TABLE I

ANTITUMOR ACTIVITY[a] OF 1-SUBSTITUTED 3-HYDROXYUREAS (**1a-g**)

Compd	Mp (°C)	Yield (%)	Formula	Analysis	Test[b] system	Dose (mg/kg)	Survivors	Tumor weight[c] —Survival (days)— Test	Control	Per cent (T/C)
1a	171-173	29[d]	$C_8H_{10}N_2O_3$	C, H, N	LE	400	4/4	9.5	9.5	100
					WM	400	6/6	4.5	5.7	78
1b	146-147	43[e]	$C_8H_{10}N_2O_2$	C, H, N	LE	400	4/4	10.0	9.5	105
					LE	200	4/4	9.5	9.5	100
1c	134-136	46[e]	$C_7H_7ClN_2O_2$	C, H, N	LE	400	4/4	9.5	9.5	100
					LE	200	6/6	9.7	9.4	103
					WM	400	4/6	1.0	5.7	17
1d	128-129	31[e]	$C_4H_{10}N_2O_2$	C, H, N	LE	400	4/6	12.5	9.6	130
						200	6/6	10.8	8.7	124
					WM	400	6/6	6.8	8.9	76
1e	116-118	16[d]	$C_7H_{14}N_2O_2$	C, H, N	LE	400	6/6	9.2	9.6	95
					WM	400	6/6	5.0	5.7	87
1f	140-142	28[d]	$CH_4N_2O_2$	C, H, N	LE[f]	200		12.3	8.1	151
						400		16.2	8.1	200
1g	125-126	43[e]	$C_3H_8N_2O_2$	C, H, N	LE[f]	200	6/6	12.0	9.4	127
						400	6/6	12.5	9.1	137
					SA[f]	375	6/6	808	1185	68
					CA[f]	337	10/10	680	1536	44

[a] Testing was done at Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md. See *Cancer Chemother. Rep.*, **25**, 1, 10 (1962). [b] LE, L-1210 lymphoid leukemia; WM, Walker carcinosarcoma 256; SA, sarcoma 180; CA, adenocarcinoma 755. [c] For test systems SA and CA total tumor weight in grams: for test systems LE and WM, survival time in days. [d,e] Recrystallization solvents chloroform and 1,2-dichloroethane, respectively. [f] See ref 6.

equal vol of $FeCl_3 \cdot 6H_2O$ (2.0557 g) in H_2O. The gas that evolved from the blue solution was bubbled through 10 ml of cold (0–5°) Et_2O using a gas dispersion tube. Five minutes after mixing, the reaction vessel was heated to 50° for 10 min, producing a nearly colorless solution. An ir spectrum of the Et_2O solution showed strong absorptions at 2335, 665 (CO_2), 2280 (N=C=O), and 2220 (N≡N→O) cm^{-1}.

Fe(III)-HU Complex.—A 7.06×10^{-1} *M* solution (25 ml) of $FeCl_3 \cdot 6H_2O$ in abs EtOH was added to an equal vol of an EtOH solution of 7.06×10^{-1} *M* HU. The solvent from the blue solution was then evaporated off at reduced pressure and the resulting dark blue oil dissolved in 2 ml of abs EtOH. The colorless residue was filtered off and the filtrate on removal of the solvent at reduced pressure gave a dark green oil. As before, the formation of Fe(III)–HU complex was shown by spectrophotometric methods.

Spectrophotometric Determination of Fe(III)–HU and Fe(III)–EHU Complexes. Continuous Variation Method. Fe(III)–HU Complex in H_2O.—Aqueous solutions (250 ml) of 2×10^{-2} *M* $FeCl_3 \cdot 6H_2O$ and HU were prepared and appropriate volumes of each were added to ten 25-ml volumetric flasks to give the following mole fractions of ligand: 0.8, 0.20, 0.28, 0.40, 0.48, 0.52, 0.60, 0.72, 0.80, and 0.92. The solutions were mixed immediately prior to the determination of the absorbance at 560 mμ. The results are plotted in Figure 1 as absorbance *vs.* mole fraction of the ligand.

Fe(III)–EHU Complex in EtOH.—Appropriate volumes of 1×10^{-3} *M* abs EtOH solutions of EHU and $FeCl_3 \cdot 6H_2O$ were added to sixteeen 25-ml volumetric flasks such that the following mole fractions of ligand, 0.40 0.08, 0.12, 0.16, 0.20, 0.40, 0.48, 0.52, 0.60, 0.80, 0.88, and 0.92 resulted. Each solution was mixed immediately prior to the determination of absorbance at 610 mμ. As before, the results are plotted as absorbance *vs.* mole fraction ligand.

