Mercury Derivatives of Allylhydantoins

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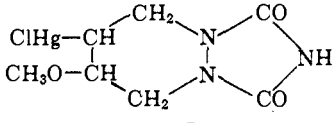
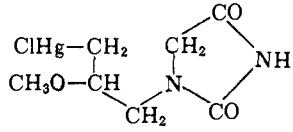
Several 1-, 3-, and 5-allylhydantoins were synthesized and mercurated. The diuretic potency of these mercurials was compared to that of chlormerodrin.

It was reported previously[1] that compounds of type I were found to be more potent, less toxic mercurial diuretics than chlormerodrin. In order to study variation of toxicity and diuretic effect with changes in chemical structure, a series of 1-, 3-, and 5-allylhydantoins were prepared and mercurated affording mercurial diuretics of the type shown in II. The present work describes the synthesis and diuretic potency of these compounds.



I



II

Methods of preparation of hydantoins are diverse and well known.[2] Following the method first described by Urech,[3] 2-amino-4-pentenoic acid[4] was dissolved in aqueous potassium cyanate solution and acidified with mineral acid to precipitate 2-allylhydantoic acid from its potassium salt. Cyclization of this acid to give 5-allylhydantoin[5] was accomplished by heating the acid in 25% hydrochloric acid solution.

Although N-allylglycine[6] readily furnished 3-allylhydantoic acid by the potassium cyanate method, ethyl N-allylglycinate[6] was a more

(1) R. L. Clarke and F. W. Gubitz, U. S. Patent 2,813,865, Nov. 19, 1957; *J. Org. Chem.*, **26**, 559 (1961).

(2) E. Ware, *Chem. Revs.*, **46**, 403 (1950).

(3) F. Urech, *Ann.*, **165**, 99 (1873).

(4) J. Fillman and N. Albertson, *J. Am. Chem. Soc.*, **70**, 171 (1948).

(5) R. Gaudry, L. Berlinguet, A. Langis and G. Paris, *Can. J. Chem.*, **34**, 502 (1956), obtained 5-allylhydantoin by treatment of 2-amino-4-pentenoic acid with potassium cyanate and concd. hydrochloric acid without isolating the intermediate 2-allylhydantoic acid reported here.

(6) R. Alpern and C. Weizmann, *J. Chem. Soc.*, **99**, 84 (1911).

readily available starting material and, upon treatment with nitrourea, afforded ethyl 3-allylhydantoate. The desired 1-allylhydantoin was obtained by cyclization of either 3-allylhydantoic acid or its ethyl ester by heating in 25% hydrochloric acid solution.

Bailey and Randolph[7] reported the preparation of 3-allylhydantoin by a devious procedure in which few experimental details were described. Direct alkylation of hydantoin with allyl bromide, however, furnished the 3-allyl derivative. Under these same conditions, 3-allyl-1-methylhydantoin was prepared from 1-methylhydantoin,[8] and 3-allyl-5,5-dimethylhydantoin was derived from 5,5-dimethylhydantoin. Similarly, with methyl iodide, 1-allyl-3-methylhydantoin, and 5-allyl-3-methylhydantoin were obtained from the corresponding 1- and 5-allylhydantoins.

The desired mercurials were made by methoxymercuration of the allylhydantoins using standard conditions, *i.e.*, mixing a methanolic solution of mercuric acetate with a methanolic solution of the unsaturated material followed by the addition of a catalytic amount of concentrated nitric acid. Conversion of the resulting acetoxymercuri compounds to the chloromercuri derivatives was carried out by treatment of the former with aqueous sodium chloride. The final products were obtained as well formed, white, crystalline solids with the exception of 1-(3-chloromercuri-2-methoxy-1-propyl)-3-methylhydantoin (compound No. 2, Table I) and 3-(3-chloromercuri-2-methoxy-1-propyl)-1-methylhydantoin (compound No. 4, Table I) which were isolated as colorless oils. In order to obtain crystalline solids, it was necessary to purify these two compounds by chromatography on silica gel.

