190.5° dec.; ν_{max}^{Nujol} 2350, 2400 (bonded N⁺–H or O–H), 1700 (C=O), 765 (C–Cl), 712 cm.⁻¹ (benzoyl CH).

Anal. Calcd. for $C_{15}H_{14}ClNO_3 \cdot HCl$: C, 54.88; H, 4.61; Cl, 21.63; N, 4.27. Found: C, 54.78; H, 4.79; Cl, 21.38; N, 4.19.

Attempted Preparation of Free Base of II.—II (1.1 g.) was added to 20% aqueous sodium bicarbonate solution, the suspension was stirred for 2 hr., and the solid was filtered, washed with water, and dried. The material (0.5 g.) was insoluble in most organic solvents, NaOH, or HCl. The melting point of the compound was above 350°. A sample was dried at 100° (0.5 mm.) over P_2O_5 and was analyzed without further purification (Found: C, 61.75; H, 5.17; N, 4.66.). Its n.m.r. spectrum in dimethyl sulfoxide-d_6 gave indistinct peaks indicating a polymer. An analogous polymerization has been observed for 2-methyl-3-hydroxy-4,5-dibromomethylpyridine hydrobromide.[6]

4-Deoxy-5-benzoyloxypyridoxine Hydrochloride (IV).—II (1.1 g.) in 20 ml. of methanol was hydrogenated with H_2 at 2.81 kg./cm.² (40 p.s.i.) for 6 hr. in the presence of 5% palladium on charcoal. Filtration, evaporation under reduced pressure, and crystallization from ethanol–water gave 4-deoxy-5-benzoyloxypyridoxine hydrochloride (0.84 g., 85%) as colorless needles, m.p. 225–226° dec.

Anal. Calcd. for $C_{15}H_{15}NO_3 \cdot HCl$: C, 61.33; H, 5.49; Cl, 12.07; N, 4.77. Found: C, 61.03; H, 5.66; Cl, 12.20; N, 4.61.

The free base precipitated from aqueous solution on addition of sodium carbonate. It was crystallized from aqueous ethanol in needles, m.p. 140°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.05; H, 6.13; N, 5.44.

The picrate formed yellow needles from ethanol, m.p. 210–211° dec.

Anal. Calcd. for $C_{15}H_{15}NO_3 \cdot C_6H_3N_3O_7$: C, 52.10; H, 3.81; N, 11.63. Found: C, 52.10; H, 3.73; N, 11.52.

4-Deoxypyridoxine.—4-Deoxy-5-benzoyloxypyridoxine (IV, 2.57 g.) was refluxed for 2.5 hr. with 2 *N* aqueous KOH. The solution was neutralized, 4-deoxypyridoxine was filtered off and converted into its hydrochloride by the ethanolic HCl. The material (1.42 g., 95%) was recrystallized from ethanol–ether and melted at 235°, which was not depressed by admixture of an authentic sample.

Anal. Calcd. for $C_8H_{11}NO_2 \cdot HCl$: Cl, 50.66; H, 6.38: Cl, 18.69; N, 7.39. Found: C, 50.40; H, 6.43; Cl, 18.94; N, 7.55.

5-Hydroxy-6-methyl-4-(sulfomethyl)-3-pyridinemethanol Benzoate (IIIa, R = SO_3H).—To 1.09 g. of II in ethanol (15 ml.) a solution of sodium bisulfite (0.71 g.) in water (5 ml.) was added, and the mixture was stirred at room temperature for 20 hr. The resulting solid was collected; from the mother liquor another crop was obtained on acidification and concentration. Recrystallization from a large volume of aqueous ethanol (charcoal) yielded the sulfonic acid (0.56 g., 50%) in needles, which did not have a melting point; ν_{max}^{Nujol} 1315, 1160 (—SO_3H), 1710 (C=O), 720 cm.⁻¹ (benzoyl CH).

Anal. Calcd. for $C_{15}H_{15}NO_6S$: C, 53.41; H, 4.48; N, 4.13; S, 9.48. Found: C, 53.11; H, 4.75; N, 3.92; S, 9.41.

