonia or benzylamine gave the desired amides with compounds 1 and 2 as well as the unanticipated[15] by-products, 3-hydroxyethylhydantoin and 3-allylhydantoin, respectively. The diester, compound 14, similarly reacted gave amides as well as a by-product, indicative of cyclization coupled with amidation, II.



II

X = H
$C_6H_5CH_2$—

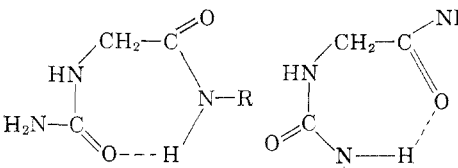
In the anticonvulsant test[16] the principal effects were noted with the δ,δ^1-polymethylenebishydantoamides (compounds 61–67). Interestingly, compound 61 potentiated metrazole convulsions, whereas compounds 63 and 66 gave 3+ anticonvulsant activity. The hexamethylene derivative (compound 65) gave the peak effect with 4+ activity.

The *m*-xylylene derivative in this group (compound 67) was without anticonvulsant action (as was compound 68), but showed good central nervous system (CNS) depressant effects[17] (LD_{min} = 500 mg./kg.), per cent reduction in activity = 23% at 20 mg./kg. Compounds 26 and 58 also showed good CNS depressant effects.

Good anti-inflammatory activity[18] was noted as follows: Compound No./LD_{min} mg./kg./units per gram: 55/100/80; 58/>1000/9; 45/200/22; 53/-300/20; 18/750/15; 23/450/10; 57/200/10; 51/-1000/7.5. Other compounds with lesser activity (< 10 units per gram) were compounds 3, 6–9, 13, 14, 16, 19, 21, 22 and 30.

Other noteworthy responses were hypotension with compounds 39 and 42, hypertension with compound 3, ganglionic block with compound 42, adrenergic block with compound 48, and bronchodilation with compounds 12 and 27. Antibacterial evaluation of selected compounds will be reported elsewhere.

The proven hydrogen-bonded cyclic structure for biurets[19] would suggest consideration of similar structures for compounds of this series as typified by IV and V.



IV

V

EXPERIMENTAL[20]

p-Chlorobenzylamide of hydantoic acid (Compound 56). A solution of 3.65 g. (0.025 mole) of ethyl hydantoate and 3.89 g. (0.028 mole) of *p*-chlorobenzylamine in 35 ml. of methanol, after standing 14 days, gave 3.99 g. (66%) of product, m.p. 195–196°.

Titrations in other runs with selected amines and ethyl hydantoate indicated: compound 49, 67% reaction in 3 days and 77% after 5 days; compound 50, 82% reaction after 9 days. In general, for compounds 46–68, the reaction mixture was stored 10–15 days at 20° before work-up.

Using 3-bis(hydroxyethyl)aminopropylamine, titration indicated complete reaction after 12 days although no pure compound was isolated. Similarly, with 1,2-propanediamine, titration indicated reaction of one equivalent of amino group with no pure compound isolated.

Using α-phenethylamine as the reactant amine, titration indicated less than 10% reaction after 8 days, and after an 8-hr. reflux period, hydantoin (19%) was isolated, m.p. 220°. This reaction failed when similarly conducted under sodium methoxide catalysis, or in water. The following sterically hindered amines also failed to give products: *d*-α-methylphenethylamine, isopropylamine, benzhydrylamine, and *N*-methylbenzylamine.

When aniline was heated with ethyl hydantoate at 150° in the absence of solvent, a rapid evolution of ammonia initiated, and 50% of reactant ester was recovered. The use of butanol as a solvent resulted in similar evolution of ammonia, and 69% recovery of ethyl hydantoate.

Sodium *p*-aminobenzoate did not react after 8 days in methanol.

Ethyl δ-p-carbethoxyphenyl hydantoate (Compound 9). A solution of 2.5 g. (0.019 mole) of carbethoxymethyl isocyanate in 50 ml. of ether was treated portion-wise with 3.5 g. (0.021 mole) of ethyl *p*-aminobenzoate, with rapid formation of product, 5.3 g. (93%), m.p. 135°.