Molar Ratio Method.—The molar ratio method of Yoe and Jones[11] was applied to the Fe(III)–HU and Fe(III)–EHU complexes. The results, as shown in Figure 2, showed the formation of 1:1 complex in each case.

Acknowledgment.—This work was supported by Grants Ca-07333 and Ca-06140 from the National Institutes of Health.

Potential Antineoplastics. III. A Series of 1-Thiocarbamoyl-3-methyl-4-arylazo-5-methyl(or phenyl)pyrazoles

H. G. GARG AND R. A. SHARMA

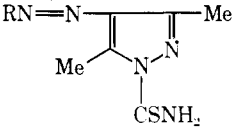
Department of Chemistry, University of Roorkee, Roorkee, India

Received October 29, 1969

The discovery that isoquinoline-1-carboxaldehyde thiosemicarbazone and its several congeners which possess the N–N–S or O–N–S tridentate ligand system, exhibit substantial antineoplastic activity,[1,2] and the

TABLE I

1-THIOCARBAMOYL-3,5-DIMETHYL-4-ARYLAZOPYRAZOLES



No.	R	Yield %	Mp, °C	Color[a]	Formula	Analyses
1	Ph	88	121–122	OYN	$C_{12}H_{13}N_5S$	N, S
2	2-MePh	85	138–139	YN	$C_{13}H_{15}N_5S$	N, S
3	4-MePh	82	142–143	YN	$C_{13}H_{15}N_5S$	N, S
4	3-ClPh	84	118–119	YN	$C_{12}H_{12}ClN_5S$	N, S, Cl
5	4-ClPh	81	150–151	ON	$C_{12}H_{12}ClN_5S$	N, S, Cl
6	2-EtOPh	78	146–147	YN	$C_{14}H_{17}N_5OS$	N, S
7	4-EtOPh	75	132–133	YP	$C_{14}H_{17}N_5OS$	N, S
8	2-MeOPh	79	147–148	YF	$C_{13}H_{15}N_5OS$	N, S
9	2-NO_2Ph	75	153–154	OYP	$C_{12}H_{12}N_6O_2S$	N, S
10	2,5-Me_2Ph	75	192–193	ON	$C_{14}H_{17}N_5S$	N, S
11	2-Cl-6-MePh	65	167–168	ON	$C_{13}H_{14}ClN_5S$	N, S, Cl

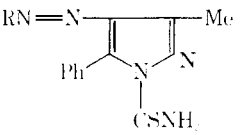
[a] B = bright; F = fibers; G = golden; N = needles; O = orange; P = plate; Pe = pale; Y = yellow.

(1) R. W. Brockman, J. R. Thomson, M. J. Bell, and H. E. Skipper, *Cancer Res.*, **16**, 167 (1956).

(2) F. A. French, and E. J. Blanz, Jr., *ibid.*, **25**, 1454 (1965); **26**, 1638 (1966).

Table II

1-Thiocarbamoyl-3-methyl-5-phenyl-4-arylazopyrazoles



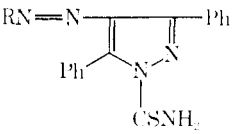
No.	R	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	Ph	80	144–145	YN	$C_{17}H_{15}N_5S$	N, S
2	2-MePh	76	163–164	OP	$C_{18}H_{17}N_5S$	N, S
3	4-MePh	79	172–173	BYN	$C_{18}H_{17}N_5S$	N, S
4	3-ClPh	84	131–133	YN	$C_{17}H_{14}ClN_5S$	N, S, Cl
5	4-ClPh	62	192–193	PeYF	$C_{17}H_{14}ClN_5S$	N, S, Cl
6	4-BrPh	70	208–209	YN	$C_{17}H_{14}BrN_5S$	N, S, Br
7	2-MeOPh	72	135–136	OYN	$C_{18}H_{17}N_5OS$	N, S
8	3-MeOPh	74	153–154	YN	$C_{18}H_{17}N_5OS$	N, S
9	3-NO_2Ph	62	193–194	PeYP	$C_{17}H_{14}N_6O_2S$	N, S
10	4-EtOPh	65	176–177	PeYF	$C_{19}H_{19}N_5OS$	N, S
11	2,4-Me_2Ph	70	179–180	YN	$C_{19}H_{19}N_5S$	N, S
12	2,5-Me_2Ph	72	191–192	YN	$C_{19}H_{19}N_5S$	N, S
13	2,6-Me_2Ph	75	143–144	ON	$C_{19}H_{19}N_5S$	N, S
14	2-Cl-6-MePh	65	128–129	OF	$C_{18}H_{16}ClN_5S$	N, S, Cl

[a] See footnote *a* of Table I.

