N,N′-Bis(5,5-dimethyl-3-hydantoinylmethyl)piperazine, gave an 85% yield and had m.p. 248–249° dec.

Anal. Calcd. for $C_{18}H_{26}N_6O_4$: N, 22.94. Found: N, 22.87.

N,N′-Bis(5,5-diphenyl-3-hydantoinylmethyl)piperazine gave a 75% yield and had m.p. 252–254° dec.

Anal. Calcd. for $C_{36}H_{34}N_6O_4$: N, 13.88. Found: N, 14.03.

Hydroxymethyl-5,5-Dimethylhydantoin.[12]—This compound was commercially available and, after recrystallization from benzene–ethanol, melted at 117–119°.

Reaction of Hydroxymethyl-5,5-dimethylhydantoin with Amines.—To a solution of 15.8 g. (0.1 mole) of hydroxymethyl-5,5-dimethylhydantoin in 15 ml. of warm ethanol was added slowly and with shaking 9.3 g. (0.1 mole) of aniline. The mixture was refluxed 1 hr., filtered, and cooled. Recrystallization from ethanol yielded 15 g. (64%) of N-3-anilinomethyl-5,5-dimethylhydantoin, m.p. 154–155°.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: N, 18.02. Found: N, 18.08.

A mixture melting point of this product with that prepared from 5,5-dimethylhydantoin, formaldehyde, and aniline by the general procedure described above (see Table I) was 153–154°; the infrared spectra of the two compounds were identical.

Similarly 0.1 mole of hydroxymethyl-5,5-dimethylhydantoin and 0.1 mole of morpholine in 10 ml. of ethanol were refluxed for 30 min., filtered, and allowed to stand overnight to crystallize. N-3-morpholinomethyl-5,5-dimethylhydantoin was obtained in 68% yield which, after recrystallization from benzene–ethanol, melted at 148.5–149.5°.

Anal. Calcd. for $C_{10}H_{17}N_3O_3$: N, 18.49. Found: N, 18.64.

To a solution of 15.8 g. (0.1 mole) of hydroxymethyl-5,5-dimethylhydantoin and 8.1 g. (0.1 mole) of 37% formaldehyde in 10 ml. of warm ethanol was added slowly 17.4 g. (0.2 mole) of morpholine. A rather vigorous reaction occurred upon the addition of morpholine. The solution was refluxed for 30 min., cooled, and allowed to stand overnight to crystallize. A 73% yield of N-1,N-3-bis(morpholinomethyl)-5,5-dimethylhydantoin was obtained which, after recrystallization from ethanol, melted at 131–132°. The reported m.p. is 134–134.5°.[13]

Basic Hydrolysis of N-3-Anilinomethyl-5-ethyl-5-phenylhydantoin.—To a solution of 3.09 g. (0.01 mole) of N-3-anilinomethyl-5-ethyl-5-phenylhydantoin in 90 ml. of ethanol was added a solution of 0.5 g. of NaOH in 20 ml. of water. After allowing the reaction mixture to stand at room temperature overnight, the solution was acidified to pH 2 with dilute sulfuric acid. Upon cooling, a quantitative yield of 5-ethyl-5-phenylhydantoin was obtained which, after recrystallization from aqueous ethanol, melted at 200.5–201.5°. A mixture melting point with 5-ethyl-5-phenylhydantoin (lit.[13] m.p. 201–202°) showed no depression, and the infrared spectra of the two products were identical.

Acknowledgment.—The authors wish to thank the Board of Directors of the American Chemical Society and the Petroleum Research Fund Advisory Board for a grant-in-aid in support of this work. We wish also to thank Richard Gluckman, George Van Dine, Ann Schwartz, Sally DeLong, Harold Schobert, Dr. Frank Cutler, and the Merck Sharp and Dohme Research Laboratories for their contributions to this study.

(12) E. S. Mackey, U. S. Patent 2,762,708; *Chem. Abstr.*, **51**, 1757c (1957).

