Studies on Methylglyoxal Bis(guanylhydrazone)[1] Analogs. II. Structural Variations on Methylglyoxal Bis(guanylhydrazone)[2]

FRED BAIOCCHI, C. C. CHENG, W. J. HAGGERTY, JR., LELAND R. LEWIS, T. K. LIAO, WAYNE H. NYBERG, DARRELL E. O'BRIEN, AND EUGENE G. PODREBARAC

Midwest Research Institute, Kansas City 10, Missouri

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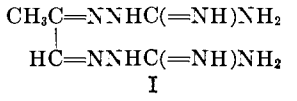
A study of analogs of methylglyoxal bis(guanylhydrazone) was conducted. Structural modifications of the parent compound, all containing the fundamental >C=N—NH—C(=NH)NH— moiety, are divided into 9 different classes. These modifications include the substitution of the methyl group, substitution of the hydrogen atom attached to the aldimine carbon, separation of the two guanidoimino and guanylhydrazonyl groups by various aliphatic moieties as well as by aromatic and alicyclic ring systems, substitution of the terminal hydrogen atoms of the guanylhydrazonyl portion, and monoguanylhydrazonyl derivatives. Several substituted benzophenone guanylhydrazones have shown confirmed activity in cell culture cytotoxicity tests.

The discovery that methylglyoxal bis(guanylhydrazone) (I) possesses the first significant remission in adult acute myelocytic leukemia[3] has initiated a systematic search in this field. A study in the homolog series of I has already been reported.[4]

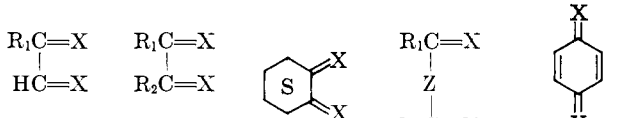


I

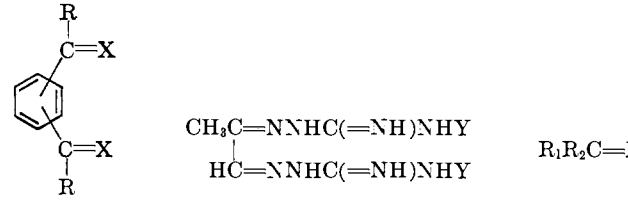
The present investigation involves the preparation of compounds with the fundamental >C=NNHC(=NH)NH— moiety in an attempt to correlate the structure–activity relationship of this still unclassified carcinostatic agent. Guanylhydrazones have been found to possess interesting biological properties: the *in vitro* growth inhibition of *Mycobacterium tuberculosis*,[5] effective against tuberculosis of warm-blooded animals[6]; prevention of the growth of mold in argicultural products[7]; bacteriostatic activities[8]; they affect the activity of monoamine oxidase, diamine oxidase and histidine decarboxylase[9]; and are effective in preventing the epidemic typhus infection in animals caused by rickettsiae.[10]

Compounds of the following types have been studied: 1. Substitution of the methyl group in I by an aryl group (II: R_1 = aryl). 2. Substitution of the hydrogen attached to the aldimine carbon in I by an alkyl group (III: R_1 = CH_3, R_2 = alkyl). 3. Substitution of the hydrogen attached to the aldimine carbon in I by an aryl group (III; R_1 = CH_3, R_2 = aryl). 4. Attachment of the two guanidoimino (=NNHC(=NH)NH_2) moieties to a cyclic ring (IV). 5. Separation of the two guanidoimino moieties by more than 2 carbon atoms (V). 6. Attachment of the two guanidoimino moieties to a quinoid ring system (VI). 7. Attachment of the two guanylhydrazonyl (>C=NNHC(=NH)NH_2) groups to an aromatic ring (VII: R = H or alkyl). 8. Substitution of the hydrogen atoms at the terminal nitrogen atoms in I by groups other than alkyl groups (VIII). 9. Compounds containing only one guanylhydrazonyl function (IX).

