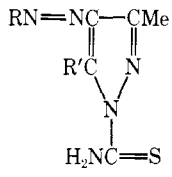
essential role of azomethine linkages play in certain biological reactions,[3,4] led us to a study of compounds having mixed structural features of these types.

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

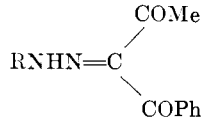
Melting points are uncorrected and were determined using a Kofler hot-stage apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

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

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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.

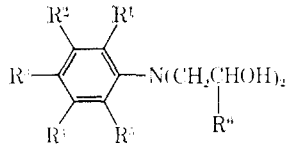
The diols were converted into the desired dichloro derivatives with $POCl_3$ utilizing the procedures of Ross[3] and Elderfield.[4] They are listed in Table II.

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).

TABLE I

N,N-BIS(2-HYDROXYETHYL)- AND *N,N*-BIS(2-HYDROXYPROPYL)ANILINES[a]



	R¹	R²	R³	R⁴	R⁵	R⁶	Yield, %	Bp, °C (mm)	$n^{25}D$	Formula	Anal.
1[b]	CH_3O	CH_3O	H	H	H	H	85	164 (0.1)	1.5476	$C_{12}H_{19}NO_4$	C, H, N
2[c]	CH_3O	H	CH_3O	H	H	H	88	169 (0.1)	1.5435	$C_{12}H_{19}NO_4$	C, H, N
3[c,d]	CH_3O	H	H	CH_3O	H	H	78	166 (0.2)	1.5497	$C_{12}H_{19}NO_4$	C, H, N
4[e]	CH_3O	H	H	H	CH_3O	H	87	149 (0.1)	1.5295	$C_{12}H_{19}NO_4$	C, H, N
5[e,f]	H	CH_3O	CH_3O	H	H	H	90	190 (0.2)		$C_{12}H_{19}NO_4$	C, H
6[g]	H	CH_3O	H	CH_3O	H	H	85	177 (0.1)	1.5678	$C_{12}H_{19}NO_4$	C, H, N
7[g]	CH_3O	CH_3O	CH_3O	H	H	H	89	195 (0.7)	1.5345	$C_{13}H_{21}NO_5$	C, H, N
8[h]	CH_3O	CH_3O	H	CH_3O	H	H	75	184 (0.2)	1.5482	$C_{13}H_{21}NO_5$	C, H, N
9[e]	CH_3O	CH_3O	H	H	CH_3O	H	59	180 (0.5)	1.5320	$C_{13}H_{21}NO_5$	C, H, N
10[i]	CH_3O	H	CH_3O	CH_3O	H	H	64	184 (0.1)	1.5427	$C_{13}H_{21}NO_5$	C, H, N
11[k,l]	CH_3O	H	CH_3O	H	CH_3O	H	61	181 (0.4)	1.5332	$C_{13}H_{21}NO_5$	C, H, N
12[e,m]	H	CH_3O	CH_3O	CH_3O	H	H	76	225 (0.5)	1.5570	$C_{13}H_{21}NO_5$	C, H, N
13[e,n]	H	Cl	CH_3	H	H	H	96			$C_{11}H_{16}ClNO_2$	C, H, Cl
14[e]	H	Cl	Cl	H	H	H	96	210–213 (1.4)	1.5936	$C_{10}H_{13}Cl_2NO_2$	C, H, N
15[e,n]	H	Cl	H	Cl	H	H	41			$C_{10}H_{13}Cl_2NO_2$	C, H, N
16[e,o]	CH_3O	H	H	H	H	CH_3	91	140 (0.3)	1.5245	$C_{13}H_{21}NO_3$	C, H
17[e,p]	H	H	CH_3O	H	H	CH_3	91	163 (0.3)	1.5435	$C_{13}H_{21}NO_3$	C, H
18[e,p]	CH_3O	H	H	CH_3O	H	CH_3	63	147–148 (0.2)	1.5359	$C_{14}H_{23}NO_4$	C, H, O
19[e,p]	H	CH_3O	CH_3O	H	H	CH_3	79	175–177 (0.2)		$C_{14}H_{23}NO_4$	C, H