5-Hydroxy-6-methyl-4-(thiocyanomethyl)-3-pyridinemethanol Benzoate (IIIb, R = SCN).—To a solution of II in anhydrous ethanol (15 ml.) potassium thiocyanate (0.68 g.) was added and refluxed for 30 min. The contents were cooled to 0° and KCl was removed by filtration. The filtrate, after clarification with charcoal, was evaporated and recrystallized from aqueous methanol to yield 0.57 g. of needles, m.p. 184° dec.; ν_{max}^{Nujol} 1428, 1316 (—SCN), 1710 (C=O), 710 cm.⁻¹ (benzoyl CH).

Anal. Calcd. for $C_{16}H_{14}N_2SO_3$: C, 61.14; H, 4.49; S, 10.18. Found, C, 60.88; H, 4.38; S, 10.15.

5-Hydroxy-4-(mercaptomethyl)-6-methyl-3-pyridinemethanol Benzoate Hydrochloride (IIIc, R = SH).—To a stirred solution of 0.82 g. of II in 10 ml. of ethanol was added a solution of 0.5 g. of sodium sulfhydrate in 2.0 ml. of water over a period of 5 min. The mixture was stirred at room temperature for 8 hr. Excess solvent was evaporated and the residue was dissolved in absolute ethanol and passed through a column of Dowex 50 in the H^+ form in order to remove Na ions. Evaporation of the solvent followed by the crystallization from aqueous ethanol afforded 0.36 g. (50% based on the amount of II not recovered) in prisms, m.p. 117–119° dec.; ν_{max}^{Nujol} 2270 (–SH), 1705 (C=O), 710 cm.⁻¹ (benzoyl CH).

Anal. Calcd. for $C_{15}H_{15}NSO_3$: C, 62.28; H, 5.23; N, 4.84; S, 11.08. Found: C, 62.09; H, 5.03; N, 4.86; S, 11.35.

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Substitution in the Hydantoin Ring. I. N-3-Aminomethyl Derivatives

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A series of N-3-aryl (and alkyl) aminomethyl hydantoins have been prepared (Tables I–III) from 5,5-disubstituted hydantoins and spirohydantoins by condensation with formaldehyde and the appropriate amine.[1-3] The hydantoins used in this study were prepared from the corresponding ketones by a modification of the Bucherer–Berg reaction as described by Goodson and co-workers.[4]

In a basic solution the aminomethyl group is cleaved from the N-3 position, and the parent hydantoin is regenerated. Thus in one experiment N-3-anilinomethyl-5-ethyl-5-phenylhydantoin was converted quantitatively into 5-ethyl-5-phenylhydantoin upon standing in an alkaline solution at room temperature.

In addition to their preparation by the general procedure as described in the Experimental section, N-3-morpholinomethyl-5,5-dimethylhydantoin and N-3-anilinomethyl-5,5-dimethylhydantoin were also prepared by the reaction of hydroxymethyl-5,5-dimethylhydantoin with morpholine and aniline, respectively.

N-1,N-3-Bis(morpholinomethyl)-5,5-dimethylhydantoin was prepared by the general procedure and by allowing hydroxymethyl-5,5-dimethylhydantoin to react with formaldehyde and 2 equiv. of morpholine. Attempts at preparing N-1,N-3-bis(anilinomethyl)-5,5-dimethylhydantoin from either hydroxymethyl-5,5-dimethylhydantoin, formaldehyde, and 2 equiv. of aniline, or from 5,5-dimethylhydantoin and 2 equiv. each of formaldehyde and aniline resulted only in the formation of N-3-anilinomethyl-5,5-dimethylhydantoin.

N,N′-Bis(5,5-disubstituted 3-hydantoinylmethyl)-piperazine derivatives of 5,5-dimethylhydantoin and 5,5-diphenylhydantoin have been prepared by permitting 2 equiv. each of the hydantoin and formaldehyde to react with 1 equiv. of piperazine.

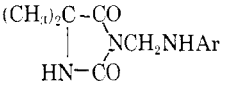
Infrared spectrograms of a number of the compounds reported here appear in the Sadtler Standard Spectra Catalog, No. 21157–21197, Sadtler Research Laboratories, Philadelphia, Pa.

