Methanesulfonylcholine Bromide (Vb).—A solution of 5.1 g. (0.025 mole) of Va in 5 ml. of dimethylformamide was mixed with 20 ml. of a 25% solution of trimethylamine in methanol and allowed to stand at room temperature for 1 day. Colorless crystals formed (46%) which were recrystallized from methanol, m.p. 143°.

Anal. Calcd. for $C_6H_{16}BrNO_3S$: C, 27.48; H, 6.15; N, 5.34; Br, 30.48. Found: C, 27.65; H, 6.31; N, 5.19; Br, 30.71.

Methanesulfonyl Thiocholine Bromide (VI).—A solution of 2.5 g. (0.001 mole) of bromocholine bromide and 1.5 g. (0.0011 mole) of sodium methanethiosulfonate[7] in 20 ml. of methanol was refluxed for 2 days. When the clear solution was cooled below 0°, 1.02 g. of colorless crystals m.p. 154° separated out. Recrystallization from abs. ethanol gave the pure compound (26%), m.p. 160°.

Anal. Calcd. for $C_6H_{16}BrNO_2S_2$: C, 25.90; H, 5.80; N, 5.04; Br, 28.72. Found: C, 25.84; H, 5.87; N, 4.96; Br, 28.64.

2-Methanesulfonoxyphenylmethyl Dimethylamine (VIIa).—The sulfonic ester was prepared from crude commercial material following method Ia, but triethylamine was used instead of 2,6-lutidine. A colorless oil was obtained (39%), b.p. 127° (0.2 mm.).

2-Methanesulfonoxyphenylmethyltrimethylammonium iodide (VIIb) was prepared in the usual way (as Ib) from VIIa, yielding 60% of colorless crystals; recrystallized from abs. ethanol, m.p. 191–192°.

Anal. Calcd. for $C_{11}H_{18}INO_3S$: C, 35.59; H, 4.89; N, 3.77; I, 34.19. Found: C, 35.98; H, 5.16; N, 3.51; I, 33.90.

Acknowledgment.—The author wishes to thank Dr. I. B. Wilson for suggesting the problem.

(7) O. Foss, *Acta Chem. Scand.*, **10**, 868 (1956). Sodium methanethiosulfonate was prepared using Wahlsted's method for sodium *p*-toluenethiosulfonate, *Acta Univers. Lund*, **16** (2) II, 9 (1879–1880); Beilstein XI, 4th ed., Julius Springer, Berlin, 1928, p. 113.

Aldehyde Hydrazone Derivatives in Cancer Chemotherapy

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In previous studies[1a-b] it has been observed and reported that some substituted aldehyde hydrazone derivatives have borderline activity

(1) (a) Richard H. Wiley and G. Irick, *J. Med. Pharm. Chem.*, **5**, 49 (1962); (b) Richard H. Wiley, G. Irick, and H. K. White, *J. Org. Chem.*, **26**, 589 (1961); (c) Richard H. Wiley and G. Irick, *ibid.*, **26**, 593 (1961); (d) Richard H. Wiley and Y. Yamamoto, *ibid.*, **25**, 1906 (1960); (e) Richard H. Wiley and G. Irick, *ibid.*, **24**, 1925 (1959); (f) Richard H. Wiley, H. K. White, and G. Irick, *ibid.*, **24**, 1784 (1959).