Substitution of the methyl group in I by alkyl groups, as well as the substitution of the hydrogen atoms at the terminal nitrogen atoms in I by alkyl groups has been studied.[4]



II III IV V VI



VII VIII IX

X = NNHC(=NH)NH_2
Y = NH_2, NO_2
Z = $(CH_2)_n$, —CH=CH—

The guanylhydrazone derivatives (see Table I) were prepared by the reaction of the aminoguanidine salts with the corresponding carbonyl compounds in an aqueous or aqueous–alcohol medium in the presence of a catalytic amount of acid. It is of interest to note that when more than one "true" carbonyl group was present in a molecule, the extent of condensation between the carbonyl groups and aminoguanidine did not depend on the amount of the latter used, but rather on the nature and solubility of its salt. For instance,

(1) The "Chemical Abstracts" name for this compound is 1,1′-[(methyl)-ethanediylidenedinitrilo]diguanidine. An acronym, "methyl GAG," was suggested by Dr. Emil Frei, III, of the National Cancer Institute.

(2) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service (Contract SA-43-ph-3025).

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TABLE I*

DISUBSTITUTED GUANYLHYDRAZONES [X = NNHC(=NH)NH$_2$]

Compounds	Formula	Recryst. solvents	Yield, %	M.p., °C. dec.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Ultraviolet absorption, mμ pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$	Activity[a] KB[b]	Activity[a] LE[c]
$C_6H_5C(=X)C(=X)H$	$C_{10}H_{11}N_8$[d,e]	f	82	237–239	36.8	5.5	33.3	37.0	5.6	33.3	288	36.0	236	31.6	—	—
$CH_3C(=X)C(=X)C_2H_5$	$C_7H_{16}N_8$[d,g]	h	82	289	26.2[i]	6.9	34.9	26.4	7.3	34.7	280	38.9			—	—
$CH_3C(=X)C(=X)(CH_2)_4CH_3$	$C_{10}H_{22}N_8$[b,e]	f	59	246–249	34.8[i]	7.6	32.4	35.0	7.4	32.4	280	35.2			±	—
$CH_3C(=X)C(=X)C_6H_5$	$C_{11}H_{16}N_8$[d]	f, j, k	67	>250	39.6	5.9	33.6	39.6	5.8	33.0	285	32.6			—	—
$(CH_2)_4C(=X)C(=X)$	$C_8H_{16}N_8$[b,e]	b	85	231	28.2	5.9	32.9	28.3	5.8	33.2	287	18.7	235	12.6	—	—
													325	13.3		
$CH_3C(=X)CH_2C(=X)CH_3$[e,l]	$C_7H_{16}N_8$[b,e]	f	18	205–207	26.2	5.9	34.9	25.9	6.3	35.2	230	14.8				
$HC(=X)(CH_2)_3C(=X)H$	$C_5H_{12}N_8$[b]	f, j, k	56	237–238	27.1	5.8	36.1	26.7	6.2	35.7	226	5.2			—	—
$HC(=X)CH_2C(=X)H$	$C_3H_8N_8$[b,e]	h, j, k	33	219–221	20.0	5.3	37.4	20.2	5.5	37.7	225	6.0			—	—
trans-$C_6H_5C(=X)CH=CHC(=X)C_6H_5$[e,l]	$C_{18}H_{20}N_8$[e,g]	b	50	270–271	51.4	6.0	26.6	51.9	5.5	26.2	300	26.4	362	41.2	±	—
$CH_3C(=X)(CH_2)_2C(=X)CH_3$[e,l,m]	$C_8H_{18}N_8$[e,g]	f	61	278	28.1	6.4	32.9	28.5	6.4	33.3					—	—
$C_6H_5CH=CHC(=X)CH=CHC_6H_5$[e,l]	$C_{18}H_{18}N_8$[d,e]	i	61	301	51.8	5.0	37.1	51.9	4.8	36.9	368	26.6	432	30.5	±	±
$C_6H_5CH(CH_3)CHC(=X)CH=CHC_6H_5$	$C_{20}H_{22}N_8$[d]	f	46	273–274	35.2	5.2	36.1	35.1	5.0	36.1	370	32.8	235	6.2	—	—
													430	21.6		
$C_6H_5N_2C(H)=C(OH)C(=X)CH=C(OH)C_6H_5$	$C_{18}H_{22}N_8O_2$[d,e]	i	70	257–260	26.6	5.0	34.0	26.6	5.1	34.3	355	34.2			—	—
$C_6H_5N_2CH=CH-C_6H_4-CH=CHC(=X)$	$C_{22}H_{24}N_8$[d,e]	i	12	287–289	39.8	5.0	34.0	39.6	4.9	34.0	283	41.9	233	9.0		
											372	31.0	314	10.9		
													430	45.0		
o-$C_6H_4(CH=X)_2$	$C_{10}H_{12}N_8$[e,g]	i	65	211–213	39.1	6.4	30.7	39.6	6.2	30.6	263	23.7				
											290	21.2				
											299	21.4				
p-$C_6H_4(CH=X)_2$[e,n]	$C_{10}H_{12}N_8$[d]		80	328–330	37.6	5.0	35.2	37.6	4.4	35.0	320	45.3	355	46.6	—	—
											321	19.7	235	14.9		
p-$C_6H_4(CH_2CH=X)_2$	$C_{12}H_{16}N_8$[e,g]	i	83	359–360	40.4	5.9	31.5	40.5	6.4	31.3	300	30.6	335	28.5	—	—
VIII, Y = NH_2	$C_5H_{11}N_{10}$[m,o]	f	54	203–205	17.2	5.8	40.2	17.2	6.0	40.0	285	8.7	336	9.0	—	—
VIII, Y = NO_2[bb]	$C_5H_9N_{10}O_1$	j	100	255	21.9	3.7	51.1	21.8	3.8	50.8	300	10.5	264	13.2		
													372	23.6		