Pharmacology.—Various chemotherapeutic and pharmacologic tests on representative members of this group of hydantoins were conducted by Merck Sharp and Dohme Research Laboratories, Division of Merck

(1) C. C. Bombardieri and A. Taurins, *Can. J. Chem.*, **33**, 923 (1955).
(2) O. O. Orazi and R. A. Corral, *Tetrahedron*, **15**, 93 (1961).
(3) J. N. Coker and M. Fields, *J. Org. Chem.*, **27**, 2226 (1962).
(4) L. H. Goodson, I. L. Honigberg, J. J. Lehman, and W. H. Burton, *ibid.*, **25**, 1920 (1960).

TABLE I

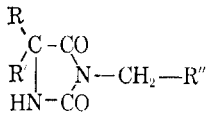
N-3-ARYLAMINOMETHYL-5,5-DIMETHYLHYDANTOINS



Ar	M.p., °C.	Yield, %	Formula	Nitrogen, %: Calcd.	Found
C_6H_5	154.5–155.0	78	$C_{12}H_{15}N_3O_2$	18.02	18.08
p-$CH_3C_6H_4$	169–170	76	$C_{13}H_{17}N_3O_2$	16.99	17.10
p-BrC_6H_4	196–196.5	76	$C_{12}H_{14}BrN_3O_2$	13.46	13.50
m-BrC_6H_4	144.5–145.5	82	$C_{12}H_{14}BrN_3O_2$	13.46	13.43
p-ClC_6H_4	193.5–194.5	72	$C_{12}H_{14}ClN_3O_2$	15.69	15.60
o-ClC_6H_4	127.5–128.0	55	$C_{12}H_{14}ClN_3O_2$	15.69	15.58
2,4-$(CH_3)_2C_6H_3$	145–145.5	62	$C_{14}H_{19}N_3O_2$	16.08	15.93
2,5-$(CH_3)_2C_6H_3$	158–159.5	48	$C_{14}H_{19}N_3O_2$	16.08	16.10
p-$C_6H_5C_6H_4$	144–145	56	$C_{18}H_{18}N_3O_2$	13.63	13.43
o-$C_6H_5C_6H_4$	132–134	52	$C_{18}H_{18}N_3O_2$	13.63	13.54
o-$CH_3OOCC_6H_4$	171–172	43	$C_{14}H_{17}N_3O_4$	14.43	14.22
o-$C_2H_5OOCC_6H_4$	154–155	72	$C_{15}H_{19}N_3O_4$	13.77	13.58
o-$C_2H_5OC_6H_4$	118–119	53	$C_{14}H_{19}N_3O_3$	15.15	14.96
p-NCC_6H_4	149–150	45	$C_{13}H_{14}N_4O_2$	21.69	21.83