TABLE I
SUBSTITUTED HYDRAZINE DERIVATIVES OF 2-METHOXY-1-NAPHTHALDEHYDE

Hydrazine	Procedure [a]	Yield, %	M.p., °C.	Solvent [b]	Formula	N Analyses Calcd.	Found
1-Amino-3-nitroguanidine	I	46	176 d.	B	$C_{13}H_{12}N_6O_3$	24.38	23.66
Benzenesulfonylhydrazide	II	60	209 d.	B	$C_{15}H_{16}N_2O_3S$	8.23	8.43
4-Bromophenylhydrazine	III	96	122	EW	$C_{18}H_{15}BrN_2O$	[c]	
Carboxymethyltrimethylammonium chloride hydrazide	II	81	255 d.	E	$C_{17}H_{22}ClN_3O_2$	12.51	12.31
2,5-Dichlorophenylhydrazine	II	68	179	D	$C_{18}H_{14}Cl_2N_2O$	8.12	8.36
2,4-Dinitrophenylhydrazine	[d]	86	278 d.	A	$C_{18}H_{14}N_4O_5$	15.30	15.21
4-Fluorophenylhydrazine	III	43	108	EW	$C_{18}H_{15}FN_2O$	[e]	
4-Hydrazinobenzenesulfonic acid	II	98	218 d.	MH	$C_{13}H_{16}N_2O_4S$	[f]	
4-Hydrazinobenzoic acid	II	92	211	E	$C_{19}H_{16}N_2O_3$	8.76	8.73
2-Hydrazinobenzothiazole	II	98	240	B	$C_{19}H_{15}N_3OS$	12.60	12.33
4-Nitrophenylhydrazine	II	82	238	EA	$C_{18}H_{15}N_3O_5$	13.08	13.31

[a] The following procedures were used in the preparations: I. To 3.75 g. (0.02 mole) of 2-methoxy-1-naphthaldehyde [N. Ph. Buu-Hoi and D. Lavit, *J. Chem. Soc.*, 2776 (1955)] in 25 ml. of hot methanol was added a warm aqueous solution of the appropriate hydrazine. Glacial acetic acid (10 ml.) was added. The reaction mixture was warmed to boiling and then cooled in an ice bath. The product was collected on a filter and recrystallized. II. To a solution of 3.75 g. (0.02 mole) of 2-methoxy-1-naphthaldehyde in 25 ml. of hot ethanol was added 0.020 mole of the appropriate hydrazine dissolved in a minimum amount of boiling ethanol. The reaction mixture was boiled for 5 min. then cooled in an ice bath. The product was collected on a filter and recrystallized. III. A solution of 2-methoxy-1-naphthaldehyde was prepared as in procedure II. The appropriate hydrazine hydrochloride was dissolved in a minimum amount of hot ethanol. The two solutions were mixed and 10 ml. of saturated aqueous sodium acetate were added. The reaction mixture was boiled for 5 min. and then cooled in an ice bath. The product was collected on a filter and recrystallized. [b] Solvents: A, glacial acetic acid; B, 1-butanol; D, benzene/petroleum ether; E, ethanol; EA, ethyl acetate; EW, ethanol/water; MH, methanol/concd. hydrochloric acid. [c] Calcd. for $C_{18}H_{15}BrN_2O$: C, 60.86; H, 4.25. Found: C, 61.04; H, 4.96. [d] See reference 4. [e] Calcd. for $C_{18}H_{15}FN_2O$: C, 73.48; H, 5.13. Found: C, 73.60; H, 5.34. [f] Calcd. for $C_{18}H_{16}N_2O_4S$: C, 60.68; H, 4.52. Found: C, 60.28; H, 4.58.

in cancer chemotherapy screening tests. Although these tests do not establish either reproducible or significant activity, they are considered to be structural leads worthy of further investigation.