[a] The compounds described in this table were prepared by allowing the appropriate aniline derivatives to react with ethylene oxide or propylene oxide as described in ref 2. [b] 2,3-Dimethoxyaniline was prepared as described by F. Mauthner, *J. Prakt. Chem.*, **149**, 328 (1937) starting from 2,3-dimethoxybenzoic acid (Aldrich Chemical Co.). [c] The required aniline derivative was purchased from Aldrich Chemical Co. [d] This diol has been described in U. S. Patent 2,044,045, A. W. Baldwin and A. H. Knight, 1936, *Chem. Abstr.*, **30**, 5426 (1936). [e] 2-Nitroresorcinol (Distillation Products Industries) was methylated according to the procedure of A. Baeyer, *Ann. Chem.*, **372**, 80 (1910) and reduced in the manner described by T. Ekstrand and N. Lofgren, *Acta Chem. Scand.*, **6**, 1016 (1952). [f] The diol melts at 72–73°. [g] 2,3,4-Trimethoxyaniline was prepared according to the procedure described by F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **23**, 19 (1958). [h] The preparation of 2,3,5-trimethoxyaniline from 5-nitrovanillin (Aldrich Chemical Co.) has been described by H. Richtzenhain and P. Nippus, *Chem. Ber.*, **82**, 408 (1949). [i] The preparation of 2,3,6-trimethoxyaniline was accomplished by the procedure described by H.-J. Teuber and M. Hasselbach, *Chem. Ber.*, **92**, 674 (1959). [j] Nitration of 1,2,4-trimethoxybenzene (Aldrich Chemical Co.) was effected in the manner described by R. Fabinyi and T. Szeki, *Chem. Ber.*, **39**, 3679 (1906). The nitro group was hydrogenated over Raney nickel. [k] 2,4,6-Trimethoxyaniline was prepared according to the procedure of M. Geisert and H. Oelschlaeger, *J. Prakt. Chem.*, **35**, 110 (1967), except that hydrogenation was effected over 5% Pd–C at low pressure. [l] The diol melts at 86° after recrystallization from C_6H_6–C_6H_{14}. [m] The diol melts at 66–67° after recrystallization (C_6H_6). [n] Mp. 75–76° after recrystallization from hexane. This diol has been described in U. S. Patent 2,830,056, H. Ruschig, D. Schmidt-Barbo, H. Leditschke, M. Schorr, and G. Lammler, April 8, 1958, *Chem. Abstr.*, **53**, 3253 (1959). [o] The diol melted at 108–110° after crystallization (C_6H_6). [p] The 2-hydroxypropyl rather than the 2-hydroxy-1-methylethyl structure was assigned to this compound according to the rule of Krassousky, K. Krassousky, *Compt. Rend.*, **146**, 236 (1908).

Experimental Section[6]

2-Allyloxyaniline.[7]—A solution of 90 g of 1-allyloxy-2-nitrobenzene[2] and 240 g (1.0 mol) of $Na_2S \cdot 9H_2O$ in 2 l of 50% EtOH was heated under reflux for 16 hr. The reaction mixture was concentrated and extracted (Et_2O). The Et_2O layer was extracted with 3 *N* HCl. This solution was made alkaline and extracted (Et_2O) and the combined ether portions were dried and distilled. A colorless oil distilled at 80° (0.3 mm), $n^{25}D$ 1.5636. The yield was 46.1 g (62%). This compound has been prepared previously by reduction with $SnCl_2$ in unstated yield,[8] lit.[8] bp 129–130° (10 mm).

***N,N*-Bis(2-hydroxyethyl)aniline and *N,N*-Bis(2-hydroxypropyl)aniline Derivatives.**—The diols not previously described by Freifelder and Stone[2] were prepared by reaction of 2 mol of ethylene oxide or propylene oxide with the appropriately substituted aniline and they are collected in Table I.

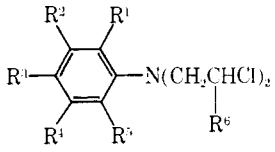
***N,N*-Bis(2-chloroethyl)aniline and *N,N*-Bis(2-chloropropyl)aniline Derivatives.**—The diols were allowed to react with $POCl_3$ according to the procedure of Ross[3] or Elderfield.[4] The products are described in Table II.