TABLE II

N-3-AMINOMETHYL DERIVATIVES OF 5,5-DISUBSTITUTED HYDANTOINS



R	R′	R″	Reflux time, hr.	Yield, %	Recrystn. solvent	M.p., °C.	Formula	Nitrogen, %: Calcd.	Found
CH_3	C_6H_5	C_6H_5NH	2	62	C_6H_6	136–136.5	$C_{17}H_{17}N_3O_2$	14.23	14.24
CH_3	C_6H_5	p-$CH_3C_6H_4NH$	2	73	C_6H_6–ligroin	136–137.5	$C_{18}H_{19}N_3O_2$	13.58	13.77
CH_3	C_6H_5	Morpholino	2	60	C_6H_6	139–140	$C_{15}H_{19}N_3O_3$	14.52	14.74
CH_3	C_6H_5	Piperidino	2	60	C_6H_6	149–151	$C_{16}H_{21}N_3O_2$	14.62	14.65
C_2H_5	C_6H_5	C_6H_5NH	1	70	C_2H_5OH	135.5–136.0	$C_{18}H_{19}N_3O_2$	13.58	13.57
C_2H_5	C_6H_5	p-$CH_3C_6H_4NH$	3	65	C_2H_5OH	153–153.5	$C_{19}H_{21}N_3O_2$	12.99	12.98
C_2H_5	C_6H_5	Morpholino	3	57	C_6H_6	135.5–136.5	$C_{16}H_{21}N_3O_3$	13.85	14.02
C_2H_5	C_6H_5	Piperidino	3	56	C_2H_5OH	118–119	$C_{17}H_{23}N_3O_2$	13.94	14.05
n-C_3H_7	C_6H_5	C_6H_5NH[a]	4	35	Aq. C_2H_5OH	132–133.5	$C_{19}H_{21}N_3O_2$	12.99	13.06
CH_3	p-ClC_6H_4	C_6H_5NH	1	93	C_2H_5OH	145.5–147.0	$C_{17}H_{16}ClN_3O_2$	12.74	12.59
CH_3	p-ClC_6H_4	p-$CH_3C_6H_4NH$	1	96	C_2H_5OH	161.5–163.0	$C_{18}H_{18}ClN_3O_2$	12.22	12.18
CH_3	p-ClC_6H_4	Morpholino	1	79	C_2H_5OH	163–164	$C_{15}H_{18}ClN_3O_3$	12.99	13.13
CH_3	p-ClC_6H_4	Piperidino	1	97	C_2H_5OH	145.5–147.0	$C_{16}H_{20}ClN_3O_2$	13.06	12.94
n-C_3H_7	n-C_3H_7	C_6H_5NH	1	93	C_2H_5OH	116–117.5	$C_{16}H_{23}N_3O_2$	14.52	14.36
n-C_3H_7	n-C_3H_7	p-$CH_3C_6H_4NH$	1	92	C_2H_5OH	114–116	$C_{17}H_{25}N_3O_2$	13.85	13.57
n-C_3H_7	n-C_3H_7	Piperidino	1	59	C_2H_5OH	193–196.5	$C_{15}H_{27}N_3O_2$	14.93	15.02
C_6H_5	C_6H_5	C_6H_5NH	1	73	C_2H_5OH	168–169	$C_{22}H_{19}N_3O_2$	11.76	11.98
C_6H_5	C_6H_5	p-$CH_3C_6H_4NH$	1	61	C_2H_5OH	171.5–172.5	$C_{23}H_{21}N_3O_2$	11.31	11.23
C_6H_5	C_6H_5	p-$CH_3OC_6H_4NH$	1	25	$(CH_3)_2CO$	167.5–169.5	$C_{23}H_{21}N_3O_3$	10.85	10.90
C_6H_5	C_6H_5	p-BrC_6H_4NH	1	10	C_2H_5OH	194.5–195.5	$C_{22}H_{18}BrN_3O_2$	9.63	9.72
C_6H_5	C_6H_5	$(C_2H_5)_2N$	0.5	5	$(CH_3)_2CO$	133–134	$C_{20}H_{23}N_3O_2$	12.45	12.59
C_6H_5	C_6H_5	Morpholino	2	12	$(CH_3)_2CO$	153–155	$C_{20}H_{21}N_3O_3$	11.96	11.98
C_6H_5	C_6H_5	Piperidino	1	40	C_2H_5OH	167–168	$C_{21}H_{23}N_3O_2$	12.03	11.91

[a] Sirupy product crystallized in 2 months.

and Co., Inc. The compounds were subjected to the following tests: screening against *Escherichia coli in vitro*, screening against several species of protozoa *in vitro*, screening against coccidiosis in chickens, testing in rats for analgesic activity, testing in mice for effects on the nervous system, and testing for anti-inflammatory activity. While slight activity was shown in a number of instances, none of the compounds appeared to be sufficiently interesting to warrant detailed studies.

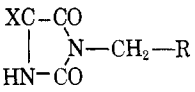
In the *E. coli in vitro* assay a paper disk was dipped into a solution of the test compound and placed on a Difco nutrient agar medium seeded with an 18-hr. *E. coli* culture. The presence of zones of inhibition was noted, the solution was successively diluted twofold, and the assay was repeated until no inhibition was observed. None of the compounds tested showed activity below concentrations of 0.5 mg./ml.

In the screening against protozoa the compounds were assayed against *Endamoeba histolytica*, *Trichomonas foetus*, and *Histomonas meleagridis in vitro* by essentially the procedure described by Cuckler and coworkers.[5] All compounds were inactive at concentrations of 100 γ/ml.