It is not certain whether the activity in these compounds should

TABLE II
SUBSTITUTED HYDRAZINE DERIVATIVES OF INDOLE-3-CARBOXALDEHYDE

Hydrazine	Procedure [a]	Yield, %	M.p., °C.	Solvent [b]	Formula	N Analyses Calcd.	N Analyses Found
1-Amino-3-nitroguanidine	I	72	235 d.	E	$C_{10}H_{10}N_6O_2$	34.13	34.11
Benzenesulfonylhydrazide	I	85	184 d.	E	$C_{15}H_{14}N_2O_2S$	14.04	14.27
4-Bromophenylhydrazine	II	27	182	E	$C_{15}H_{12}BrN_3$	13 37	13.32
1-(Carboxymethyl)-pyridinium chloride hydrazide	I	97	238	E	$C_{15}H_{15}ClN_4O$	17.80	17.66
Carboxymethyltrimethylammonium chloride hydrazide	I	100	180	E	$C_{14}H_{19}ClN_4O$	19.01	19.30
2,5-Dichlorophenylhydrazine	I	72	188	D	$C_{15}H_{11}Cl_2N_3$	13.81	13.94
2,4-Dinitrophenylhydrazine	[c]	58	284	EEA	$C_{15}H_{11}N_5O_4$	21.53	21.36
2,4-Dinitrophenylsemicarbazide	I	47	273 d.	N	$C_{16}H_{12}N_6O_5$	22.82	22.64
Ethyl 4-hydrazinobenzoate	I	95	255 d.	E	$C_{18}H_{17}N_3O_2$	13.66	13.40
2-Hydrazinobenzothiazole	I	69	277	B	$C_{15}N_{12}N_4S$	19.16	19.04
3-Nitrophenylhydrazine	II	70	274 d.	N	$C_{15}H_{12}N_4O_2$	19.99	20.12
4-Nitrophenylhydrazine	II	62	265 d.	EW	$C_{15}H_{12}N_4O_2$	19.99	20.08

[a] The following procedures were used in the preparations: I. A solution of 2.9 g. (0.02 mole) of indole-3-carboxaldehyde (Aldrich Co.) in 25 ml. of hot ethanol was prepared. The appropriate hydrazine (0.02 mole) was dissolved in a minimum amount of hot ethanol and the two solutions were mixed. The reaction mixture was heated for 5 min. and then cooled in an ice bath. The product was collected on a filter and recrystallized. II. To a solution of 2.9 g. of indole 3-carboxyaldehyde dissolved in 25 ml. of hot ethanol was added an equimolar solution of the appropriate hydrazine hydrochloride. Saturated sodium acetate solution (10 ml.) was added, and the reaction mixture heated for 5 min. The mixture was cooled in an ice bath and the product collected on a filter and recrystallized. [b] Solvents: B, 1-butanol; D, benzene/petroleum ether; E, ethanol; EEA, ethanol/ethyl acetate; EW, ethanol/water; N, nitrobenzene. [c] See ref. 4.

be attributed to the hydrazone function or to the aldehyde structure. In order to evaluate this aspect of the structure–activity relations involved, we have prepared, and characterized, an extensive series of hydrazone derivatives of three aldehydes of particular interest: 2-methoxy-1-naphthaldehyde, indole-3-carboxaldehyde, and pyridoxal. The characterization data are given in Tables I, II, and III.

Screening data[2] presently available for these compounds have shown that the following are active in inhibiting growth of anaerobic bacteria: 2-methoxy-1-naphthaldehyde *p*-sulfophenylhydrazone (±), isonicotinoylhydrazone (+), thiosemicarbazone (++), and 1-carboxyphenylhydrazone (+); pyridoxal isonicotinoylhydrazone (±); and indole-3-carboxyaldehyde oxime (±). The following are

(2) The authors are indebted to Drs. C. C. Stock, Ralph Barclay, and D. A. Clarke of the Sloan-Kettering Institute for these data. Rating scales have been explained previously See Reference 1 (e),