The mercurials were administered orally as suspensions to unanesthetized female dogs weighing 6–9 kg. The medications were made up in 25 ml. of 0.5% gum tragacanth, and washed down with 25 ml. of 0.85% sodium chloride solution. The diuretic response was calculated in terms of ml./kg./6 hr., and chloride (as sodium chloride) in terms of mg./kg./6 hr. The chlorides were determined using the titrimetric method of Schales and Schales.[9] Acute oral toxicities were determined in white mice after administration of the compounds as suspensions in 1% gum tragacanth. The LD_{50} values and their

(7) J. Bailey and C. Randolph, *Ber.*, **41**, 2494 (1908).
(8) E. Miller and W. Robson, *J. Chem. Soc.*, 1910 (1938).
(9) O. Schales and S. S. Schales, *J. Biol. Chem.*, **140**, 879 (1941).

standard errors were estimated by the method of Miller and Tainter.[10] Emesis studies were carried out simultaneously with the routine testing of the diuretic efficacy of the drugs. A comparison of these data with those obtained for chlormerodrin is presented in Table I.

Experimental[11]

2-Allylhydantoic Acid.—A mixture of 23 g. (0.2 mole) of 2-amino-4-pentenoic acid,[4] 20.3 g. (0.25 mole) of potassium cyanate, and 100 ml. of water was heated for 10–15 min. on the steam-bath until a homogeneous solution was obtained. The solution was cooled, filtered to remove suspended impurities, and strongly acidified with concentrated hydrochloric acid. The precipitated product was collected and recrystallized once from water to give 26.5 g. (84% yield) of colorless platelets, m.p. 154–156° (gas evolution).

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.56, H, 6.37: N, 17.72, neut. equiv., 158. Found: C, 46.1, H, 6.6, N, 17.6, neut. equiv., 159.

5-Allylhydantoin.[5]—A mixture of 16 g. (0.1 mole) of 2-allylhydantoic acid and 20 ml. of 25% hydrochloric acid was heated on the steam bath for 2 hr. When the solution was cooled, the product crystallized as slender colorless needles. One recrystallization from chloroform afforded 8.4 g. (60% yield) of colorless blades, m.p. 105–107°, lit.[5] m.p. 104°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42, H, 5.75; N, 20.00. Found: C, 51.2, H, 5.8, N, 19.8.

5-(3-Chloromercuri-2-methoxy-1-propyl)-hydantoin.—A solution of 4.2 g. (0.03 mole) of 5-allylhydantoin in 150 ml. of hot methanol was added to a solution of 9.6 g. (0.03 mole) of mercuric acetate in 150 ml. of methanol. After 3 drops of concd. nitric acid had been added, the solution was placed in the refrigerator for 3 days. The acetoxymercuri compound separated as a chalky, white suspension which could not be collected by ordinary filtration procedures. It was, however, separated by centrifugation at 2500 r.p.m. The solid was dissolved in dilute acetic acid, and the solution treated with 3.5 g. (0.06 mole) of sodium chloride in 50 ml. of water. When the solution was cooled, it deposited 9.8 g., m.p. 165–167° dec. (uncorr.) of white microneedles. After one recrystallization from a solution of 50 ml. of dimethylformamide and 50 ml. of water, the chloromercuri compound weighed 8.7 g. (71% yield), m.p. 165-166° dec.

Anal. Calcd. for $C_7H_{11}ClHgN_2O_3$: C, 20.64; H, 2.72; N, 6.88; Hg, 49.26. Found: C, 20.6; H, 2.7; N, 6.9; Hg, 48.3.