(5) A. C. Cuckler, A. B. Kupfenberg, and N. Milhaud, *Antibiot. Chemotherapy*, **5**, 540 (1955).

TABLE III

N-3-AMINOMETHYL DERIVATIVES OF SOME SPIROHYDANTOINS



X	R	Reflux time, hr.	Yield, %	Recrystn. solvent	M.p., °C.	Formula	—Nitrogen, %— Calcd.	Found
$-(CH_2)_4-$	C_5H_5NH[a]	0.5	36	C_6H_6	147–148	$C_{14}H_{17}N_3O_2$	16.21	16.12
$-(CH_2)_5-$	C_5H_5NH[a]	0.5	90	$(CH_3)_2CO$	188.5–189.0	$C_{15}H_{19}N_3O_2$	15.37	15.19
$-(CH_2)_5-$	p-$CH_3C_6H_4NH$[a]	0.5	71	Dioxane–petr. ether	202–203	$C_{16}H_{21}N_3O_2$	14.62	14.59
$-(CH_2)_5-$	Morpholino	1	80	Dioxane	182–183[b]	$C_{13}H_{21}N_3O_3$	...	...
$-(CH_2)_5-$	Piperidino[a]	0.5	60	Dioxane–petr. ether	189–191[c]	$C_{14}H_{23}N_3O_2$	...	...
$-CH_2CH_2CH(CH_3)CH_2CH_2-$	C_5H_5NH[a]	0.5	86	$(CH_3)_2CO$	220–221	$C_{16}H_{21}N_3O_2$	14.62	14.72
$-CH_2CH_2CH(CH_3)CH_2CH_2-$	p-$CH_3C_6H_4NH$[a]	0.5	72	$(CH_3)_2CO$	208 dec.	$C_{17}H_{23}N_3O_2$	13.94	13.98
$-CH_2CH_2CH(CH_3)CH_2CH_2-$	Morpholino	4	91	C_2H_5OH	186.5–188.0	$C_{14}H_{23}N_3O_3$	14.94	14.90
$-CH_2CH_2CH(CH_3)CH_2CH_2-$	Piperidino	4	83	C_2H_5OH	189–191	$C_{15}H_{25}N_3O_2$	15.04	15.10
$-(CH_2)_5-$	C_5H_5NH	4	73	C_6H_6–C_6H_{14}	167.5–168.5	$C_{16}H_{21}N_3O_2$	14.62	14.43
$-(CH_2)_5-$	p-$CH_3C_6H_4NH$	4	68	C_6H_6–C_6H_{14}	162–163.5	$C_{17}H_{23}N_3O_2$	13.94	14.01
$-(CH_2)_5-$	Morpholino	4	79	C_6H_6–C_6H_{14}	160.5–162.0	$C_{14}H_{23}N_3O_3$	14.93	15.03
$-(CH_2)_5-$	Piperidino	4	60	C_6H_6–C_6H_{14}	166–167.5	$C_{15}H_{25}N_3O_2$	15.04	15.09
(−)-$CH_2CH(CH_3)CH_2CH_2CHCH(CH_3)_2$ |	C_5H_5NH	2	90	C_6H_6–$HCON(CH_3)_2$	236–237	$C_{19}H_{27}N_3O_2$	12.76	12.79
(−)-$CH_2CH(CH_3)CH_2CH_2CHCH(CH_3)_2$ |	p-$CH_3C_6H_4NH$	2	90	C_6H_6–$HCON(CH_3)_2$	227.5–228.5	$C_{20}H_{29}N_3O_2$	12.24	12.36
(−)-$CH_2CH(CH_3)CH_2CH_2CHCH(CH_3)_2$ |	Morpholino	2	70	$(CH_3)_2CO$–H_2O	137–138	$C_{17}H_{29}N_3O_3$	12.99	12.84
(−)-$CH_2CH(CH_3)CH_2CH_2CHCH(CH_3)_2$ |	Piperidino	2	54	C_2H_5OH–H_2O	155–156	$C_{18}H_{31}N_3O_2$	13.07	12.98
	C_5H_5NH	1	89	$(CH_3)_2CO$–$HCON(CH_3)_2$	208–209.5	$C_{19}H_{19}N_3O_2$	13.08	12.89
	p-$CH_3C_6H_4NH$	1	97	$(CH_3)_2CO$–$HCON(CH_3)_2$	220–222	$C_{20}H_{21}N_3O_2$	12.53	12.73
	Morpholino	1	85	$(CH_3)_2CO$–$HCON(CH_3)_2$	192–193	$C_{17}H_{21}N_3O_3$	13.33	13.34
	Piperidino	1	79	$(CH_3)_2CO$–$HCON(CH_3)_2$	139.5–140.5	$C_{18}H_{23}N_3O_2$	13.41	13.21