TABLE III
SUBSTITUTED HYDRAZINE DERIVATIVES OF PYRIDOXAL

Hydrazine	Procedure [a]	Yield, %	M.p., °C.	Solvent [b]	Formula	N Analyses Calcd.	Found
Aminoguanidine	I	86	178	M	$C_9H_{13}N_5O_2$	31.38	31.16
1-Amino-3-nitroguanidine	I	63	249 d.	DW	$C_9H_{12}N_6O_4$	31.33	31.31
4-Bromophenylhydrazine	I	67	231 d.	M	$C_{14}H_{14}BrN_3O_2$	12.50	12.47
1-(Carboxymethyl)-pyridinium chloride hydrazide	II	63	288 d.	[c]	$C_{15}H_{15}Cl_2N_4O_3$	15.01	15.10
Carboxymethyltrimethylammonium chloride hydrazide	II	92	265 d.	M	$C_{13}H_{22}Cl_2N_4O_3$	15.86	15.14
2,5-Dichlorophenylhydrazine	III	40	279 d.	M	$C_{14}H_{13}Cl_2N_3O_2$	12.88	13.07
2,4-Dinitrophenylhydrazine	[d]	88	260 d.	E	$C_{14}H_{13}N_6O_6 \cdot HCl$	18.30	18.13[e]
4-Fluorophenylhydrazine	I	89	215	E	$C_{14}H_{14}FN_3O_2$	15.26	15.08
4-Hydrazinobenzenesulfonic acid	I	88	290 d.	[c]	$C_{14}H_{15}N_3O_6S$	12.46	12.50
2-Hydrazinobenzothiazole	III	47	320 d.	[c]	$C_{15}H_{14}N_4O_2S$	17.82	17.52

[a] The following procedures were used in these preparations: I. To 4.50 g. (0.022 mole) of pyridoxal hydrochloride (Nutritional Biochemicals Co.) in 25 ml. of hot water was added 3.50 g. of sodium acetate in 10 ml. of hot water. The appropriate hydrazine was dissolved in a minimum amount of hot water and the pyridoxal solution added in one portion. The mixture was heated for 5 min. and then cooled in an ice bath. The product was collected on a filter and recrystallized. II. A solution of pyridoxal hydrochloride (4.50 g.) in 25 ml. hot water was prepared. The appropriate hydrazine was dissolved in a minimum amount of hot ethanol and the pyridoxal hydrochloride solution added. The solution was heated for 5 min. and cooled to precipitate the product. The product was collected on a filter and recrystallized. III. To a solution of pyridoxal hydrochloride (4.50 g.) in 25 ml. of hot ethanol was added 3.50 g. of sodium acetate in 10 ml. of hot water. The precipitated sodium chloride was separated by filtration and the pyridoxal solution was added in one portion to a hot alcoholic solution of the appropriate hydrazine. The mixture was heated for 5 min., cooled in an ice bath and the product collected on a filter and recrystallized. [b] Solvents: C, chloroform; DW, dioxane/water; E, ethanol; EW, ethanol/water; M, methanol. [c] Washed with ethanol then with ether. [d] See ref. 4. [e] Calcd. for pyridoxal-2,4-dinitrophenylhydrazone hydrochloride.

non-reproducibly active in Sarcoma-180 tests: indole-3-carboxaldehyde dimethylhydrazone (± 250; 125, 250, 500); pyridoxal dinitrophenylhydrazone (−125, ±⁻500); methylhydrazone (−, ±8; toxic 30, 125); indole-3-carboxaldehyde 2,5-dichlorophenylhydrazone (±⁻125). Two are reproducibly active in Sarcoma-180 tests: indole-3-carboxaldehyde *p*-bromophenylhydrazone (−125; ±⁻, ±, ⁺500), and 2-benzothiazolylhydrazone (−125; ±⁻, ±, ⁻500).

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Penetration of Brain and Brain Tumors by Intravascular Injection of Alkylating Agents. IV[1]

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Maximum effectiveness of cytotoxic agents in the treatment of cancer may be achieved if they preferentially concentrate in the neoplasm. Following this hypothesis, cerebral perfusion of anticancer agents for the therapy of brain tumors has certain distinctive advantages. Whereas the normal and neoplastic tissues of the same organ generally show no differential permeability, primary and secondary neoplasms in the central nervous system (CNS) have a markedly increased permeability to many substances in contrast with adjacent normal areas.[2,3] Therefore, it may be possible to devise cancerocidal agents which, by cerebral perfusion, will achieve a maximum differential concentration in the tumor.

Lipid solubility has been noted to be an important factor in determining the penetration of a compound into brain tissue.[4-6] The

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