Molecular composition	Calcd., % C	H	N	S	Found, % C	H	N	S
$C_9H_{12}N_6OS \cdot C_2H_5OH$	44.3	6.1	28.2	10.7	43.9	6.0	27.8	11.0
$C_{10}H_{14}N_6S$	48.0	5.6	33.6	12.8	47.8	5.8	33.5	13.0
$C_9H_{12}N_6S$	45.7	5.1	35.6	13.6	45.6	5.3	35.3	13.7
$C_9H_{11}N_5O_2S$	42.7	4.4	27.7	12.7	42.3	4.4	27.3	12.3
$C_{10}H_{13}N_5OS \cdot C_2H_5OH$	48.5	6.4	23.6	10.8	48.3	6.5	23.6	11.1
$C_9H_{11}N_5OS$	45.6	4.7	29.5	13.5	45.5	5.1	29.4	13.4
$C_8H_{11}N_7O$	43.4	5.0	44.3		43.8	5.4	44.3	
$C_9H_{13}N_7$	49.3	6.0	44.7		49.0	6.2	45.0	
$C_8H_{11}N_7$	47.8	5.4	46.8		47.3	5.7	46.4	
$C_8H_{10}N_6O_2$	42.5	4.5	37.2		42.7	4.8	37.4	
$C_9H_{12}N_6O$	49.1	5.5	38.2		49.4	5.5	38.0	
$C_8H_{10}N_6O$	46.6	4.9	40.8		47.0	5.1	40.4	
$C_9H_{12}N_6O$	49.1	5.5	38.2		49.4	5.8	38.6	
$C_7H_{10}N_6O$	43.3	5.2	43.3		43.0	5.2	42.8	

addition of glacial acetic acid to pH 7. [d] Compound recrystallized from boiling H_2O with addition of sufficient ethanol to effect solution.

dissolved in formamide (3 ml.) and heated at 170° for 1 hr. Addition of ethanol and ether gave a formyl derivative (0.16 g.), m.p. above 300°.

Anal. Calcd. for $C_8H_{10}N_6O_2$: C, 43.2; H, 4.5; N, 37.8. Found: C, 42.9; H, 4.7; N, 38.1.

The formyl compound (0.1 g.) was deformylated by solution in water and treatment with a few drops of NH_4OH. A solid soon separated which was collected and recrystallized from water to yield white needles (0.065 g.).

Hydroxymethylglyoxal Bisguanylhydrazone[1]

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Several derivatives of guanylhydrazine have been reported to be active in inhibiting animal and human tumors.[3a-c] One of the most active compounds of this group, hydroxymethylglyoxal bisguanylhydrazone, was purportedly prepared by an osazone type of reaction between 1 mole of hydroxyacetone and 3 moles of aminoguanidine sulfate in aqueous acetic acid.[3b] The detailed synthetic procedure and the characterization of the compound have so far not been published. From available chemical, physicochemical, and biological evidence[4] it soon became apparent that the presumed hydroxymethylglyoxal bisguanylhydrazone was actually methylglyoxal bisguanylhydrazone instead. In view of the ready isomerization of dihydroxyacetone into methylglyoxal[5a-d] and the possible failure of the osazone reaction we decided to prepare the hydroxymethylglyoxal bisguanylhydrazone by the direct condensation of aminoguanidine with hydroxymethylglyoxal freshly prepared by the mild oxidation[6] of dihydroxyacetone. This proved to be successful, and the product so obtained was significantly different from the compound previously reported.[3b] Because elementary analysis cannot differentiate between methylglyoxal bisguanylhydrazone dihydrochloride monohydrate ($C_5H_{16}Cl_2N_8O$) and hydroxymethylglyoxal bisguanylhydrazone dihydrochloride ($C_5H_{14}Cl_2N_8O$) it was necessary to resort to n.m.r. spectroscopy. The data reported below are consistent with the conclusion that the present condensation product is indeed hydroxymethylglyoxal bisguanylhydrazone.