(13) H. T. Buchherer and V. A. Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

Substitution in the Hydantoin Ring. II. N-3-Acetic Acid Derivatives

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N-3-Acetic acid derivatives of a number of 5,5-disubstituted hydantoins have been prepared and their pharmacological behavior has been investigated. The alkylation of 5,5-disubstituted hydantoins with either ethyl chloro- or bromoacetate in the presence of sodium ethoxide resulted in the formation of ethyl 5,5-disubstituted hydantoin-3-acetates (Table I), which, upon saponification, were converted into 5,5-disubstituted hydantoin-3-acetic acids (Table II).

5,5-Disubstituted hydantoin-3-acetamide derivatives (Table III) were prepared from the corresponding acetic acid derivatives by reaction with thionyl chloride and either ammonium hydroxide, aniline, or *p*-toluidine. The hydantoins used in this study were prepared from the corresponding ketones by a modification of the Bucherer–Berg reaction as described by Goodson, *et al.*[1]

Pharmacology.—Chemotherapeutic and pharmacologic tests on representative members of this group of hydantoins were conducted by Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc. The compounds were subjected to the following programs: screening against *Escherichia coli in vitro*, screening against coccidiosis in chickens, testing in animals for antiinflammatory activity, testing in rats for diuretic activity, and testing in mice for effects on the nervous system. While marginal activity was observed in several instances, none of the compounds appeared to warrant detailed studies.

In the *E. coli in vitro* assay a paper disk was dipped into a solution of the test compound and placed on a synthetic medium comprised of glutamate, dextrose, and salts and which was seeded with an 18-hr. *E. coli* culture. The presence of zones of inhibition was noted, the solution was successively diluted twofold, and the assay was repeated until no inhibition was observed. The compounds tested were inactive at a level of 1 mg./ml.

In the coccidiosis test the compounds were assayed against coccidia by the procedure described by Cuckler.[2]

Antiinflammatory activity was determined by using an antiedema test as described by Winter, *et al.*[3] The compounds were inactive at 100 mg./kg.

Diuretic activity was determined in rats dosed at 10 and 100 mg./kg. i.p. The general methodology is described by Baer and Beyer.[4]

In the test for effects on the nervous system, mice were dosed intraperitoneally, the test compounds being administered initially at a low dose and then at successively higher doses over a practical range. The following observations were made visually: mortality, pupil dilatation, depression of exploratory activity, ptosis, ataxia, loss of righting reflex, tremors, tonic and clonic convulsions, excitement, corneal reflex, pinna twitch reflex, bar grasp, and analgesia (Haffner test). In addition, anticonvulsant activity was determined as described by Swinyard, *et al.*,[5] and Torchiana, *et al.*[6]

(1) L. H. Goodson, I. L. Honigberg, J. J. Lehman, and W. H. Burton, *J. Org. Chem.*, **25**, 1920 (1960).

(2) A. C. Cuckler, *Proc. Soc. Exptl. Biol. Med.*, **98**, 167 (1958).

(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *ibid.*, **111**, 544 (1962).

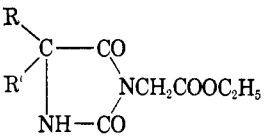
(4) J. E. Baer and K. H. Beyer, *Am. J. Pharm.*, **132**, 5 (1960).

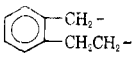
(5) E. A. Swinyard, W. C. Brown, and L. C. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(6) M. L. Torchiana, K. L. Meckelnburg, S. F. McKinney, and C. E. Stone, *Proc. Soc. Exptl. Biol. Med.*, **101**, 750 (1959).