* Footnotes for Tables I and II are at the end of Table II.

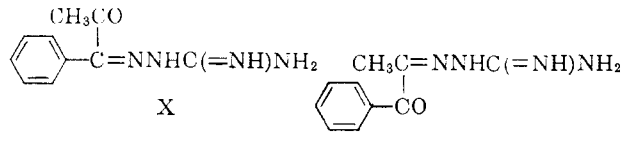
TABLE II

MONOSUBSTITUTED GUANYLHYDRAZONES [X = NNHC(=NH)NH$_2$]

Compounds	Formula	Recryst. solvents	Yield, %	M.p., °C. dec.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Ultraviolet absorption, mμ pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$	Activity[a] KB[b]	Activity[a] LE[c]
$CH_3CH{=}X$[cc,ee]	$C_3H_8N_4$[s]	i	75	146–148	18.2	5.6	28.3	18.3	5.7	28.6			239	12.5	−	−
$CH_3CH_2CH{=}X$	$C_4H_{10}N_4$[s]	i	60	126–129	22.6	6.1	26.4	22.4	6.4	26.4	228	16.1	237	17.4	−	−
$H_2NCH_2CH{=}X$	$C_3H_9N_5$[m,e]	p	61	235	15.6	5.7	30.3	15.7	5.6	30.9	224	13.2	241	11.4	+	−
$(CH_3)_2C{=}X$	$C_4H_{10}N_4$[t]	j	69	220–222	41.3	8.1	32.2	41.1	8.1	32.1	225	10.8	236	10.1	−	−
$(CH_3)_2C{=}X$	$C_4H_{10}N_4$[v,n]	h + j	61	246–248	27.9	7.0	32.5	28.0	6.8	32.6	224	10.4	237	9.1	−	−
$(CH_2)_5C{=}X$[ee]	$C_7H_{14}N_4$[o]	j	82	192–194	44.0	7.9	29.4	43.9	7.9	29.7	225	2.3	239	4.2	−	−
$CH_3COC(=X)C_6H_5$[p]	$C_{10}H_{12}N_4O$[u]	f + h	56	210	47.5	5.1	22.2	47.2	5.3	22.3	265	16.4			−	−
$C_6H_5COCH_2C(=X)C_6H_5$	$C_{16}H_{16}N_4$[o,e]	j	93	212	60.3[w]	6.0	17.6	60.0	5.9	17.8	280	22.3			−	−
$C(=X)CONH(o\text{-}C_6H_4)$[ii]	$C_9H_9N_5O$[u,g]	h	65	225	37.6	4.9	24.4	37.6	4.9	24.5	246	22.8			−	−
											263	14.4				
											314	18.8				
$COC(=X)CO(o\text{-}C_6H_4)$	$C_{10}H_8N_4O_2$[v,e]	x	51	190	42.4	3.9	19.8	42.6	4.2	19.3	253	11.1			++	−
											290	2.3				