(6) Microanalyses were provided by Mr. Elmer F. Shelberg, Mr. Orville Kolsto and their associates of the Abbott microanalytical laboratory. Pressure reactions and catalytic hydrogenations were carried out by Mr. Morris Freifelder and Mr. George Stone. Where analyses are indicated only by symbols of the elements, analytical results for those elements are within ±0.4% of the theoretical values.

(7) Catalytic reduction of 1-allyloxy-2-nitrobenzene was unsuccessful; see ref 2.

(8) J. v. Braun and O. Braunsdorf, *Chem. Ber.*, **54**, 685 (1921).

Table II: *N*,*N*-Bis(2-chloroethyl)- and *N*,*N*-Bis(2-chloropropyl)anilines[a]



	R¹	R²	R³	R⁴	R⁵	R⁶	Yield, %	Bp, °C (mm)	$n^{25}D$	Mp, °C	Formula	Anal.
1[b]	CH_3O	H	H	H	H	H	72	130 (0.5)	1.5471		$C_{11}H_{15}Cl_2NO$	C, H
2[c]	H	CH_3O	H	H	H	H	83	132 (0.1)	1.5690		$C_{11}H_{15}Cl_2NO$	C, H
3[d]	H	H	CH_3O	H	H	H	62	146 (0.5)		50–51		
4	CH_3O	CH_3O	H	H	H	H	73	142 (0.2)	1.5483	37–38	$C_{12}H_{17}Cl_2NO_2$	C, H, N
5	CH_3O	H	CH_3O	H	H	H	84	129 (0.1)	1.5422		$C_{12}H_{17}Cl_2NO_2$	C, H
6	CH_3O	H	H	CH_3O	H	H	83	132 (0.2)	1.5493		$C_{12}H_{17}Cl_2NO_2$	C, H
7	CH_3O	H	H	H	CH_3O	H	53	129 (0.1)		75–78	$C_{12}H_{17}Cl_2NO_2$	C, H
8	H	CH_3O	CH_3O	H	H	H	70	147 (0.2)	1.5646	45–45.5	$C_{11}H_{17}Cl_2NO_2$	C, H
9	H	CH_3O	H	CH_3O	H	H	83	155 (0.1)	1.5655	64–67	$C_{12}H_{17}Cl_2NO_2$	C, H
10	CH_3O	CH_3O	CH_3O	H	H	H	54	147 (0.1)	1.5365		$C_{13}H_{19}Cl_2NO_3$	C, H, N
11	CH_3O	CH_3O	H	CH_3O	H	H	6			90–92	$C_{13}H_{19}Cl_2NO_3$	C, H
12	CH_3O	CH_3O	H	H	CH_3O	H	55	162 (1.0)	1.5389		$C_{13}H_{19}Cl_2NO_3$	C, H, N
13	CH_3O	H	CH_3O	CH_3O	H	H	57	159 (0.1)		68–69	$C_{13}H_{19}Cl_2NO_3$	C, H
14	CH_3O	H	CH_3O	H	CH_3O	H	65			75–77	$C_{13}H_{19}Cl_2NO_3$	C, H, N
15	H	CH_3O	CH_3O	CH_3O	H	H	57	169 (0.1)	1.5555	51–53	$C_{13}H_{19}Cl_2NO_3$	C, H, N
16	CH_2=$CHCH_2O$	H	H	H	H	H	23	136 (0.3)	1.5563		$C_{13}H_{17}Cl_2NO$	C, H
17	C_2H_5O	H	H	H	H	H	70	141 (0.4)	1.5381		$C_{12}H_{17}Cl_2NO$	C, H
18	$CH_3(CH_2)_3O$	H	H	H	H	H	94	156 (1.5)	1.5281		$C_{14}H_{21}Cl_2NO$	C, H
19	H	$CH_3(CH_2)_3O$	H	H	H	H	42	172 (1.9)	1.5434		$C_{14}H_{21}Cl_2NO$	C, H
20	H	H	$CH_3(CH_2)_3O$	H	H	H	60	172 (1.0)	1.5425		$C_{14}H_{21}Cl_2NO$	C, H
21	C_6H_5O	H	H	H	H	H	82	139 (0.1)	1.5829		$C_{16}H_{17}Cl_2NO$	C, H
22	Cl	H	H	H	H	H	77	132 (0.4)	1.5572		$C_{10}H_{12}Cl_3N$	C, H
23[e]	H	Cl	H	H	H	H	95	158 (2.0)	1.5837	36–38	$C_{10}H_{12}Cl_3N$	C, H
24[f]	H	H	Cl	H	H	H	66			71–72		
25[g]	H	CF_3	H	H	H	H	80	138 (3.0)	1.5170		$C_{11}H_{12}Cl_2F_3N$	C, H
26[b]	CH_3	H	H	H	H	H	82	118 (0.3)	1.5409		$C_{11}H_{15}Cl_2N$	C, H
27[h]	H	CH_3	H	H	H	H	90	125 (0.1)	1.5654		$C_{11}H_{15}Cl_2N$	C, H
28	H	Cl	Cl	H	H	H	54			57–59	$C_{10}H_{11}Cl_4N$	C, H, Cl
29	H	Cl	H	Cl	H	H	71			104–106	$C_{10}H_{11}Cl_4N$	C, H, N
30[i]	H	Cl	CH_3	H	H	H	55	162–166 (0.8)	1.5777		$C_{11}H_{14}Cl_3N$	C, H
31[j]	H	H	CH_3O	H	H	CH_2	78	154–157 (0.8)	1.5430		$C_{13}H_{19}Cl_2NO$	C, H
32	CH_3O	H	H	CH_3O	H	CH_3	65	137–138 (0.3)	1.5355		$C_{14}H_{21}Cl_2NO_2$	C, H, N
33	H	CH_3O	CH_3O	H	H	CH_3	69	146 (0.2)	1.5459		$C_{14}H_{21}Cl_2NO_2$	C, H

