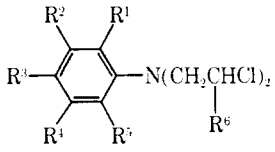
Table II: N,N-Bis(2-chloroethyl)- and N,N-Bis(2-chloropropyl)anilines[a]



	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	$C_{12}H_{17}Cl_2NO_2$	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	$C_{10}H_{11}Cl_3N$	C, H, Cl
29	H	Cl	H	Cl	H	H	71			104–106	$C_{10}H_{11}Cl_3N$	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

D. W. Boykin, Jr., and R. S. Varma

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

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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-**

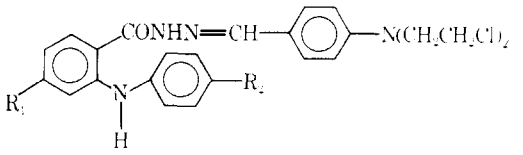
(1) M. G. Dhapalapur, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **11**, 1014 (1968); C. T. Bahner, D. Brotherton, and M. K. Brotherton, *ibid.*, **11**, 405 (1968); S. S. Sabnis, *Indian J. Chem.*, **5**, 619 (1967); F. D. Popp, *J. Med. Chem.*, **7**, 210 (1964).

(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).

Table I



Cmpd[a]	R_1	R_2	% Yield	Mp, °C	Formula[c]
1	Cl	Cl	70	196–198	$C_{24}H_{22}Cl_4N_4O$
2	H	OCH_3	80	215–217	$C_{25}H_{26}Cl_2N_4O_2$
3	H	Cl	80	194–196	$C_{24}H_{23}Cl_3N_4O$
4[b]	H	Br	85	198–199.5	$C_{24}H_{23}BrCl_2N_4O$

[a] All compounds were recrystallized from EtOH unless otherwise noted. [b] Recrystallization from MeCN. [c] All compounds were analyzed for C, H, N.

idene Hydrazides.—In a typical reaction, 3.06 g (0.01 mol) of *N*-(4-bromophenyl)anthranilic acid hydrazide, 2.46 g (0.01 mol) of *p*-*N*,*N*-bis(2-chloroethyl)aminobenzaldehyde in 40 ml of EtOH containing 1 drop of HOAc were refluxed for 4 hr. The reaction mixture was cooled, the precipitate filtered to yield 5.1 g of crude material, mp 195–199°. Recrystallization from MeCN raised the melting point to 198–199.5°.

Some Substituted [*p*-(*p*-Ethoxyphenyl)anilino]acetamides

G. Brancaccio, G. Lettieri, A. Larizza, R. Viterbo, and G. C. Perri

Research Laboratories, Richardson–Merrell S.p.A., Naples, Italy

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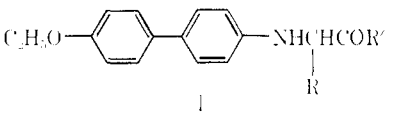
In further search for pharmacologically active arylaminoacylamide derivatives[1] we have synthesized a series of compounds of the general formula I. However, none of the compounds described here (see Table I) was active when screened for analgetic or antiinflammatory activity.



I

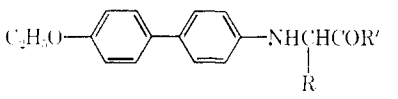
Experimental Section[2]

General Procedure.—A solution of 0.1 mol of *p*-(*p*-ethoxyphenyl)aniline and 0.1 mol of the appropriate halogenoacylamide in 200 ml of *n*-PrOH was refluxed in the presence of an excess of $NaHCO_3$ for 3–4 days. The cooled reaction mixture was concentrated, diluted (H_2O), and filtered. The solid obtained was recrystallized till the compound was chromatographically pure.