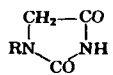
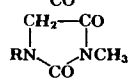
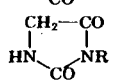
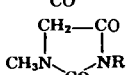
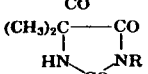
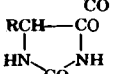
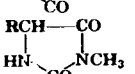
3-Allylhydantoic Acid.—N-Allylglycine[6] (m.p. 156–158°, uncorr.) (9.4 g., 0.08 mole) was dissolved in a solution containing 8.2 g. (0.1 mole) of potassium cyanate in 25 ml. of water. Acidification of this solution with concd. hydrochloric acid caused deposition of 9.3 g. of crude product. One recrystallization from 2-propanol gave 5.3 g. (41% yield) of colorless prisms, m.p. 105–110° dec.

(10) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

(11) All melting points are corrected unless otherwise noted. All boiling points are uncorrected. Analyses were carried out by the Institute's microanalytical staff under the direction of Mr. K. D. Fleischer.

TABLE I

DOSE, 4 MG. HG/KG.

	Structure R = —$CH_2CH(OCH_3)CH_2HgCl$	No. of dogs	Mean total (6 hr.) post medication response: Urine excretion: Ml./kg.	Urine excretion: Relative potency chlormerodrin = 1	Chloride excretion (NaCl): Mg./kg.	Chloride excretion (NaCl): Relative potency chlormerodrin = 1	Toxicity: Emesis, %	Toxicity: Acute LD_{50}[a] mg. Hg/kg. (24 hr.)
1		5	18 ± 6	1.6	195	1.5	40	779 ± 222
2		5	6 ± 2	0.5	88	0.7	60	298[b]
3		5	15 ± 4	1.4	225	1.7	100	358 ± 64
4		5	5 ± 2	0.5	64	0.5	60	264 ± 44
5		5	11 ± 4	1.0	171	1.3	100	346[b]
6		10	8 ± 1	0.7	93	0.7	30	3320 ± 354
7		5	10 ± 1	0.9	156	1.2	40	715 ± 188
8	Chlormerodrin, $H_2NCONHR$	10	11 ± 2		129		60	306 ± 38

[a] In mice. [b] ALD_{50}.

Anal. Calcd. for $C_6H_{10}N_2O_3$: N, 17.72; neut. equiv., 158. Found: N, 17.8, neut. equiv., 161.

1-Allylhydantoin.—Ethyl N-allylglycinate[6] (b.p. 77–80° (15 mm.), $n^{25}D$ 1.4350) (48.3 g., 0.34 mole) was allowed to react in 95% ethanol with 36.8 g. (0.34 mole) of nitrourea at 50–70°. After gas evolution had ceased, the solvent was removed by warming *in vacuo*. The residue, containing crude ethyl 3-allylhydantoate, was heated on the steam-bath for 2 hr. with 75 ml. of 25% hydrochloric acid. The solution was concentrated by warming *in vacuo*, and the residue treated with boiling 1-butanol. The mixture was filtered to remove suspended impurities, and the filtrate chilled to give 35.3 g., m.p. 91–96° (uncorr.) of crude 1-allylhydantoin. One recrystallization from 1-butanol afforded 30.6 g. (65%) of colorless blades, m.p. 95–98°.

Alternately, 1-allylhydantoin was obtained by suspending 26.5 g. (0.17 mole) of 3-allylhydantoic acid in 50 ml. of 25% hydrochloric acid, and heating at about 90° for 2 hr. Crude product, left on removal of water and hydrochloric acid, was recrystallized once from 1-butanol. There was obtained 14.3 g. (61%) of colorless blades, m.p. 96–98°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 20.00. Found: C, 51.4; H, 6.0; N, 19.8.

1-(3-Chloromercuri-2-methoxy-1-propyl)-hydantoin.—A solution containing 4.2 g. (0.03 mole) of 1-allylhydantoin in 100 ml. of methanol was mixed with 9.6 g. (0.03 mole) of mercuric acetate in 50 ml. of hot methanol, and the resulting solution treated with 2 drops of concd. nitric acid. On standing at 25°, solid 1-(3-acetoxymercuri-2-methoxy-1-propyl)-hydantoin separated. An additional 50 ml. of methanol was added to dissolve the precipitate. Addition of 3 g. of sodium chloride in 10 ml. of water to the methanol solution caused precipitation of the chloromercuri compound. It was recrystallized once from water, and obtained as white blades (11.8 g., 96% yield), m.p. 154–158° dec.