TABLE I

ETHYL 5,5-DISUBSTITUTED HYDANTOIN-3-ACETATES

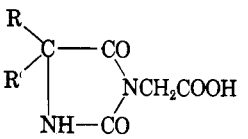


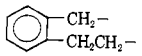
R	R'	Yield, %	M.p., °C.	Recrystn. solvent	Formula	% N Calcd.	% N Found
C_2H_5	C_2H_5	68	69.5–70.5	H_2O	$C_{11}H_{18}N_2O_4$	11.56	11.40
n-C_3H_7	n-C_3H_7	95[a]	59–61.5	C_2H_5OH	$C_{13}H_{22}N_2O_4$	10.36	10.26
CH_2CH_2CH	CH_2CH_2CH	60	83–83.5	C_2H_5OH–H_2O	$C_{13}H_{18}N_2O_4$	10.52	10.92
CH_3	C_6H_5	81	86–87[b]	C_2H_5OH–H_2O	$C_{14}H_{16}N_2O_4$	...	...
CH_3	p-ClC_6H_4	95[a]	83–85[c]	C_2H_5OH	$C_{14}H_{15}ClN_2O_4$	9.02	8.91
C_2H_5	C_6H_5	96	120–121[d]	C_2H_5OH–H_2O	$C_{15}H_{18}N_2O_4$	9.65	9.79
n-C_3H_7	C_6H_5	83	109–110	$(CH_3)_2CO$–H_2O	$C_{16}H_{20}N_2O_4$	9.21	9.21
C_6H_5	C_6H_5	70	185–186[e]	$(CH_3)_2CO$–C_2H_5OH	$C_{19}H_{18}N_2O_4$	...	...
$-(CH_2)_4-$		72	108.5–109.5	C_2H_5OH	$C_{11}H_{16}N_2O_4$	11.93	12.12
$-(CH_2)_5-$		78	128.5–129[f]	C_2H_5OH–H_2O	$C_{12}H_{18}N_2O_4$	...	...
(—)-$CH_2CHCH_2CH_2CH$– CH_3 $(CH_3)_2CH$		31	95–96	C_2H_5OH–H_2O	$C_{16}H_{26}N_2O_4$	9.02	8.86
		79[a]	155–157	C_2H_5OH	$C_{16}H_{18}N_2O_4$	9.27	9.27

[a] Ethyl bromoacetate was used as the alkylating agent. [b] O. O. Orazi and R. A. Corral, [*Anales asoc. quim. Arg.*, **42**, 177 (1954)] report m.p. 87.5–88.5°; K. Schloegl, F. Wessely, O. Kraupp, and H. Stormann [*J. Med. Pharm. Chem.*, **4**, 231 (1961)] report m.p. 88–91°. [c] The melt cleared at 91°. [d] Schloegl, *et al.*,[b] report m.p. 121–123°. [e] Orazi, *et al.*,[b] report m.p. 184–185°; F. Sandberg [*Acta Physiol. Scand.*, **24**, 149 (1951)] reports 178–180°. [f] Orazi, *et al.*,[b] report m.p. 128.5–129.5°.

TABLE II

5,5-DISUBSTITUTED HYDANTOIN-3-ACETIC ACIDS

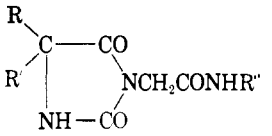


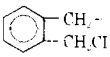
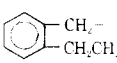
R	R'	Yield, %	M.p., °C.	Formula	% N Calcd.	% N Found
C_2H_5	C_2H_5	68	171–172[a]	$C_9H_{14}N_2O_4$	13.08	12.90
n-C_3H_7	n-C_3H_7	77[b]	121–124[c,d]	$C_{11}H_{18}N_2O_4$	11.56	11.69
CH_2CH_2CH	CH_2CH_2CH	60	177–177.5	$C_{11}H_{14}N_2O_4$	11.76	11.49
CH_3	C_6H_5	80	169–170.5[e]	$C_{12}H_{12}N_2O_4$	...	...
CH_3	p-ClC_6H_4	85[b]	234.5–236[c]	$C_{12}H_{11}ClN_2O_4$	9.91	9.81
CH_3		60	176–178[f]	$C_{10}H_{10}N_2O_4S$	11.02	10.90
C_2H_5	C_6H_5	66	87–89[g]	$C_{13}H_{14}N_2O_4 \cdot 0.5H_2O$	10.33	10.34
			137–138[h]	$C_{13}H_{14}N_2O_4$	10.68	10.84
n-C_3H_7	C_6H_5	77	168–168.5	$C_{14}H_{16}N_2O_4$	10.14	10.06
C_6H_5	C_6H_5	92	292.5–294[i,j]	$C_{17}H_{14}N_2O_4$	...	...
$-(CH_2)_4-$		46[k]	194–195[a]	$C_9H_{12}N_2O_4$	13.20	13.38
$-(CH_2)_5-$		74	221–222[l]	$C_{10}H_{14}N_2O_4$	...	...
(—)-$CH_2CHCH_2CH_2CH$– CH_3 $(CH_3)_2CH$		53	192–193	$C_{14}H_{22}N_2O_4$	9.92	10.06
		50[b]	223.5–226[c]	$C_{14}H_{14}N_2O_4$	10.23	10.35