Table III

Summary of the Screening Results against L-1210 Lymphoid Leukemia, Ascitic Fluid Implanted Intraperitoneally in BDF$_1$ Mice

No.	R	Survivors	T/C,[b] %	No.	R	Survivors	T/C,[b] %
1-Thiocarbamoyl-3,5-dimethyl-4-arylazopyrazoles[c]				8	3-MeOPh	4/6[q]	101
1	Ph	6/6[r]	107			6/6[f]	96
2	2-MePh	5/6[r]	95	9	3-NO_2Ph	6/6[r]	92
3	4-MePh	6/6[d]	103	10	4-EtOPh	6/6[s]	88
4	3-ClPh	5/6[r]	108			6/6[r]	94
		6/6[r]	105			6/6[d]	103
		6/6[d]	100	11	2,4-Me_2Ph	6/6[r]	95
		6/6[f]	96	12	2,5-MeO_2Ph	6/6[r]	95
5	4-ClPh	6/6[r]	94	13	2,6-Me_2Ph	5/6[r]	95
6	2-EtOPh	6/6[r]	102	14	2-Cl-6-MePh	6/6[r]	88
7	4-EtOPh	6/6[r]	94				
8	2-MeOPh	6/6[r]	114	1-Thiocarbamoyl-3,5-diphenyl-4-arylazopyrazoles[t,u]			
9	2-NO_2Pb	4/6[r]	111				
10	2,5-Me_2Ph	6/6[r]	107				
11	2-Cl-6-MePh	6/6[r]	102				



1-Thiocarbamoyl-3-methyl-5-phenyl-4-arylazopyrazoles[s]			
1	Ph	4/6[d]	101
		6/6[f]	95
2	2-MePh	6/6[r]	92
3	4-MePh	5/6[r]	85
		5/6[d]	90
		6/6[f]	94
4	3-ClPh	6/6[r]	101
		6/6[d]	104
5	4-ClPh	6/6[r]	94
6	4-BrPh	6/6[r]	92
7	2-MeOPh	6/6[r]	100

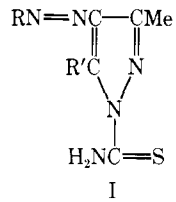
1	2-MePh	6/6	88
2	4-MePh	4/6	98
3	4-SO_2NH_2Ph	6/6	91
4	3-ClPh	6/6	95
5	4-ClPh	6/6	85
6	4-BrPb	6/6	85
7	3-NO_2Ph	6/6	76
8	2-MeOPh	6/6	88
9	4-MeOPh	6/6	98
10	2,4-Me_2Ph	6/6	90
11	2,5-Me_2Ph	6/6	89
12	2,6-Me_2Ph	6/6	95

[b] See formula of Table I. [c] Ratio of mean survival time of test animals (T) to control animals (C), %. Mean survival time of control is 30 days. [d] 400 mg/kg. [e] 150 mg/kg. [f] 300 mg/kg. [g] 75 mg/kg. [h] See formula of Table II. [i] 40 mg/kg. [j] 20 mg/kg. [k] 10 mg/kg. [l] See ref 5. [m] All doses for these compounds were 400 mg/kg.

essential role of azomethine linkages play in certain biological reactions,[3,4] led us to a study of compounds having mixed structural features of these types.

The present investigation reports (a) the synthesis of several 1-thiocarbamoyl-3-methyl-4-arylazo-5-methyl (or phenyl)pyrazoles and (b) the antinematic potency and host toxicity of 3,5-dimethyl-, 3-oplasyl-5-phenyl-, and 3,5-diphenyl[5]-1-thiocarbamoyl-4-arylazopyrazoles against L-1210 lymphoid leukemia.

The new 1-thiocarbamoylpyrazoles (I, R′ = Me or Ph) which were prepared by using the conditions for the preparation of 1-thiocarbamoyl-3,5-diphenyl-4-arylazopyrazoles in our laboratory earlier,[5] are listed in Tables I and II.



I

R = Substited phenyl
R′ = Me or Ph

Biological Results.—In a screen in BDF_1 mice for antitumor activity against *L-1210 lymphoid leukemia* (Table III) the compounds showed the following order of decreasing potency: 3,5-dimethyl-, 3-methyl-5-phenyl-, and 3,5-diphenyl-1-thiocarbamoyl-4-arylazopyrazoles. 1-Thiocarbamoyl-3-methyl-5-phenyl-4-(2,5-dimethoxyphenylazo)pyrazole was screened against *Human epidermoid carcinoma* in a nasopharynx cell culture tube assay and found inactive.