Anal. Calcd. for $C_7H_{11}ClHgN_2O_3$: C, 20.64; H, 2.72; N, 6.88; Hg, 49.26. Found: C, 21.0; H, 2.6; N, 6.8; Hg, 49.5.

3-Allylhydantoin.[7]—Hydantoin (Eastman Organic Chemicals, m.p. 221–223°) (30 g., 0.3 mole) dissolved in a solution of 200 ml. of methanol and 50 ml. of water containing 28 g. (0.43 mole) of 86% potassium hydroxide, was treated with 60.5 g. (0.5 mole) of allyl bromide. Heat was evolved, and potassium bromide precipitated. After 1 hr. at reflux, the mixture was cooled, filtered and the filtrate concentrated by warming *in vacuo*. The residue was treated with boiling ethyl acetate, with Darco G-60 added, and filtered to remove suspended salts and yellow color. The product separated from the cooled filtrate in long, colorless needles. It was used without further purification, m.p. 77–80° (uncorr.); reported,[7] m.p. 78°.

3-(3-Chloromercuri-2-methoxy-1-propyl)-hydantoin.—A solution of 5.6 g. (0.04 mole) of 3-allylhydantoin in 150 ml. of methanol was mixed with a hot solution of 12.8 g. (0.04 mole) of mercuric acetate in 50 ml. of methanol. Two drops of concd. nitric acid catalyst was added. A test for mercuric ion using 2 *N* sodium hydroxide solution indicated that methoxymercuration was complete in a few minutes. A solution containing 4.6 g. (0.08 mole) of sodium chloride was added, the solution was concentrated to one-half its volume by warming on the steam-

bath, cooled, and the crude chloromercuri compound (14.3 g., m.p. 143–145°, uncorr.) collected and dissolved in 115 ml. of hot (90°) water containing 1 g. of sodium chloride. On cooling, the desired product was obtained as white, massive prisms, 12 g. (74% yield), m.p. 144–146°.

Anal. Calcd. for $C_7H_{11}ClHgN_2O_3$: C, 20.64; H, 2.72; Hg, 49.26. Found: C, 20.5; H, 3.4; Hg, 49.0.

3-Allyl-1-methylhydantoin.—Fifty-one grams (0.5 mole) of 1-methylhydantoin[8] (m.p. 158–160°, uncorr.) was dissolved in 500 ml. of boiling methanol containing 35 g. (0.65 mole) of sodium methoxide (Matheson, Coleman and Bell). The boiling solution was treated with 72.6 g. (0.6 mole) of allyl bromide and refluxed for 3 hr. After removal of methanol by warming *in vacuo*, the residue was treated with water, and the product separated from this mixture by extraction with ether. Distillation at 68–71° (0.08 mm.) of the oil left on evaporation of the ether furnished 35.5 g. (47% yield) of colorless oil, $n^{25}D$ 1.4963.

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.6; H, 6.7; N, 18.0.

3-(3-Chloromercuri-2-methoxy-1-propyl)-1-methylhydantoin.—A solution containing 7.7 g. (0.05 mole) of 3-allyl-1-methylhydantoin in 25 ml. of methanol was mixed with 10.0 g. (0.05 mole) of mercuric acetate in 50 ml. of hot methanol, and the resulting solution left to stand at 25° for 18 hr. To this solution was added 5.8 g. (0.1 mole) of sodium chloride in 25 ml. of water. The methanol and water were removed by warming *in vacuo*. The residual colorless oil was dissolved in 150 ml. of methylene dichloride, dried over Drierite, filtered, and poured onto a chromatographic column containing 1000 g. of silica gel.[12] The column was eluted with 15 l. of absolute ether to remove a mercury-free, colorless oil. Elution with 1:99 acetone–ether, and 2:98 acetone–ether gave mercury-containing oil which failed to crystallize. This oil was chromatographed again under similar conditions to give a colorless oil which solidified. Two recrystallizations from absolute alcohol afforded 4.6 g. (22%) of the product as white needles, m.p. 86–87°.