[a] The product crystallized from the reaction mixture 3–5 min. after refluxing was started. [b] Lit.[2] m.p. 181–182°. [c] Lit.[2] m.p. 191–193°.

In the coccidiosis test the compounds were assayed against coccidia by the procedure described by Cuckler.[6]

In the test for effects on the nervous system mice were dosed intraperitoneally and the following observations were made visually: mortality, pupil dilatation, depression of exploratory activity, ptosis, ataxia, righting reflex loss, 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.*,[7] and Torchiana, *et al.*[8] In the case of N-3-anilinomethyl-5,5-diphenylhydantoin and N-3-anilinomethyl-5-methyl-5-phenylhydantoin, the ED_{50} was estimated at 50–75 mg./kg. in mice dosed intraperitoneally 2 hr. before shocks.

In the rat test for analgesic activity, the method of D'Amour and Smith[9] was employed with the variation that the foot, rather than the tail of the rat, was used.

Antiinflammatory activity was determined by inhibition of granuloma formation in rats dosed orally, using the procedure described by Winter, *et al.*[10]

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

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

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

(9) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(10) C. A. Winter, E. A. Risley, and G. W. Nuss, *ibid.*, **141**, 369 (1963).

Experimental[11]

N-3-Aminomethyl Derivatives of 5,5-Dimethylhydantoin, 5,5-Disubstituted Hydantoins, and Spirohydantoins.—The appropriate 5,5-disubstituted hydantoin or spirohydantoin (0.05 mole) was dissolved in hot ethanol (20 ml. or more, depending upon the solubility of the hydantoin). 2-Tetralonespirohydantoin was dissolved in a mixture of ethanol and dimethylformamide. To this solution was added 0.051 mole of the amine dissolved in a small amount of ethanol, and 0.051 mole (4.13 g.) of 37% formaldehyde. The reaction mixture was refluxed 1 hr., filtered hot, then cooled to room temperature, usually overnight. Portions of the solvent were allowed to evaporate in a hood. The product was collected, washed with a small amount of cold, aqueous ethanol, dried, then recrystallized, generally from ethanol. In a few instances the product precipitated out of solution shortly after refluxing had begun. In such cases the reaction mixture was refluxed for 0.5 hr.

N,N,'-Bis(5,5-disubstituted 3-hydantoinylmethyl)piperazine.—A solution of 0.115 mole of the hydantoin (15 g. of 5,5-dimethylhydantoin, 29 g. of 5,5-diphenylhydantoin) and 0.05 mole (4.3 g.) of anhydrous piperazine in 100 ml. of ethanol (more in the case of 5,5-diphenylhydantoin) was placed in a flask equipped with a reflux condenser and a dropping funnel. After refluxing was started, 0.12 mole (12.5 ml.) of 37% formaldehyde was added dropwise, and the product began to crystallize out of the boiling solution. The reaction mixture was refluxed for 1 hr., the solution was evaporated almost to dryness and filtered, and the product was recrystallized from dimethylformamide.

(11) Nitrogen analyses are by the semimicro Kjeldahl method. Infrared spectra were obtained using the Perkin-Elmer Model 137B Infracord with sodium chloride plates and Nujol mull. Melting points were determined either in a liquid bath or by using a Mel-Temp apparatus and are corrected.

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

Anal. Calcd. for $C_{16}H_{28}N_6O_4$: 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°.[4]

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.

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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]

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