Experimental Section

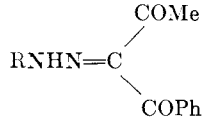
Melting points are uncorrected and were determined using a Kofler hot-stage apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

3-Arylhydrazono-2,3,4-pentanetriones were prepared by the method of Garg and Sharma.[5]

2-Arylhydrazono-1-phenyl-1,2,3-butanetriones were synthesized by the procedure of Garg and Singh.[6] Characteristics of new derivatives are summarized in Table IV.

1-Thiocarbamoyl-3-methyl-4-arylazo-5-methyl(or phenyl)-pyrazoles were obtained by the route used for the preparation of 3,5-diphenyl congeners.[5] Characteristics of 1-thiocarbamoyl-3,5-dimethyl-4-arylazopyrazoles (I, R′ = Me) and 1-thiocarbamoyl-3-methyl-4-arylazo-5-phenylpyrazoles (I, R′ = Ph) are given in Tables I and II, respectively.

TABLE IV
CHARACTERISTICS OF
2-ARYLHYDRAZONO-1-PHENYL-1,2,3-BUTANETRIONES



No.	R	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	Ph	80	97–98	PeYN	$C_{16}H_{14}N_2O_2$	C, H, N
2	4-BrPh	72	103–104	YN	$C_{16}H_{13}BrN_2O_2$	N, Br
3	2,6-Me_2Ph	65	90–91	GYP	$C_{18}H_{18}N_2O_2$	C, H, N
4	2-Cl-6-MePh	70	101–102	GYP	$C_{17}H_{15}ClN_2O_2$	N, Cl
5	3-ClPh	75	81–82	YN	$C_{16}H_{13}ClN_2O_2$	N, Cl

[a] See footnote *a*, Table I.

Acknowledgment.—The authors are greatly indebted to Drs. H. B. Wood and H. W. Bond of the Cancer Chemotherapy National Service Center for their cooperation and for making the screening data available. We are also thankful to Professor W. U. Malik, Head of the Chemistry Department, for providing the necessary facilities for this work and the C.S.I.R., New Delhi (India) for a Junior Research Fellowship (held by R. A. S.).

(3) D. D. Metzler, M. Ikawa, and E. E. Snell, *J. Amer. Chem Soc.*, **76**, 648 (1954).
(4) E. E. Snell, *Physiol. Rev.*, **33**, 516 (1953).
(5) H. G. Garg, and R. A. Sharma, *J. Med. Chem.*, **12**, 1122 (1969).
(6) H. G. Garg, and P. P. Singh, *J. Chem. Soc. C*, 1141 (1969).

Synthesis of Mono-, Di-, and Trimethoxy Derivatives of *N*,*N*-Bis(2-chloroethyl)aniline and Related Compounds as Antitumor Agents

A. H. SOMMERS, URSULA BIERMACHER, SANDRA BORGWARDT BREHM, AND JAMES H. SHORT

Organic Chemistry Department, Division of Experimental Therapy, Abbott Laboratories, North Chicago, Illinois 60064

Received November 10, 1969

The observation[1] that *N*,*N*-bis(2-chloroethyl)-2,3-dimethoxyaniline, originally prepared in these laboratories, caused significant inhibition of a number of test tumors including carcinoma 755 and Walker carcinoma 256 led us to synthesize the other dimethoxy isomers as well as the analogous mono- and trimethoxy derivatives for screening as antitumor agents. Other analogs including chloro and trifluoromethyl derivatives, as well as some 2-chloropropyl homologs, are also described.

The desired compounds were prepared in two steps starting with the appropriately substituted aniline. The latter compound was alkylated with ethylene oxide or propylene oxide as described in a previous publication.[2] The diols not described in that paper are collected in Table I.

The diols were converted into the desired dichloro derivatives with $POCl_3$ utilizing the procedures of Ross[3] and Elderfield.[4] They are listed in Table II.

In agreement with an unproven but often-observed rule, the activity of the other compounds in Table II was of a lower order than that of *N*,*N*-bis(2-chloroethyl)-2,3-dimethoxyaniline (**4**). The antitumor screening data for many of the compounds in Table II have been published.[5]

(1) J. Leiter, A. R. Bourke, S. A. Schepartz, and I. Wodinsky, *Cancer Res.*, **20**, 760 (1960).
(2) M. Freifelder and G. R. Stone, *J Org. Chem.*, **26**, 1477 (1961).
(3) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).
(4) R. C. Elderfield, I. S. Covey, J. B. Geiduschek, W. L. Meyer, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, **23**, 1749 (1958).
(5) J. Leiter, B. J. Abbott, S. A. Schepartz, and I. Wodinsky, *Cancer Res.* **24**, 383, 1066 (1964); **25**, 27, 164 (1965).