are presented in Table III. Compound **14** displayed no activity and some evidence of toxicity at the 75 mg/kg dose level. This result is noteworthy since the parent compound, 5,8-deazaaminopterin (**9**), was shown to be toxic to mice at very low dosage levels.[15] This implies that enzymatic deformylation of **9** does not occur appreciably under these test conditions. Compound **19**, on the other hand, showed modest activity using three different regimens. Since these results were obtained using ten times more tumor cells in the inoculum than in the protocol employed by the National Cancer Institute, additional testing of **19** appears warranted.

Experimental Section

All analytical samples were dried in vacuo at 100 °C (P_2O_5) and gave combustion values for C, H, and N within ±0.4% of the theoretical values. Melting points were determined with a Mel-Temp apparatus and are uncorrected. All target compounds were free of significant impurities on TLC (Gelman SAF). NMR spectra were determined with a Varian T-60 spectrometer and the chemical shifts deemed critical to structural assignments are presented in parts per million (δ) downfield from Me_4Si as an internal standard. Diethyl 4-aminobenzoyl-L-glutamate was prepared according to the literature method[19] while diethyl 4-aminobenzoyl-L-aspartate was obtained according to the procedure of Davoll and Johnson.[10]

Method A (2, 4, 6, 8, 10, and 12). Each of these diethyl esters was prepared by the reductive condensation of the appropriately substituted 6-cyanoquinazoline with diethyl 4-aminobenzoyl-L-glutamate or diethyl 4-aminobenzoyl-L-aspartate in the presence of Raney nickel as originally described by Davoll and Johnson.[10] However, in the case of **10** and **12** final purification was achieved by column chromatography on silica gel using benzene–MeOH as the eluent. Compound **8**, which was not purified in the earlier work, was obtained in the following manner. The hydrogenation solvent (70% HOAc) was removed in vacuo and the remaining syrup was dissolved in EtOAc. The solution was extracted with 5% Na_2CO_3, washed with H_2O, dried over $MgSO_4$, and then concentrated in vacuo. The resulting solid was suspended in benzene and isolated by filtration.

Method B (3, 5, 7, 9, 11, and 13). In each case the requisite diethyl ester was dissolved in EtOH and treated with excess 0.1 N NaOH. When the reaction was complete as adjudged by TLC, the solution was filtered (if necessary) and then neutralized to pH 4 with 0.5 N HCl. The precipitate was separated by filtration and washed with H_2O.

Method C (14 and 19). A mixture of 0.50 g (1.13 mmol) of 5,8-deazafolic acid (**16**)[11] and 10 mL of 98% formic acid was heated at 90 ± 5 °C for 1 h. The volatile material was removed in vacuo and the residue neutralized to pH 8.5 with 1 N NH_4OH. After filtration, the solution was acidified to pH 4 with 0.5 N HCl and the resulting precipitate was separated on a filter and washed repeatedly with H_2O. After drying in vacuo at 100 °C (P_2O_5), there was obtained 0.40 g (75%) of **19** as a light tan powder. The NMR spectrum (CF_3COOD) was consistent with the assigned structure: δ 8.37 (s, 1, NCHO). Compound **14** was prepared in similar fashion and had an NMR spectrum (CF_3COOD) which was virtually identical with that of **19**.

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Hydantoins as Antitumor Agents

Thomas R. Rodgers, Maurice P. LaMontagne, Anica Markovac,* and Arthur B. Ash

Ash Stevens Inc., Detroit, Michigan 48202.

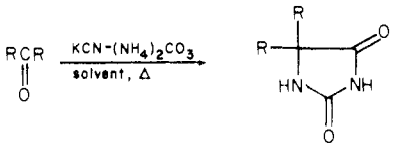
Received April 6, 1976

A series of 27 hydantoins was prepared and tested as antitumor agents. These were variously substituted in the 5 position but with special emphasis on the substituents (chloro, acetyl, chloroacetyl, and methyl) in the 1 and/or 3 positions. The most active compound was 5,5-bis(4-chlorophenyl)-1,3-dichlorohydantoin with a T/C value of 190% against P-388 lymphocytic leukemia in mice.