[a] These dichloro compounds were obtained by the action of $POCl_3$ on the corresponding diols as described in ref 3 and 4. Those compounds which solidified were crystallized from C_6H_{14} or C_6H_6–C_6H_{14}. The required diols not described in Table I are described in ref 2. [b] This compound has been described by Ross, ref. 3, as the picrate. [c] W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955), have reported $n^{25}D$ 1.5708 for this compound. [d] Ross, ref 3, reported mp 52°. [e] W. Schulze and H. Willitzer, *J. Prakt. Chem.*, **31**, 136 (1966) found mp 36° for this compound. [f] Ross, ref 3, reported mp. 74–75°. [g] This compound has been reported in British patent 948,766, A. S. F. Ash, A. M. Creighton, and W. R. Wragg, to May and Baker, Ltd., Feb. 5, 1964, *Chem. Abstr.*, **60**, 12028 (1964). [h] Ross, ref 3, has described the starting diol. He reported mp 33° for the dichloro compound. [i] The recorded bp is 182–183° (4 mm). For reference see Table I, footnote *n*. [j] The reported melting point for this compound is 68–70° according to J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949).

New Compounds

Benzylidene Hydrazides as Potential Anticancer Agents

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Received November 29, 1969

Based on reports of antitumor activity of aromatic Schiff bases,[1-3] the N-mustards shown in Table I were prepared from substituted *N*-phenylanthranilic acid hydrazides,[4] as described in the Experimental Section. They were evaluated by the CCNSC, National Cancer Institute, Bethesda, Md. against L1210 lymphoid leukemia in mice by i.p. injection, and were found to be nontoxic and inactive in this test.

Experimental Section

All melting points were obtained on a Thomas-Hoover Unimelt and are uncorrected. Satisfactory ir spectra were recorded for all compounds. The ir spectra were recorded using a Perkin-Elmer Model 337 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for these elements were within ±0.4% of the theoretical values.

***N*-Phenylanthranilic Acid *p*-Bis(2-chloroethyl)aminobenzyl-**

(1) M. G. Dhapalapur, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **11**, 1014 (1968); C. T. Bahner, D. Brotherton, and M. K. Brotherton, *ibid.*, **11**, 405 (1968); S. S. Sabnis, *Indian J. Chem.*, **5**, 619 (1967); F. D. Popp, *J. Med. Chem.*, **7**, 210 (1964).

(2) 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); R. C. Elderfield and T. K. Lido, *ibid.*, **26**, 4996 (1961).

(3) M. G. Dhapalapur, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **11**, 154 (1968).

(4) N. H. Berner, R. S. Varma, and D. W. Boykin, Jr., *ibid.*, **13**, 552 (1970).