$NHCH{=}C(CH{=}X){-}(o\text{-}C_6H_4)$	$C_{10}H_{11}N_5$[u]	p	75	299–300	48.0	4.8	28.0	48.0	5.0	27.9	243	10.1	239	10.0	±	−
											264	12.4	263	11.1		
											302	18.9	303	17.6		
$C(=X)CONHCONHCO$	$C_5H_6N_6O_3$[o]	j	81	>360	25.5	3.0	35.7	25.4	3.1	35.2	297	20.4	233	8.2	−	−
													358	33.4		
$CH_3C(=X)C_6H_5$[ii]	$C_9H_{12}N_4$[o]	j	71	207–209	50.8	6.2	26.3	50.7	6.2	26.2	267	18.2	289	15.7	±	−
$CH_3C(=X)(p\text{-}FC_6H_4)$	$C_9H_{11}FN_4$[o,n]	j	54	257–259	45.4	5.5	23.4	45.9	5.4	23.5	267	18.2	285	16.3	−	−
$CH_3C(=X)(p\text{-}ClC_6H_4)$	$C_9H_{11}ClN_4$[o]	j	57	248–250	43.7	4.9	22.7	43.6	5.0	22.3	273	22.5	295	18.3	++	−
$CH_3C(=X)(p\text{-}NH_2C_6H_4)$	$C_9H_{13}N_5$[o]	j	67	185–187	47.4	6.2	30.7	47.5	6.4	30.5	268	19.5	303	28.4	±	−
$CH_3C(=X)(\beta\text{-}C_5H_4N)$	$C_8H_{11}N_5$[s]	h	69	253–254	34.9	5.1	25.4	34.9	5.3	25.1	274	16.2	294	15.1	−	−
$C_6H_5C(=X)(o\text{-}FC_6H_4)$	$C_{14}H_{13}FN_4$[o]	j	55	265–267	57.3	4.8	19.1	57.2	5.0	18.9	279	21.0	308	17.2	++	−
$C_6H_5C(=X)(p\text{-}FC_6H_4)$	$C_{14}H_{13}FN_4$[o]	j	63	259–261	57.3	4.8	19.1	57.6	5.1	18.9	279	19.0	303	14.6	++	−(+)[y]
$C_6H_5C(=X)(p\text{-}CH_3C_6H_4)$	$C_{15}H_{16}N_4$[o]	j	59	280–282	62.3	6.0	19.3	62.7	6.1	19.6	270	20.1	306	15.0	++	−
$(p\text{-}CH_3C_6H_4)C(=X)(p\text{-}CH_3C_6H_4)$	$C_{16}H_{18}N_4$[o]	j	38	322–323	63.4	6.3	18.5	63.5	6.4	18.5	284	20.6	306	15.4	++	−
$(p\text{-}CH_3OC_6H_4)C(=X)(p\text{-}CH_3OC_6H_4)$	$C_{16}H_{18}N_4O_2$[o]	j	43	230–231	56.3	5.7	16.8	56.6	5.6	16.9	287	22.0	310	17.3	++	−