This paper reports the synthesis and antitumor testing of a series of hydantoins, variously substituted in the 5 position but with special emphasis on substituents (chloro, acetyl, chloroacetyl, and methyl) in the 1 and/or 3 positions.

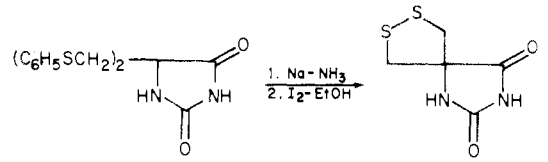
This work, in part, was prompted by the known activity of 1,3-dichloro-5,5-bis(4-chlorophenyl)hydantoin (**2**) against leukemia strain P-388.[1] Another stimulation to evaluate hydantoins further as antitumor agents was provided by the reported high concentrations of 5,5-diphenylhydantoin

Scheme I



1, 8, 10, 17, 20, 26

Scheme II



26 27

in brain tissue and its preferred location in primary brain tissue;[2] the major metabolite in man is 5-(4-hydroxyphenyl)-5-phenylhydantoin.[3]

In the present work, seven new analogues of 1 were prepared to pursue the lead represented by the 1,3-dichloro derivative **2**. A further objective of the program was to evaluate hydantoins bearing sulfur and oxygen heterocyclic groups in the 5 position; to this end, nine 5-(2-thienyl)- and three 5-(2-chlorothienyl)hydantoins were prepared together with four 5-(2-furyl)hydantoins. In addition, 5,5-spiro-(3,4-dithiacyclopentyl)hydantoin was prepared based on the potential antitumor activity of substituted 1,2-dithiacyclopentanes reported by European workers.[4]

Chemistry. The structure and physical data for the 27 compounds prepared in the course of this work are listed in Table I by structural category.

The precursor hydantoins (R′ = R″ = H) were prepared from the appropriate ketones by the Buchener–Berg procedure which has been reviewed by Ware[5] and modified by Henze,[6] Spurlock,[7] and Abshire and Berlinguet[8] (Scheme I).

5,5-Bis(4-chlorophenyl)hydantoin (1)[9] and 5,5-bis(4-trifluoromethylphenyl)hydantoin (8) were prepared with DMF as solvent (replacing ethanol) at 135–145 °C (autoclave)[3] in 85 and 75% yields, respectively.

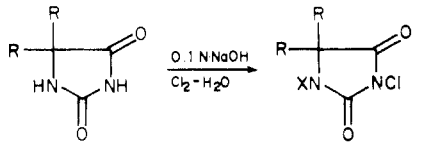
5,5-Bis(2-thienyl)hydantoin (**20**) was synthesized in 25% yield by the same procedure, except that urea was required to raise the conversion above 5% or so. 5-Methyl-5-(2-thienyl)hydantoin (**10**) was reported by Spurlock[7] and 5-methyl-5-(2-chlorothienyl)hydantoin (**17**) was prepared by the same procedure in yields of 53 and 84%, respectively. 5-(2-Furyl)-5-methylhydantoin (**22**) was prepared as described by Abshire and Berlinguet[8] in 67% yield.

5,5-Bis(benzylthiomethyl)hydantoin (**26**) was prepared recently (1970) by Shen and Wolford[10] from 1,3-bis(benzylthio)acetone.[11] Reduction of **26** with sodium and liquid ammonia gave crude 5,5-bis(thiomethyl)hydantoin (65%) which was treated with iodine in ethanol to give 5,5-spiro(3,4-dithiacyclopentyl)hydantoin (**27**) (40%) (Scheme II).

Active chlorine substituents were placed in the 5 or 3,5 positions of hydantoins 1, 8, 10, 17, 20, and 22 by dissolving the compounds in a 2–10% excess of 0.1 N NaOH, followed by the addition of stoichiometric amounts of saturated chlorine water (titrated before use) (Scheme III).