Experimental[7]

Hydroxymethylglyoxal.—This was prepared according to the published procedure[6] from dihydroxyacetone by oxidation either

(1) The correct chemical name is 1,1-[(hydroxymethyl)ethanediylidine dinitrilo]diguanidine.

(2) The work at Riker Laboratories, Inc., was supported by Contract SA-43-ph-3764 from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service.

(3) (a) B. L. Freedlander and F. A. French, *Cancer Res.*, **18**, 360 (1958); (b) B. L. Freedlander and F. A. French, *ibid.*, **18**, 1286 (1958); (c) J. F. Holland, E. Milhich, B. Bryant, and A. I. Mulhern, *ibid.*, **21**, (1961).

(4) J. D. Davidson, R. R. Engle, and R. W. Mancuso, *Cancer Chemotherapy Rept.*, in press.

(5) (a) K. Bernhauer and B. Görlich, *Biochem. Z.*, **212**, 462 (1929); (b) H. O. L. Fischer and L. Feldmann, *Ber.*, **62**, 863 (1929); (c) H. O. L. Fischer and C. Traube, *ibid.*, **57**, 1502 (1924); (d) G. Pinkus, *ibid.*, **31**, 36 (1898).

(6) G. Hesse, F. Ramisch, and K. Renner, *ibid.*, **89**, 2137 (1956).

(7) All melting points are corrected.

in water (slow oxidation, product isolated as the trimer ethanolate) or in methanol (rapid oxidation). In the latter case, nitrogen was substituted for carbon dioxide without affecting the course of the reaction. The crystalline methanolated trimer of hydroxymethylglyoxal was obtained by flash evaporation at 30° of the final supernatant liquid. As reported in the literature, it was an amorphous material without definite melting point, but softened at 150°. It was used in the condensation with aminoguanidine without further purification.

Condensation of Hydroxymethylglyoxal with Aminoguanidine.—A solution of 21 g. (67 mmoles) of hydroxymethylglyoxal trimer ethanolate (or equivalent methanolate) in 50 ml. of water was depolymerized by warming at 60° for 10 min. A slurry of 47 g. (346 mmoles) of aminoguanidine bicarbonate in 150 ml. of 99% ethanol was treated with concentrated hydrochloric acid (about 33 ml.) dropwise with stirring until evolution of carbon dioxide ceased. This slurry was cooled in an ice bath and the solution of hydroxymethylglyoxal was added dropwise over 20 min. After standing at 0° for 1 hr., the reaction mixture was poured slowly, with agitation, into 1600 ml. of cold acetone. The white precipitate was collected by filtration, washed with acetone and ether, and dried *in vacuo* at room temperature, m.p. 186–188° dec., yield, 17.7 g. After standing overnight in the refrigerator, a second crop of 1.5 g., m.p. 191–193° dec., was obtained from the combined filtrate and washings, total yield, 37.5%. Recrystallization from 99% ethanol raised the m.p. to 197–198° dec.; log ϵ in pH 4 acetate buffer, 4.60 at λ_{max} 285 mμ. Paper chromatography, descending, on Whatman No. 1 paper: R_f 0.39 in 1-propanol–*N* HCl–H_2O (3:1:1); R_f 0.41 in 70% ethanol saturated with ammonium bicarbonate (run in the dark).

Anal. Calcd. for $C_5H_{12}N_8O{\cdot}2HCl$: C, 21.99; H, 5.17; N, 41.02. Found: C, 21.79; H, 5.37; N, 40.99.

Nuclear Magnetic Resonance Spectroscopy.—This was run in deuterium oxide, using dioxane (τ 6.30) as an internal standard. The spectrum of our product showed singlets at τ 5.43 (water), τ 5.28 (methylene protons), and τ 2.36 (vinyl proton), and the three peaks are in the ratio of 12:2:1. On the other hand, methylglyoxal bisguanylhydrazone showed singlets at τ 7.90 (methyl protons), τ 5.35 (water), and τ 2.32 (vinyl proton), and the methyl and vinyl peaks are in a 3:1 ratio.