3-Dimethylaminopropylhydantoin. A solution of 9.7 g. (0.08 mole) of carbethoxymethyl isocyanate in 100 ml. of ether was maintained at 0–20° during the addition of 8.4 g. (0.08 mole) of dimethylaminopropylamine. Evaporation of the ether afforded a gelatinous residue which on distillation, b.p. 146–150° (0.2 mm.) gave 1.65 g. of an oil which crystallized. Recrystallization (ethyl acetate–hexane) afforded the product (9%), m.p. 86–87°.

Anal. Calcd. for $C_8H_{15}N_3O_2$: C, 51.9; H, 8.2; N, 22.7. Found: C, 52.3; H, 8.2; N, 22.4.

N^1-[(N-Carbethoxymethyl)carbamido]-N^4-methylpiperazine (Compound 13). A solution of 9.7 g. (0.075 mole) of carbethoxymethyl isocyanate in 50 ml. of ethyl acetate was maintained at 0° during the addition of 7.62 g. (0.075 mole) of *N*-methylpiperazine. After 3 days, 1.65 g. of crystals were separated (solid A) and the filtrate concentrated to an oily residue which after trituration with ether gave 0.65 g. (solid B). Evaporation of the ether filtrate gave an oil which was extracted repeatedly with hexane (total 1.2 l.), and which on standing and clearing with ethyl acetate gave 7.7 g. (45%) of product, m.p. 65–66°.

(15) L. L. McKinney, U. S. Pat. 2,829,157 (Apr. 1, 1958), indicates the δ-substituted hydantoic acid esters cyclize to hydantoins under the influence of heat or acid, with reversal of this reaction under alkaline conditions.

(16) For method of testing see S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3996 (1959).

(17) For method of testing see S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, 80, 1648 (1958).

(18) For method of testing see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, 46, 333 (1957).

(19) (a) W. D. Kumler and C. M. Lee, American Chemical Society, Cleveland Meeting, 1960, p. 35N; (b) I. C. Kogon, *J. Am. Chem. Soc.*, 79, 2253 (1957); (c) M. Nardelli and I. Chierici, *J. Chem. Soc.*, 1952 (1960).

(20) Descriptive data shown in the table are not reproduced in the Experimental. Typical examples of the synthesis are given.

Solid A, recrystallized (ethyl acetate–ethanol) gave 0.65 g., m.p. 207–208°, identical with compound 17.[21]

Solid B, recrystallized (ethyl acetate–hexane) gave 0.37 g., m.p. 140–144° of unproved structure[22] which fits the following empirical formula.

Anal. Calcd. for $C_9H_{16}N_2O_5$: C, 46.6; H, 6.9; N, 12.1. Found: C, 47.2; H, 6.8; N, 12.2.

δ-p-Carbethoxyphenylhydantoamide (Compound 26). A solution of 2.42 g. (0.008 mole) of compound 9 in 30 ml. of methanol was maintained below 35° while saturated with ammonia and stoppered. After 3 days at 20°, 1.6 g. of product separated, m.p. 204–205°. The filtrate on standing gave an additional 0.35 g., m.p. 204–205° (total yield 90%).

N-Benzyl-δ-hydroxyethylhydantoamide. A solution of 3.2 g. (0.016 mole) of compound 1 in 20 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, 100 ml. of ether was added. On standing, 1.17 g. of crystals was obtained, m.p. 90–95°. The filtrate was evaporated and on solution in 40 ml. of ethyl acetate and seeding yielded 0.8 g. of crystals. Repetition of this process gave 0.32 g. of the above, total 2.29 g. This was dissolved in a mixture of 3 ml. of ethanol and 55 ml. of ethyl acetate. The initial crop of crystals was separated (0.25 g.), m.p. 135–141°, and recrystallized (ethanol–ethyl acetate) to give 0.1 g. of product, m.p. 140–141°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.4; H, 6.8; N, 16.7. Found: C, 57.4; H, 6.6; N, 17.1.

The filtrate on further standing gave a different solid which recrystallized (ethanol-hexane), m.p. 103.5–104°, proved to be 3-hydroxyethylhydantoin.[23]

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.7; H, 5.6. Found: C, 41.7; H, 5.4.