[a] Recrystallized from water. [b] The ethyl ester was saponified for 24 hr. [c] Purified by dissolving in aqueous sodium bicarbonate, filtering, and acidifying with dilute H_2SO_4. [d] The product oiled out of solution and was extracted with benzene. Evaporation of the benzene produced the crystalline product. [e] Orazi, *et al.*, Table I, footnote *b*, report m.p. 170.5–171.5°; Schloegl, *et al.*, Table I, footnote *b*, report 168–171°. [f] Recrystallized from benzene–acetone. [g] The product, as obtained from the reaction mixture or upon recrystallization from aqueous ethanol, was hydrated. Schloegl, *et al.*, Table I, footnote *b*, report m.p. 90°. [h] Upon boiling the hydrated product with benzene until the solution cleared, then adding petroleum ether (30–60°) and cooling, the anhydrous product was obtained. [i] Recrystallized from ethanol–acetone. [j] Orazi, *et al.*, Table I, footnote *b*, report m.p. 284–287°; Sandberg, Table I, footnote *e*, reports m.p. 282–284°; C. Hoffmann [*Bull. soc. chim. France*, 659 (1950)] reports m.p. 285°. [k] This yield was obtained by proceeding directly to the acid without isolating the intermediate ethyl ester. [l] Orazi, *et al.*, Table I, footnote *b*, report m.p. 222–223°.

TABLE III

5,5-DISUBSTITUTED HYDANTOIN-3-ACETAMIDE DERIVATIVES



R	R′	R″	M.p., °C.	Formula	% N Calcd.	% N Found
n-C_3H_7	*n*-C_3H_7	H	209–211	$C_{11}H_{19}N_3O_3$	17.41	17.26
n-C_3H_7	*n*-C_3H_7	C_6H_5	175–176.5	$C_{17}H_{23}N_3O_3$	13.24	13.06
CH_3	C_6H_5	H	199.5–200	$C_{12}H_{13}N_3O_3$	17.00	17.11
CH_3	C_6H_5	C_6H_5	220.5–221.5[a]	$C_{18}H_{17}N_3O_3$	13.00	12.97
CH_3	C_6H_5	*p*-$CH_3C_6H_4$	199.5–201	$C_{19}H_{19}N_3O_3$	12.46	12.24
CH_3	*p*-ClC_6H_4	H	204–206	$C_{12}H_{12}ClN_3O_3$	14.92	14.75
CH_3	*p*-ClC_6H_4	C_6H_5	230–232	$C_{18}H_{16}ClN_3O_3$	11.75	11.71
C_2H_5	C_6H_5	H	188	$C_{13}H_{15}N_3O_3$	16.08	15.93
C_2H_5	C_6H_5	C_6H_5	180–181[b]	$C_{19}H_{19}N_3O_3$	12.46	12.46
n-C_3H_7	C_6H_5	H	192[b]	$C_{14}H_{17}N_3O_3$	15.26	15.28
C_6H_5	C_6H_5	H	248–250[c]	$C_{17}H_{15}N_3O_3$	13.59	13.55
C_6H_5	C_6H_5	C_6H_5	246–247	$C_{23}H_{19}N_3O_3$	10.90	10.73
C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$	262.5–264	$C_{24}H_{21}N_3O_3$	10.52	10.67
-$(CH_2)_3$-		H	202–203	$C_8H_{13}N_3O_3$	19.90	19.71
-$(CH_2)_4$-		C_6H_5	162.5–163	$C_{15}H_{17}N_3O_3$	14.63	14.46
-$(CH_2)_5$-		H	208–209	$C_9H_{15}N_3O_3$	18.66	18.38
-$(CH_2)_5$-		C_6H_5	230–231	$C_{16}H_{19}N_3O_3$	13.95	13.85
-$(CH_2)_6$-		*p*-$CH_3C_6H_4$	259–260	$C_{17}H_{21}N_3O_3$	13.33	13.32
		H	193–195[c]	$C_{11}H_{11}N_3O_3$	15.38	15.40
		C_6H_5	224–225	$C_{17}H_{15}N_3O_3$	12.03	11.92

