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.[3a] 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[e]	60	7.5
	MeGAG[f]	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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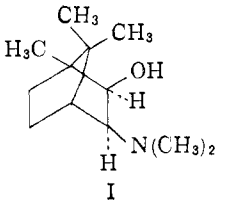
(3) S. Kuroda, *ibid.*, **63**, 548 (1943).

(4) We wish to thank Dr. T. O. King (now of Ortho Research Foundation, Raritan, N. J.) and Dr. W. M. Govier (McNeil Laboratories, Inc., Fort Washington, Pa.) and their staffs for the pharmacological testing.



I

Experimental[5]

dl-exo-**3-Dimethylaminoisoborneol** was prepared from *dl*-camphor. Camphorquinone (m.p. 196.5–197.5°) was produced in 86% yield by Riley oxidation[6] of camphor, converted to 3-methylaminocamphor (91% crude yield, purified *via* the perchlorate, m.p. 179–181°),[6] methylated to 3-dimethylaminocamphor (52% yield of pure perchlorate, m.p. 209–213°),[7] and then reduced in quantitative yield, to *dl-exo*-3-dimethylaminoisoborneol by catalytic hydrogenation in ethanol with Raney nickel catalyst,[6,7] at *ca.* 40 kg./cm.^{2} The product separated from hexane as needles, m.p. 106.5–108°. Some batches required conversion to the perchlorate (m.p. 242–243° with sintering at 239°, after crystallization from ethanol–ether), followed by regeneration of the base, and crystallization to obtain pure *dl*-3-dimethylaminoisoborneol melting at 111–112°. Especially thorough drying was required to reach this melting point. Duden and Pritzkow[8] reported an isomer which melted at *ca.* 80°.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.16; H, 11.77; N, 7.11. Found: C, 73.05; H, 11.80; N, 7.13.[9]

***dl*-3-Dimethylaminoisobornyl Acetate.**—A mixture of 5.0 g. (0.026 mole) of *dl*-3-dimethylaminoisoborneol with 200 ml. of acetic acid and 50 ml. of acetic anhydride was refluxed for 1 day and then the acid and anhydride were removed *in vacuo*. The residue was fractionated to give 4.4 g. of acetate, b.p. 72–73° (0.4 Torr.).

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.35; H, 10.58. Found: C, 70.05; H, 10.54.

The **hydrobromide** was prepared in propanol-2, and crystallized from propanol-2 and hexane as dull white needles, m.p. 239.5–242° with intumescence.

Anal. Calcd. for $C_{14}H_{25}NO_2 \cdot HBr$: C, 52.54; H, 8.19; N, 4.38. Found: C, 52.76; H, 8.64; N, 4.60, 4.37.

The **methobromide** was obtained by treatment of a methanolic solution of the base with methyl bromide at −30°, followed by allowing the mixture to reflux for several hours prior to removal of solvents. A creamy product resulted; it was necessary to crystallize the quaternary salt four times from propanol-2 and hexane to give pure white, fluffy needles, m.p. 183.5–185° with intumescence.

Anal. Calcd. for $C_{15}H_{28}BrNO_2$: C, 53.94; H, 8.45; N, 4.19. Found: C, 53.80; H, 8.72; N, 4.50.

***dl*-3-Dimethylaminoisobornyl Diphenylacetate.**—Excess diphenylacetic anhydride (30.0 g., made after the method of Hurd, *et al.*[10]) was added to a solution of 5.0 g. (0.026 mole) of 3-dimethylaminoisoborneol, and the mixture was refluxed for 36 hr. The benzene was removed and the residue dissolved in boiling ether. Chilling caused crystallization of the excess anhydride, which was removed, and then the filtrates were treated with hydrogen chloride. The **hydrochloride** separated slowly from methanol–ethyl acetate as prismatic crystals, m.p. 220–248° dec. A yield of 8.6 g. (79%) was obtained.

Anal. Calcd. for $C_{26}H_{33}NO_2 \cdot HCl$: C, 72.96; H, 8.01; N, 3.27. Found: C, 72.66; H, 8.14; N, 3.16.

The **base** was liberated from the hydrochloride and crystallized from methanol by addition of ethylene glycol. A cryptocrystalline solid resulted, m.p. 63–64°.

Anal. Calcd. for $C_{26}H_{33}NO_2$: C, 80.03; H, 8.50; N, 3.58. Found: C, 80.03; H, 9.01; N, 3.86.

(5) All melting points were measured on a Fisher–Johns block. Analyses were carried out by Mr. J. Weinberger.

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(9) Basic nitrogen determination by the method of G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).

(10) C. D. Hurd, R. Christ, and C. L. Thomas, *J. Am. Chem. Soc.*, **55**, 2589 (1933).

The **methobromide** was made in methanol and crystallized, with some difficulty, from a 1:2:4 mixture of methanol, propanol-2, and hexane. The creamy product melted at 213–250° dec. and appeared to be a hemihydrate.

Anal. Calcd. for $C_{27}H_{36}BrNO_2 \cdot 0.5H_2O$: C, 65.51; H, 7.53; N, 2.83. Found: C, 65.56; H, 7.43; N, 2.85.

Aromatic Azo Acids as Possible Antineoplastic Compounds[1]

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As a part of a program designed to synthesize azo and hydrazo fatty acids and derivatives as possible anticancer agents,[2] it appeared to be of interest to prepare some aromatic azo acids for comparative purposes. The carboxy substituted 4-alkyl- and 4,4′-dialkylazobenzenes described in Table I seemed to afford a simple approach to the desired structures. They were obtained by a conventional condensation of properly substituted aromatic amines with aromatic nitroso compounds, which were prepared by known synthetic procedures.

Pharmacological Results.—The data which are available to date indicate that the azo acids listed in Table I are inactive against Sarcoma 180, Lymphoid Leukemia L-1210, and Adenocarcinoma 755. The results were supplied by Dr. Joseph Leiter, Cancer Chemotherapy National Service Center, Bethesda, Maryland. Information in regard to test procedures may be located in publications from the National Service Center.[3]

Experimental[4]

Materials.—Nitrosobenzene,[5] *p*-carboxy-,[6] *p*-ethyl-,[7] and *p*-methylnitrosobenzene[8] were prepared from the corresponding nitro compounds. *p*-Aminobenzoic acid was a commercial product, and *p*-aminophenylacetic acid was obtained by the ammonium polysulfide reduction of *p*-nitrophenylacetic acid.[9] *p*-Ethylaniline[10] was prepared from *p*-ethylacetophenone,[11] through the corresponding oxime,[12] which was rearranged by means of polyphosphoric acid to *p*-ethylacetanilide[13] which then was hydrolyzed by alkali to the desired amine. A similar series

(1) Supported in part through Grant CY-4662 from the Cancer Chemotherapy National Service Center, National Cancer Institute, U. S. Public Health Service.

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