[a] Preliminary testing work was carried out by Contract Screeners of CCNSC. − inactive, ± moderately active, + active, ++ activity confirmed. [b] Tissue culture (cell line), cultivated on Eagle's basal medium plus 10% serum. [c] Lymphoid leukemia L-1210. [d] Dihydrochloride. [e] Monohydrate. [f] From methanol. [g] Dihydrate. [h] From water. [i] Calcd.: Cl, 22.1; Found: 22.4. [j] From ethanol. [k] Calcd.: Cl, 20.5; Found: 20.5. [l] From isopropyl alcohol. [m] Monosulfate. [n] Hemihydrate. [o] Monohydrochloride. [p] From 5% sulfuric acid. [q] Ethanolate. [r] Calcd.: Cl, 22.2; Found: 22.3. [s] Monophosphate, actually in the form of $M^{+}H_2PO_4^{-}$. [t] Acetate. [u] Hemisulfate. [v] Paper chromatography measurements done at 25°, descending: R_f 0.82 (50% butanol–30% water–20% acetic acid); R_f 0.48 (butanol saturated with 0.2 *N* hydrochloric acid; R_f 0.75 (3% ammonium chloride). [w] Calcd.: Cl, 11.1; Found: 11.2 [x] Not recrystallized, attempted recrystallization resulted in decomposition. [y] Active in LE-1210 when the compound was introduced through diet.[z] [z] Mr. Frederic A. French, personal communication. [aa] See ref. 5. [bb] See ref. 7. [cc] See ref. 12. [dd] See ref. 13. [ee] See ref. 14. [ff] See ref. 15. [gg] See ref. 16. [hh] See ref. 17. [ii] See ref. 18. [jj] See ref. 19. [kk] See ref. 8g.

when 1-phenyl-1,2-propanedione was condensed with excess aminoguanidine dihydrochloride, the desired 1,-1′-(methylphenylethanediylidenedinitrilo)-diguanidine (III, $R_1 = CH_3$, $R_2 = C_6H_5$) was obtained. On the other hand, when aminoguanidine sulfate was used, only one carbonyl group reacted. The resulting monoguanylhydrazone derivative was assigned the α-acetylbenzylideneaminoguanidine structure (X) rather than its β isomer (XI). This was, in part, due to the hyperconjugation effect exerted by the methyl group of 1-phenyl-1,2-propanedione which would tend to make the carbonyl group next to the methyl group



X XI

less susceptible toward nucleophilic attack by the basic aminoguanidine. Hence, the formation of XI is less likely and structure X is preferred. This postulation was further substantiated by the fact that the product gave a positive iodoform test. The possibility that XI might also be present as a minor product was ruled out by paper chromatographic studies. Only one spot was observed when the condensation product was developed in three different systems.

The preparation of 1,1′-(methylethanediylidenedinitrilo)-bis(3-aminoguanidine) (VIII, Y = NH_2) was accomplished by a 3-step synthesis. Methylation of thiosemicarbazide with methyl iodide yielded S-(methylthio)-semicarbazide.[11] Treatment of the latter with hydrazine gave N,N′-diaminoguanidine hydriodide in good yield. To facilitate isolation of the final product, the hydriodide was converted to the sulfate salt by means of silver sulfate.[11] Condensation of the resulting N,N′-diaminoguanidine sulfate with methyl glyoxal afforded the desired compound (VIII, Y = NH_2).

Preliminary antitumor screening results of the guanylhydrazones are listed in Tables I and II.[12-19] With the information presently available it appears that in the bisguanylhydrazone group several generalizations can be made: (1) replacement of the methyl group in I by an alkyl or aryl group results in loss of the original activity, (2) the presence of the aldimine hydrogen is essential for activity, (3) the original activity is relinquished when the hydrogen atom at the terminal nitrogen atom in I is replaced by functional groups. In the monoguanylhydrazone series, the simple aliphatic analogs are totally inactive. Several substituted benzophenone guanylhydrazones have shown confirmed activity in cell culture cytotoxicity tests.