[a] Recrystallized from ethanol–acetone. [b] Recrystallized from aqueous acetic acid. [c] F. Sandberg (Table I, footnote *c*) reports m.p. 248–249°. [d] Recrystallized from acetone.

Experimental[7]

Ethyl 5,5-Disubstituted Hydantoin-3-acetates.—In a 500-ml. flask were placed 200 ml. of absolute ethanol and 2.3 g. (0.1 g.-atom) of sodium. After the sodium had dissolved, 0.1 mole of the 5,5-disubstituted hydantoin and 13.5 g. (0.11 mole) of ethyl chloroacetate were added. Alternately 18.4 g. (0.11 mole) of ethyl bromoacetate was used as the alkylating agent in several preparations. The mixture was refluxed for 24 hr., and the hot solution was filtered to remove the precipitated NaCl or NaBr. The volume of the solution was reduced to one-half or more by concentration *in vacuo*. Upon either cooling or the addition of ice, the product separated and was recrystallized.

5,5-Disubstituted Hydantoin-3-acetic Acids.—In a 500-ml. flask were placed 0.1 mole of the ethyl 5,5-disubstituted hydantoin-3-acetate and 200 ml. of absolute ethanol. To this solution was added 4 g. (0.1 mole) of NaOH dissolved in a minimum of water. The mixture was refluxed with stirring until saponification was completed, usually 1–4 hr. The sodium 5,5-disubstituted hydantoin-3-acetate began to precipitate out of solution shortly after refluxing was started. The sodium salt was filtered, washed with a small amount of absolute ethanol or petroleum ether, and dried. The salt was dissolved in a small amount of water, the solution was filtered, then acidified with dilute H_2SO_4. The acidified solution was thoroughly chilled, concentrated if necessary, and the 5,5-disubstituted hydantoin-3-acetic acid which crystallized out was purified by dissolution and reprecipitation from aqueous sodium bicarbonate, then recrystallized from aqueous ethanol.

Amide and Anilide Derivatives of 5,5-Disubstituted Hydantoin-3-acetic Acids.—A mixture of 0.1 mole of the 5,5-disubstituted hydantoin-3-acetic acid in benzene was refluxed with 47.6 g. (0.4 mole) of thionyl chloride for 1 hr. after solution had occurred. One drop of pyridine was added as a catalyst. The excess thionyl chloride was removed by several flushes of benzene and concentration *in vacuo*. The substituted amides and anilides were prepared by carefully adding ammonium hydroxide or aniline to the chilled benzene solution of the acid chloride until the solution was basic to litmus. After refluxing for 3 hr., the benzene solvent was exchanged for acetone by flushing with acetone and concentrating *in vacuo*. Upon dilution with water the product was obtained and recrystallized from water, ethanol, or aqueous ethanol.

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(7) Infrared spectrograms were obtained on the Perkin-Elmer 137B Infracord with sodium chloride plates and Nujol mull and on the Beckman IR1 with potassium bromide wafers. These spectrograms appear in the Sadtler Standard Spectra Catalog, No. 22606–22650. Melting points were determined either in a liquid bath or in a Mel-Temp apparatus and are corrected. Nitrogen analyses are by the semimicro Kjeldahl method.

N,N-Diethyl-2,2-dimethylpropane-1,3-diamine

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A need in this laboratory for pure N,N-diethyl-2,2-dimethylpropane-1,3-diamine (III) as an intermediate in an antihypertensive program led to a comparison of two methods of preparation.