Ethyl Ester of *N*-[*p*-(*p*-Ethoxyphenyl)phenyl]glycine.—*p*-(*p*-Ethoxyphenyl)aniline (30 g), 24 g (16 ml) of ethyl bromoacetate, and 15 g of $NaHCO_3$ in 200 ml of *n*-PrOH, were refluxed for 4 days. The cooled reaction mixture was filtered and the solid residue was partitioned (Et_2O–H_2O). The Et_2O layer was separated, dried (Na_2SO_4), and concentrated to dryness (26 g, yield 58%). A sample recrystallized from EtOH had mp 137–139°. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

[*p*-(*p*-Ethoxyphenyl)anilino]acetyl(*N*-methyl)piperazide.—A mixture of 5.5 g of *N*-[*p*-(*p*-ethoxyphenyl)phenyl]glycine ethyl ester and 4.4 ml of freshly distilled *N*-methylpiperazine was refluxed for 4 days. The reaction mixture was then treated with EtOAc and filtered (see Table I).

Table I



R	R′	Mp, °C	Recrystn solvent[a]	Formula[b]
H	EtNH	152–154	A	$C_{18}H_{22}N_2O_2$
H	*n*-PrNH	159–161	A	$C_{19}H_{24}N_2O_2$
H	*i*-PrNH	150–151	A	$C_{19}H_{24}N_2O_2$
H	*n*-BuNH	153–155	B	$C_{20}H_{26}N_2O_2$
H	*sec*-BuNH	113–115	A + D	$C_{20}H_{26}N_2O_2$
H	*i*-BuNH	165–167	A	$C_{20}H_{26}N_2O_2$
H	*t*-BuNH	129–131	A + D	$C_{20}H_{26}N_2O_2$
CH_3	*n*-PrNH	124–126	B	$C_{20}H_{26}N_2O_2$
H	Et_2N	151	C	$C_{21}H_{26}N_2O_2$
H	*n*-Pr_2N	124–125	C	$C_{22}H_{30}N_2O_2$[c]
H	Pyrrolidino	176–178	E	$C_{20}H_{24}N_2O_2$
H	Piperidino	169–171	A	$C_{21}H_{26}N_2O_2$
H	Morpholino	145–147	A	$C_{20}H_{24}N_2O_3$
H	*N*-Methylpiperazino	166–168	F	$C_{21}H_{27}N_3O_2$

[a] A, EtOAc; B, EtOH; C, 95° EtOH; D, petr ether (bp 40–68°); E, MeCN; F, dioxane. [b] All compounds were analyzed for C, H, N. The analytical results obtained are within ±0.3% of the theoretical values. [c] C: calcd, 74.54; found, 74.11.

Acknowledgment.—We are indebted to Dr. A. De Leonibus for the microanalyses and to Dr. M. L. Reviglio for the tlc.

Substituted Chroman-6-ylureas and Thioureas

G. Lettieri, G. Brancaccio, A. Larizza, and R. Viterbo

Research Laboratories, Richardson–Merrell S.p.A., Naples, Italy

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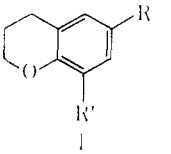
In connection with our interest in pharmacological properties of 6-aminochroman derivatives[1] we have synthesized compounds of structure I where R represents an alkyl or arylurea, or thiourea moiety; and



I

R′ can be H, Cl or Me. These compounds are related to the pharmacologically active 2,3-dihydro-2-methylbenzofuranyl analogs.[2]

Experimental Section[3]

***N*-Methyl-6-aminochromane.**—A mixture of 6-aminochroman[4] (9 g) and 90% HCO_2H (3 ml) was boiled for 90 min.

(1) A. Larizza and G. Brancaccio, U.S. Patent 3,264,349; G. Brancaccio, A. Larizza, G. Lettieri, and R. Viterbo, *Farmaco Ed. Sci.*, **22**, 930 (1967); and the references indicated therein.

(2) Melting points were determined in capillary tubes in a heated copper block and are uncorrected. Tlc was carried out on silica gel using PhH–MeAc–petr ether (1:1:1) as the solvent system.

(1) G. Lettieri, G. Brancaccio, A. Larizza, R. Viterbo, and G. C. Perri, *Farmaco Ed. Sci.*, **24**, (1970), in press.

(2) David R. Herbst, U. S. 3,252,999 [*Chem. Abstr.*, **66**, 3835 (1966)].

(3) Melting points were determined in open capillary tubes and are uncorrected.

(4) V. Hach, *Collect. Czech. Chem. Commun.*, **24**, 3136 (1959).