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Experimental[20]

General Preparation of Guanylhydrazones.—Various salts of aminoguanidine were prepared *in situ* from commercially available aminoguanidine bicarbonate.[21]

To a solution of 0.11 mole (15 g.) of aminoguanidine bicarbonate in 125 ml. of water was added slowly the desired acid (a few drops of amyl alcohol were added in order to prevent foaming) until the pH of the solution was less than 7. The solution was filtered from trace amounts of insoluble solids. The appropriate carbonyl compound was then added slowly to the slightly acid filtrate at *ca.* 60°. The amount of carbonyl compound used was such that the ratio of aminoguanidine per carbonyl function was 1:1. If the carbonyl compound did not dissolve in the aqueous mixture, ethanol was added until the reaction mixture was homogeneous. The solution was then stirred at room temperature for 16 hr. If a precipitate was formed the solid product was isolated by filtration. Otherwise the reaction mixture was evaporated until a solid residue was obtained. Recrystallization solvents are listed in Tables I and II.

1,1′-[(Methyl)ethanediylidenedinitrilo]diguanidine Hemihydrate (I, Free Base).—A solution of 15 g. of I sulfate monohydrate in 250 ml. of 30% aqueous ammonia was stirred for 30 min. at 10°. The yellow solution was then extracted with 500 ml. of butanol. The butanol extract was evaporated *in vacuo* to yield 5.5 g. of pale yellow solid. This crude product was dissolved in absolute ethanol and hexane added, causing the precipitation of yellow microcrystals. Recrystallization of the product from isopropyl alcohol yielded 5.0 g. (52%) of I as off-white crystals. It decomposed at 225°. $\lambda_{max}^{pH\ 1}$ 283 mμ (ε 38,400); $\lambda_{max}^{pH\ 11}$ 325 mμ (ε 33,500).

Anal. Calcd. for $C_5H_{12}N_8 \cdot 0.5H_2O$: C, 31.1; H, 6.8; N, 58.1. Found: C, 31.5; H, 6.5; N, 58.2.

N,N′-Diaminoguanidine Hydriodide.—To a suspension of 23.3 g. (0.1 mole) of 2-(methylthio)semicarbazide hydriodide in 250 ml. of absolute methanol was added 3.3 g. (0.1 mole) of 98% hydrazine. The mixture was then stirred for 3 hr. at room temperature. The resulting solution was chilled and shining white platelets were deposited. The product was collected by filtration and recrystallized from hexane to give 17 g. (75%) of white platelets, m.p. 134–136°.

Anal. Calcd. for $CH_7N_5 \cdot HI$: C, 5.50; H, 3.7; N, 32.3. Found: C, 5.60; H, 3.9; N, 32.6.

The product was converted to the sulfate salt by dissolving 35 g. (0.16 mole) of the hydriodide salt in 200 ml. of water followed by the addition of 24.5 g. (0.08 mole) of silver sulfate and 8 drops of glacial acetic acid. After stirring for 30 min. a yellow precipitate formed. Recrystallization of the product from a mixture of ethanol and water gave 20 g. (66%) of a white solid, m.p. 245° (with effervesce).

1,1′-(Methylethanediylidenedinitrilo)-bis(3-aminoguanidine) Sulfate (VIII, Y = NH_2).—A solution of 13 g. (0.07 mole) of 1,3-diaminoguanidine sulfate in 125 ml. of water and 3 drops of concd. sulfuric acid was carefully heated to 70°. To this solution was slowly added 5.1 g. (0.035 mole) of 43% methylglyoxal. A heavy, off-white precipitate formed immediately. The mixture was stirred at 65–70° for 15 min. and then allowed to cool. The solid product was isolated by filtration and washed with water. It was then recrystallized from dilute sulfuric acid to give 12 g. of light tan powder (see Table I).

1,1′-(Methylethanediylidenedinitrilo)-bis(3-nitroguanidine (VIII, Y = NO_2).—To a suspension of 25 g. (0.2 mole) of 1-amino-3-nitroguanidine[22] in 1,500 ml. of methanol was added 17.2 g. (0.1 mole) of 43% methylglyoxal. The mixture was stirred for 3 days at room temperature. The resulting yellow solid was filtered, washed with water, ethanol and methanol and dried at room temperature to give a quantitative yield of the desired product which decomposed violently at 255°, (Lit.,[17] m.p. 344° dec.). The product isolated was of analytical purity (see Table I).