In the case of hydantoins 1, 8, 10, and 17, the dichloro derivatives **2**, **9**, **15**, and **19**, respectively, precipitated directly from solution. The monochloro derivative **14** was prepared from **10** by using but 1 equiv of chlorine water. However, in the case of hydantoins **20** and **22**, the monochloro derivatives **21** and **25** precipitated from solution;

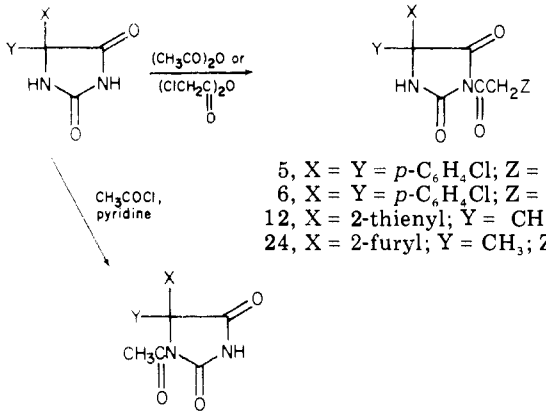
Scheme III



1, 2, X = Cl
8, 9, X = Cl
10, 14, X = H
10, 15, X = Cl

17, 19, X = Cl
20, 21, X = H
22, 25, X = H

Scheme IV



5, X = Y = p-C_6H_4Cl; Z = H
6, X = Y = p-C_6H_4Cl; Z = Cl
12, X = 2-thienyl; Y = CH_3; Z = Cl
24, X = 2-furyl; Y = CH_3; Z = Cl

3, X = Y = p-C_6H_4Cl
11, X = 2-thienyl; Y = CH_3
18, X = 5-chloro-2-thienyl; Y = CH_3
23, X = 2-furyl; Y = CH_3

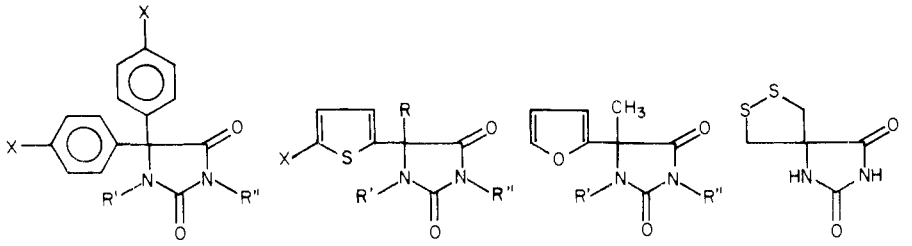
attempts to prepare the dichloro analogues of **20** and **22** (excess base and chlorine) were unsuccessful. Yields in all cases were fair to good (Table I). The assignment of the chloro atom to the 3 position rather than the 1 position is based on the work of Corral and Orazi.[12]

The 1-acetyl derivatives **3**, **11**, **18**, and **23** were obtained in 50–60% yields by refluxing **1**, **10**, **17**, and **22**, respectively, in pyridine with 1 equiv of acetyl chloride for 1 h (Scheme IV). The 3-acetyl derivative **5** and the three 3-chloroacetyl derivatives **6**, **12**, and **24** were prepared by treating the hydantoins with acetic anhydride or chloroacetic anhydride (Scheme IV). The positions of the acetyl and chloroacetyl substituents were assigned based on the NMR chemical shifts of the N_1 and N_3 protons.[13] The observed acetylation at the N_3 position with acetic anhydride neat is consistent with the results obtained by Salmon and Kozlowski[14] in the 5,5-dimethylhydantoin series. To further document the position of acetylation with each reagent, we subjected 5,5-dimethylhydantoin to acetylation with acetic anhydride (neat) and with acetyl chloride in pyridine. With acetic anhydride, we obtained the known N_3-acetyl derivative and, with acetyl chloride in pyridine, we obtained the known N_1-acetyl derivative.

In recording the NMR spectra of the N_1-acylated compounds, we experienced difficulty in observing the signal for the N_3 proton. In most cases, it appeared as a very broad absorption between ca. δ 4 and 6. A similar pattern was observed by Corral and Orazi[13] upon addition of a small amount of sodium acetate to their NMR samples. We found, however, that the addition of a small amount of dry hydrogen chloride to the NMR sample gave rise to a sharp signal for the N_3 proton with concomitant disappearance of the broad signal at δ 4–6.

The 1-acetyl-3-chloro derivatives **4** and **12** were synthesized in 53% yield by dissolving the 1-acetylhydantoins **3** and **11** in water containing 1 equiv of sodium carbonate and adding 1 equiv of saturated chlorine water.