Anal. Calcd. for $C_8H_{13}ClHgN_2O_3$: C, 22.81; H, 3.11; N, 6.65; Hg, 47.62. Found: C, 22.9; H, 2.9; N, 6.6; Hg, 47.7.

3-Allyl-5,5-dimethylhydantoin.—Commercial (Matheson, Coleman and Bell) 5,5-dimethylhydantoin (m.p. 176–178°) was treated with allyl bromide (25.4 g., 0.21 mole) in 500 ml. of methanol containing 4.6 g. (0.2 mole) of dissolved sodium. The mixture was refluxed for 6 hr., the solvent was removed by warming *in vacuo*, and the residue extracted with several portions of boiling ether. The combined ether extracts were heated to boiling, and diluted with pentane to the point of permanent cloudiness. When this solution was cooled, 3-allyl-5,5-dimethylhydantoin precipitated as colorless blades. Two recrystallizations from ether–pentane gave 8.1 g. (24% yield), m.p. 61–70°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12: H, 7.19; N, 16.66. Found: C, 57.1; H, 7.4; N, 16.6.

3-(3-Chloromercuri-2-methoxy-1-propyl)-5,5-dimethylhydantoin.—Solutions containing 4.8 g. (0.03 mole) of 3-allyl-5,5-dimethylhydantoin in 50 ml. of methanol, and 9.6 g. (0.03 mole) of mercuric acetate in 50 ml. of hot methanol were

(12) The silica gel was obtained from W. R. Grace and Co., Davidson Chemical Division, Baltimore, Md.

mixed and treated with 3 drops of concd. nitric acid. After refluxing the solution for 15 min., a test for ionic mercury using 2 *N* sodium hydroxide solution indicated that mercuration was complete. A solution containing 5.8 g. (0.1 mole) of sodium chloride in 25 ml. of water was added, and the solvent was removed by warming *in vacuo*. The residual oil was dissolved in chloroform, the solution was washed with water, and the chloroform was evaporated on the steam-bath to give a pale yellow oil. The oil was dissolved in ethyl acetate and chilled to give 3.6 g., m.p. 110–117° (uncorr.) of crude product. Two recrystallizations from ethyl acetate afforded 2.1 g. (17% yield, m.p. 114–116°) of white microprisms.

Anal. Calcd. for $C_5H_{15}ClHgN_2O_3$: N, 6.44; Hg, 46.08; Found: N, 6.4; Hg, 45.5.

1-Allyl-3-methylhydantoin.—Calcined potassium carbonate (27.6 g., 0.2 mole) was ground to a powder and suspended in a solution containing 14.0 g. (0.1 mole) of 1-allylhydantoin in 500 ml. of dry acetone. After the mixture had been refluxed for 1 hr., 28.4 g. (0.2 mole) of methyl iodide was added, and refluxing was continued for 12 hr. The mixture was filtered, and the filtrate concentrated by warming *in vacuo* to a yellow oily residue. The crude product was separated from inorganic salts by extraction with ether. The residue after evaporation of the ether was distilled at 77–78° (0.1 mm.) to give a yellow oil which was redistilled, b.p. 71–73° (0.08 mm.). There was obtained 12.9 g. (84% yield) of 1-allyl-3-methylhydantoin as a colorless oil, $n^{25}D$ 1.4970.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.7; H, 6.4; N, 18.1.