(20) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2, and the infrared spectra were taken with a Perkin-Elmer Infracord.
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Synthesis of Possible Cancer Chemotherapeutic Compounds Based on Enzyme Approach. IV. Aziridine Derivatives[1]

K. C. TSOU, K. HOEGERLE, AND HELEN C. F. SU

Central Research Laboratory, The Borden Chemical Company, A Division of The Borden Company, Philadelphia 24, Pa.

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Several β-(1-aziridinyl)propionate esters, 1,1′-acylaziridines of dibasic acids, (1-aziridinyl)formates, β-(1-aziridinyl)ethyl esters, and other ethylenimine derivatives have been prepared as possible cancer chemotherapeutic compounds based on enzyme rationale. The acylbisaziridines of dibasic acids are in general unstable. In the preparation of 1,1′-malonyl bisaziridine, only the compound from ring opening, malonic acid bis-(β-chloroethyl)-diamide was obtained. The β-(1-aziridinyl)propionate ester of ethyleneglycol was found to be active in the S-180, CA-755, and L-1210 systems. 1,1′-(2,2-Dimethylpropylene)bis-aziridinyl formate was designed to simulate the well known muscle relaxant, 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate. Infrared spectra and biological activities of the compounds are discussed.

In order to take advantage of the known difference in esterase activity in normal and neoplastic tissues,[2,3] several series of compounds containing $ClCH_2CH_2S$– groups as the alkylating moiety have been prepared and evaluated as possible cancer chemotherapeutic agents.[4,5] To extend this rationale, many ethylenimine derivatives have also been prepared. This paper reports the synthesis of these compounds together with discussions of some of the interesting observations made in the course of this work.

hydrolyzed by esterase to β-(aziridinyl)alanine, a much less toxic compound. The methyl ester (I) has been prepared by the Michael addition of ethylenimine to the acrylic esters, similar to the method used by Bestian.[6]

The vinyl (II) and allyl (III) esters were made by a slightly modified procedure. Attempts to add a second molecule of ethylenimine to the double bond of the alcohol moiety of these unsaturated esters have thus far failed. When the reaction was carried out in the presence of metallic sodium as a catalyst only a rubbery polymer was obtained. Ethylene glycol di-β-(1-aziridinyl)-propionate (IV) was prepared by the transesterification of methyl β-(1-aziridinyl)propionate and ethylene glycol. Several 1,1′-acylbisaziridines of dibasic acids which are related to these compounds were also prepared (Table II). Although synthesis of these

TABLE I

β-(1-AZIRIDINYL)PROPIONIC ACID ESTERS 

Compound	—R	B.p., °C. (mm.)	Refractive index at n°	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
I	CH_3	63–65 (23)	1.4312^{24}	44.0	$C_6H_{11}NO_2$	55.82	55.96	8.58	8.70	10.84	10.85
II	$CH{=}CH_2$	56–64 (15–18)	1.4490^{22}	52.0	$C_7H_{11}NO_2$	59.59	59.70	7.86	7.80	9.93	10.20
III	$CH_2CH{=}CH_2$	105–106 (30)	1.4482^{23}	76.7	$C_8H_{13}NO_2$	61.91	61.84	8.44	8.50	9.03	9.01
IV	$CH_2CH_2OCOCH_2CH_2N$ 	145–147 (0.2)	1.4660^{23}	38.3	$C_{12}H_{20}N_2O_4$	56.23	56.49	7.87	7.93	10.93	10.89

TABLE II

ACYLBISAZIRIDINES OF DIBASIC ACIDS 

Compound	—R	M.p., °C.	Refractive index at n°	Yield, %	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
VI	$—CH_2—$	unstable, characterized only by its derivative, see Experimental									
VIII	$—CH_2CH_2—$	72–73		20.5	$C_8H_{12}N_2O_2$	57.12	57.20	7.19	7.40	16.66	16.50
IX	$—(CH_2)_8—$		1.4921^{25}	22.0	$C_9H_{14}N_2O_2$	59.32	59.08	7.74	7.90	15.37	15.58

The β-(1-aziridinyl)propionate esters (Table I) contain only one alkylating group. These compounds are

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