Table I. Structure and Physical Data



I II III IV

No.	X	R	R'	R''	Mp, °C (solvent)	Yield, %	Formula	Analyses[a]
					Structure I			
1	Cl		H	H	315-317[b] (EtOH-acetone)	85		
2	Cl		Cl	Cl	229-230 ($CHCl_3$-CCl_4)	60	$C_{15}H_8Cl_4N_2O_2$	Cl
3	Cl		$C(O)CH_3$	H	256-258 (CH_3CN)	60	$C_{17}H_{12}Cl_2N_2O_3$	
4	Cl		$C(O)CH_3$	Cl	170-172 (CH_3OH)	46	$C_{17}H_{11}Cl_3N_2O_3$	Cl
5	Cl		H	$C(O)CH_3$	181-182 (CH_3CN)	35	$C_{17}H_{12}Cl_2N_2O_3$	Cl
6	Cl		H	$C(O)CH_2Cl$	240-243 ($CHCl_3$-petr ether)	36	$C_{17}H_{11}Cl_3N_2O_2$	Cl
7	Cl		H	CH_3	248-250 (EtOH)	83	$C_{16}H_{12}Cl_2N_2O_2$	
8	CF_3		H	H	283-286 (CH_3CN)	58	$C_{17}H_{10}F_6N_2O_2$	
9	CF_3		Cl	Cl	142-143 ($CHCl_3$-CCl_4)	53	$C_{17}H_8Cl_2F_6N_2O_2$	Cl
					Structure II			
10	H	CH_3	H	H	133-134[c]	53		
11	H	CH_3	$C(O)CH_3$	H	163-164 (ether)	63	$C_{10}H_{10}N_2O_3S$	S
12	H	CH_3	H	$C(O)CH_2Cl$	128-133 (ether)	49	$C_{10}H_9ClN_2O_3S$	Cl
13	H	CH_3	$C(O)CH_3$	Cl	113-115 ($CHCl_3$-CCl_4)	53	$C_{10}H_9ClN_2O_3S$	Cl
14	H	CH_3	H	Cl	141-143	79	$C_8H_7ClN_2O_2S$	Cl
15	H	CH_3	Cl	Cl	100-103	55	$C_8H_6Cl_2N_2O_2S$	Cl
16	H	CH_3	H	CH_3	182-185 (ether)	90	$C_9H_{10}N_2O_2S$	
17	Cl	CH_3	H	H	181-183 (EtOH)	84	$C_8H_7ClN_2O_2S$	S
18	Cl	CH_3	$C(O)CH_3$	H	133-136 (ether)	53	$C_{10}H_9ClN_2O_3S$	S
19	Cl	CH_3	Cl	Cl	128-131	78	$C_8H_5Cl_3N_2O_2S$	Cl
20	H	2-Thienyl	H	H	216-219 (aqueous acetone)	25	$C_{11}H_8N_2O_2S_2$	S
21	H	2-Thienyl	H	Cl	148-151	61	$C_{11}H_7ClN_2O_2S_2$	Cl
					Structure III			
22			H	H	174-177[d]	67		
23			$C(O)CH_3$	H	172-175 (ether)	51	$C_{10}H_{10}N_2O_4$	
24			H	$C(O)CH_2Cl$	159-162 (ether)	42	$C_{10}H_9ClN_2O_4$	Cl
25			H	Cl	141-144	64	$C_8H_7ClN_2O_3$	Cl
					Structure IV			
26					178-181[e]	63		
27					241-244 (EtOH)	26	$C_5H_6N_2O_2S_2$	S

[a] Elements analyzed other than C, H, and N (all values were within 0.3%). [b] Lit.[9] mp 320 °C. [c] Lit.[7] mp 134-137 °C. [d] Lit.[8] mp 176-177 °C. [e] 5,5-Bis(benzylthiomethyl)hydantoin, lit.[11] mp 182-187 °C.

The 3-methyl derivatives **7** and **16** were prepared by refluxing the sodium salts of **1** and **10**, respectively, with 1 equiv of dimethyl sulfate. The products precipitated from the solution upon cooling in 90% yield.