1-(3-Chloromercuri-2-methoxy-1-propyl)-3-methylhydantoin.—Mercuric acetate (4.6 g., 0.023 mole) was dissolved in 50 ml. of hot methanol. To this solution was added 3.5 g. (0.023 mole) of 1-allyl-3-methylhydantoin. The solution was left at 25° for 16 hr., and then was treated with 3.0 g. (0.05 mole) of sodium chloride in 10 ml. of water. Evaporation of the solvent by heating *in vacuo* left an oily residue which was dissolved in chloroform. The chloroform solution was washed with water, dried and concentrated to a colorless oil. A 0.5-g. portion of the oil was dissolved in 25 ml. of methylene dichloride, and the solution poured onto a chromatographic column containing 50 g. of silica gel.[12] Elution of the column with 500 ml. of absolute ether gave a colorless mercury-free oil. Elution with 1:4 acetone–ether gave a colorless oil containing mercury. Since this material failed to crystallize, it was chromatographed again, the column being eluted first with ether, then with 2:98 acetone–ether. The latter solvent mixture eluted the pure product as an oil which solidified. When a few crystals of this solid were introduced as seed into the main batch of oil, it also solidified. After two recrystallizations from methanol, the product was obtained as white platelets, 1.9 g. (20% yield), m.p. 147–149° dec.

Anal. Calcd. for $C_8H_{13}ClHgN_2O_3$: C, 22.81; H, 3.11; Hg, 47.62. Found: C, 23.2; H, 3.0; Hg, 46.9.

5-Allyl-3-methylhydantoin.—Calcined potassium carbonate (27.6 g., 0.2 mole) was finely powdered and suspended in a solution of 14.0 g. (0.1 mole) of 5-allylhydantoin in 250 ml. of dry acetone. The mixture was refluxed for 1 hr., treated with 28.4 g. (0.2 mole) of methyl iodide, and continued at reflux for an additional 12 hr. Filtration removed insoluble by-products, and evaporation by warming

in vacuo left an oily yellow residue. The residue was extracted with 250 ml. of boiling absolute ether, and the extract was treated with Darco G-60, filtered, and chilled to give colorless needles of 5-allyl-3-methylhydantoin. Recrystallization once from absolute ether, and once from ether–acetone gave 11.0 g. (71% yield) m.p. 90–92°.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 53.53; H, 6.54; N, 11.87. Found: C, 54.2; H, 6.6; N, 18.1.

5-(3-Chloromercuri-2-methoxy-1-propyl)-3-methylhydantoin.—Solutions of 5-allyl-3-methylhydantoin (3.5 g., 0.023 mole) in 75 ml. of hot methanol, and 4.6 g. (0.023 mole) of mercuric acetate in 75 ml. of hot methanol were mixed, and treated with 2 drops of concd. nitric acid. After 5 min. the clear solution was treated with 5.8 g. (0.1 mole) of sodium chloride in 25 ml. of water. The product, obtained from the cooled solution as white needles, was recrystallized once from aqueous methanol to give 5.2 g. (55% yield), m.p. 142–154°.

Anal. Calcd. for $C_8H_{13}ClHgN_2O_3$: C, 22.81; H, 3.11; N, 6.65; Hg, 47.62. Found: C, 22.6; H, 3.2; N, 6.5; Hg, 46.4.

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Potential Uricosuric Agents Derived from 1,3-Diphenylbarbituric Acid

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1,3-Diphenylbarbituric acids with 5-acyl, carbamoyl and alkyl substituents have been prepared and tested for possible uricosuric activity as indicated by their ability to cause retention of phenol red in the circulation of the rat. The compounds were 67 to 128% as active as phenylbutazone. The synthesis of 1,3-diphenylbarbituric acid has been investigated and a by-product, 5-(α-carbethoxyacetyl)-1,3-diphenylbarbituric acid, characterized.

Compounds containing an easily replaceable hydrogen as part of a β-dicarbonyl system have divergent biological actions. These actions include antibacterial (*e.g.*, tetracyclines), anthelmintic (*e.g.*,