δ-Hydroxyethylhydantoamide (Compound 18). A solution of 4.0 g. (0.02 mole) of compound 1 in 20 ml. of methanol was saturated with ammonia. After storage for 3 days at 20° and seeding, 1.65 g. of crude product was obtained. The filtrate on dilution with 200 ml. of ether gave 0.85 g. of crude 3-hydroxyethylhydantoin, m.p. 90–96°.

N-Benzyl-δ-allylhydantoamide (Compound 34). A solution of 3.0 g. (0.016 mole) of compound 2 in 30 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, upon seeding and cooling at 10° for 4 hr., 0.9 g. of product was obtained, m.p. 186–188°. Concentration of the filtrate and trituration with ethyl acetate gave an additional 0.6 g. of product, m.p. 186–187°; total yield 38%. The ethyl acetate was removed from the filtrate and the residue triturated with hexane gave 1.35 g. (60%) of crystals of 3-allylhydantoin,[24] m.p. 75°; recrystallized (ethyl acetate–hexane) m.p. 78°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 50.8; H, 5.8; N, 20.1.

Under similar conditions, employing ammonia and compound 2, *δ-allyl-hydantoamide* (compound 19) was obtained in 47% yield, and *3-allylhydantoin* (m.p. 78°) was obtained in 19% yield.

δ,δ¹-Trimethylenebishydantoamide (Compound 32). A solution of 4.0 g. (0.012 mole) of compound 14 in 45 ml. of methanol was maintained below 30° while saturated with ammonia. After 24 hr., 2.57 g. of crystals were obtained and dissolved in 60 ml. of water, yielding 0.8 g. (24%), m.p. 224–225°. The aqueous filtrate was concentrated to 10 ml. to give 0.85 g. (24%) of crystals, m.p. 180–184°, which analysis indicated to be the hydantoin II, X = H.

Anal. Calcd. for $C_9H_{15}N_5O_4$: C, 42.0; H, 5.9. Found: C, 41.5; H, 6.2.

δ,δ¹-Trimethylene(bis-N-benzylhydantoamide). A solution of 3.3 g. (0.01 mole) of compound 14 in 30 ml. of methanol was treated with 4.28 g. (0.04 mole) of benzylamine. After 4 days the formed solid (1.6 g.) was separated, m.p. 160–190°, and recrystallized (dimethylformamide) to give 0.52 g. (12%) of product, m.p. 195–207°.

Anal. Calcd. for $C_{23}H_{30}N_6C_4$: N, 18.5. Found N, 18.1.

Evaporation of the filtrate and trituration with ether gave 1.4 g. of white solid, recrystallized from water to give 0.7 g. (20%) of crystals which analysis indicated to be the hydantoin II, X = $C_6H_5CH_2$—.

Anal. Calcd. for $C_{16}H_{21}N_5O_4$: C, 55.3; H, 6.1; N, 20.2. Found: C, 55.3; H, 5.6; N, 20.3.

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(21) This may have resulted from the presence of piperazine as an impurity in the *N*-methylpiperazine.

(22) E. Fischer, *Ber.*, **34**, 440 (1901), reports carbonyldiglycindiethyl ester, m.p. 146°, prepared from phosgene and glycine diethyl ester.

(23) A. C. Smith, Jr., and C. C. Unruh, *J. Org. Chem.*, **22**, 442 (1957), report m.p. 98–101°.

(24) Beilstein, XXIV, p. 250, reports m.p. 78°.

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Amino Acid Analogs. I. Analogs of the Glutamic Acid, Proline Interconversion. Part I. ω-Methyl- and ω-Phenylketoglutamic Acids and 5-Methyl- and 5-Phenylprolines

HERMAN GERSHON AND ALFRED SCALA

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Some analogs of glutamic acid, Δ′-pyrroline-5-carboxylic acid and proline were synthesized.

The interconversion of glutamic acid and proline in both animal tissues and microorganisms has been reviewed by Stetten[1] and Vogel.[2] This relationship consists essentially of the following series of reversible transformations: glutamic acid ⇌ glutamic-γ-semialdehyde ⇌ Δ′-pyrroline-5-carboxylic

(1) M. R. Stetten, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 277.

(2) H. J. Vogel, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 335.