Biological Data. The 27 compounds were screened for antitumor activity against L1210 lymphoid leukemia and P-388 lymphocytic leukemia in mice by the Drug Development Branch, National Cancer Institute.[15] A compound is considered active in these systems if the ratio of survival times for treated to control tumor-bearing mice (T/C) exceeds 125%. None of the compounds were active against L1210. Against P-388, only 5,5-bis(4-chlorophenyl)-1,3-dichlorohydantoin (**2**) was active; T/C was a maximum of 190% with good dose–response characteristics.[1] Unfortunately, none of the seven analogues of **2** displayed any significant antitumor activity. Additionally, compound **2** failed in a brain tumor test against P-388.

Experimental Section

Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR spectra were recorded on a Varian T-60A spectrometer using tetramethylsilane as an internal standard. The following procedures are typical of those used to prepare the compounds in Table I.

1-Acetyl-5,5-bis(4-chlorophenyl)hydantoin (3). To a solution of 5,5-bis(4-chlorophenyl)hydantoin (15 g, 4.7 mmol) in pyridine (50 mL) at 0–5 °C was added acetyl chloride (3.64 g, 4.7 mmol). The solution was heated at reflux for 0.75 h and allowed to set at room temperature overnight. The reaction mixture was poured into ice water and extracted with ether (twice). The ether layer was washed with water (twice), dried (K_2CO_3), and concentrated to dryness. The residue was dissolved in acetonitrile (45 mL) and diluted with water (10 mL). The crystals which formed were collected to yield the title compound (10.2 g, 69%): mp 256–258 °C; NMR (Me_2SO-d_6) δ 12.6 (s, 1 H), 7.5 (s, 8 H), 2.6 (s, 3 H).

3-Acetyl-5,5-bis(4-chlorophenyl)hydantoin (5). A solution of 5,5-bis(4-chlorophenyl)hydantoin (2.0 g, 6.3 mmol) in acetic anhydride (50 mL) was heated at reflux for 1 h. The excess acetic anhydride was removed under reduced pressure. The residual oil which crystallized on standing was recrystallized from acetonitrile to yield the title compound (0.75 g, 33%): mp 181–182 °C; NMR (Me_2SO-d_6) δ 10.2 (s, 1 H), 7.6 (s, 8 H), 2.6 (s, 3 H).

3-Chloroacetyl-5,5-bis(4-chlorophenyl)hydantoin (6). A mixture of 5,5-bis(4-chlorophenyl)hydantoin (5 g, 0.0156 mol) and chloroacetic anhydride (10 g) was stirred in an oil bath at 160 °C for 4 h. The clear solution was cooled to 30 °C and diluted with ether (100 mL). The insoluble starting material was filtered. To

the clear mother liquor, petroleum ether (100 mL, bp 30–60 °C) was added and the solution was refrigerated overnight. The solid was filtered and recrystallized from $CHCl_3$–petroleum ether to yield the title compound (2.4 g, 36%): mp 240–243 °C (with shrinking and darkening ~200 °C); NMR (DMF-d_7) δ 10.13 (s, 1 H), 7.63 (s, 8 H), 5.13 (s, 2 H).

3-Methyl-5,5-bis(4-chlorophenyl)hydantoin (7). 5,5-Bis-(4-chlorophenyl)hydantoin (6 g, 0.0187 mol) was suspended in a solution of sodium hydroxide (0.8 g, 0.02 mol) in water (80 mL) and stirred until a clear solution was obtained. Dimethyl sulfate (10 mL, 0.103 mol) was added to the above solution (with vigorous stirring). After 4 h, the solid product was filtered, washed with water, and recrystallized from ethanol to give 5.2 g (83%) of white crystals: mp 248–250 °C; NMR (Me_2SO-d_6) δ 10.05 (s, 1 H), 7.57 (s, 8 H), 3.03 (s, 3 H).

1,3-Dichloro-5-methyl-5-(2-thienyl)hydantoin (15). To a solution of **10** (4.0 g, 20.2 mmol) in 0.1 N NaOH (420 mL, 42.0 mmol) was added chlorine water (400 mL, 44.0 mmol). The precipitate was collected, dried, slurried with carbon tetrachloride (50 mL), and filtered to give 3.1 g (55%) of the title compound, mp 100–103 °C.