Antitumor Screening.—This compound was tested for antitumor activity in three mouse tumors: advanced leukemia L1210, leukemia P1534 (ascites), and a plasma cell tumor YPC-1 (ascites).[8] Methylglyoxal bisguanylhydrazone was used as a reference compound on account of its known activity in L1210.[3b] Both drugs were injected subcutaneously daily. The inability of hydroxymethylglyoxal bisguanylhydrazone to increase survival time of mice bearing these tumors is readily seen in Table I. This again is in contrast to the reported activity of the compound claimed to be hydroxymethylglyoxal bisguanylhydrazone.[3b]

TABLE I

MEDIAN SURVIVAL TIME OF MICE[a] AT OPTIMAL TREATMENT

Tumor	Treatment	Optimal dose, mg./kg.	Median survival, days
L1210[b]	None		7
	HOMeGAG[c]	60	7.5
	MeGAG[d]	65	15.5
P1534[c]	None		10.5
	HOMeGAG	60	10.5
	MeGAG	60	13
YPC-1[d]	None		10
	HOMeGAG	45	11.5
	MeGAG	45	14.5

[a] Ten animals in each group. [b] Treatment, day 5 until death. [c] Treatment, day 1 through day 10. [d] Treatment, day 1 until death. [e] Hydroxymethylglyoxal bisguanylhydrazone. [f] Methylglyoxal bisguanylhydrazone.

(8) The plasma cell tumor YPC-1 used in this study arose spontaneously in a CAF$_1$ mouse; see S. T. Yancey, *J. Natl. Cancer Inst.*, in press.

4-(1-Carboxyethyl)-1,4-oxathianium Bromide

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In the preparation of sulfonium salts the advantage of reaction at or near room temperature was noted.[2] This method has been extended to the reaction of α-bromopropionic acid (I) with thioxane (II) by allowing a long reaction period. A mixture of 15.3 g. (0.10 mole) of I and 10.0 g. (0.10 mole) of II was kept for 98 months at room temperature (approximately 29°). The unreacted liquid was decanted from the solid product, and the latter was washed with ethanol, then with acetone; yield 10.8 g. (43%) of off-white crystals, m.p. 116–119°.

Anal. Calcd. for $C_7H_{13}BrSO_3$: C, 32.66; H, 5.10. Found: C, 32.80; H, 5.07.[3]

Screening data provided by the Cancer Chemotherapy National Service indicated that it was ineffective against Sarcoma 180, Leukemia L-1210, and solid Friend Virus Leukemia at a dose level of 175 mg./kg. by daily i.p. injection and that the ED_{50} against KB cells in tissue culture was more than 100 μg./ml.

(1) This research was supported by grants from the Research Corporation and the National Cancer Institute.

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(3) Analyses by Weiler & Strauss, Oxford, England.

Some Esters of *dl-exo*-3-Dimethylaminoisoborneol

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Basic esters, and salts thereof, have frequently exhibited practical levels of pharmacological activity. Our interest lay in determining whether building a 2-dimethylaminoethanol unit into the terpenoid skeleton might lead to useful products (*cf.* ref. 2, 3). By way of accessibility, *exo*-3-dimethylaminoisoborneol (I) was chosen as the basic alcohol and converted to the acetate and diphenylacetate. Acid addition salts and methobromides of the esters were tested *in vitro* for antispasmodic activity. In direct comparison, none of the compounds showed more than 5% the activity of atropine on the guinea pig ileum stimulated with acetylcholine. Similarly, less than 10% of the activity of papaverine was found for all products in countering barium chloride spasms of the isolated ileum.

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(3) S. Kuroda, *ibid.*, **63**, 548 (1943).

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