3,5-Dimethyl-5-(2-thienyl)hydantoin (16). Compound **10** (5.0 g, 25.5 mmol) and dimethyl sulfate (3.3 g, 26 mmol) were added to a sodium methoxide solution prepared from sodium (600 mg, 0.026 g-atom) and methanol (100 mL). The solution was refluxed for 2 h, cooled, and filtered to give the title compound (4.8 g, 90%), mp 182–185 °C.

5,5-Bis(2-thienyl)hydantoin (20). Di(2-thienyl) ketone (23.2 g, 0.12 mol) in dimethylformamide (120 mL), potassium cyanide (10 g, 0.15 mol) in water (24 mL), ammonium carbonate (46.1 g, 0.48 mol), and urea (10.8 g, 0.18 mol) were heated in an autoclave at 135 °C for 36 h. The reaction mixture was poured into water (600 mL) and acidified. The resulting solid was collected, slurried in 5% sodium hydroxide, and refiltered to give 14.5 g of recovered starting material. The basic mother liquor was charcoaled and acidified to give the title compound (7.96 g, 25%), mp 216–219 °C. The analytical sample was prepared by recrystallization from acetone–water. The melting point was unchanged.

5,5-Spiro(3,4-dithiacyclopentyl)hydantoin (27). 5,5-Bis-(benzylthiomethyl)hydantoin (**26**)[11] (12.0 g, 33.2 mmol) was dissolved in liquid ammonia (700 mL) at −70 °C. Sodium (3.20 g, 0.139 g-atom) was added in small pieces until the blue color remained. Excess sodium was destroyed with ammonium chloride and the mixture was evaporated to dryness. The residue was dissolved in water (150 mL) and acidified with concentrated hydrochloric acid (20 mL). The solution was extracted with benzene (once) and with ethyl acetate (four times). The combined ethyl acetate extract was dried (Na_2SO_4) and evaporated below 40 °C to give 4.1 g (65%) of crude the 5,5-bis(mercaptomethyl)hydantoin intermediate. This was dissolved in ethanol (350 mL) and added dropwise to 0.2 N aqueous iodine (250 mL). Excess iodine was destroyed ($Na_2S_2O_3$) and the solution was evaporated to ca. 100 mL. Upon cooling, the product crystallized. Recrystallization from ethanol gave the title compound (1.6 g, 40%), mp 241–244 °C dec.

Acknowledgment. Except for compounds **1–9**, the work reported herein was supported by Contract No. N01-CM-12314 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare. The helpful assistance and encouragement throughout the program of Dr. M. Benton Naff, the Project Officer, National Cancer Institute, was greatly appreciated.

References and Notes

(1) Compound **2** was tested some 15–20 years ago as NSC 23306 (C. L. Stevens and C. H. Chang, Wayne State University) and received limited clinical testing. Adverse characteristics of **2** were its very low solubility in water as well as its reactivity toward oxidizable vehicles. More recently (early 1970), the compound was retested as NSC 152498 and, as stated in the text, gave T/C values against P-388 lymphocytic leukemia as high as 190% with good dose–response characteristics.
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Antiallergic Agents. Xanthone-2,7-dicarboxylic Acid Derivatives

Winton D. Jones, Jr., William L. Albrecht,* Nancy L. Munro, and Kenneth T. Stewart

Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215. *Received September 1, 1976*

Xanthone-2,7-dicarboxylic acid (1), a known inhibitor of the rat passive cutaneous anaphylaxis (PCA) assay by the iv route, was found to lack oral activity. Conversion of 1 into bis(carboxamide) derivatives afforded orally active compounds.

An orally effective antiallergic agent possessing a mode of action similar to that of disodium cromoglycate[1,2] would be most welcome in the treatment of certain allergic conditons. Pfister et al.[3] reported that xanthone-2-carboxylic acid derivatives were effective in the rat passive cutaneous anaphylaxis (PCA) assay by the iv route and that 7-propyl and 7-propoxy substitution afforded orally active compounds. They reported that xanthone-2,7-dicarboxylic acid (1) was active by the iv route. We were interested in 1 as a potential antiallergic agent and ob-