upon attempted recrystn of the salt from MeOH. The gum afforded 8.8 g (40%) of **2**·2HCl.2MeOH as cryst from $CHCl_3$–Et_2O; mp 183–185°; nmr (D_2O) δ 6.85 (symm 6 line m, 2 H, C_6H_2), 4.0–2.5 (m, 18 H, $PhCH_2CH_2$, PhCH, CH_2NCH_2, NCH_3, $2CH_3O$), and 2.5–1.3 ppm (m, 7 H, $CH_2CH(CH_2)CH_2$). *Anal.* ($C_{20}H_{38}Cl_2N_2O_4$) C, H, N.

Potential Anticancer Agents. Nitrogen Mustards of Aminophenylthiazoles

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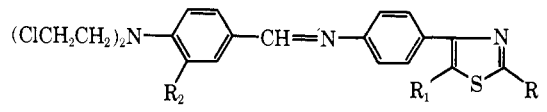
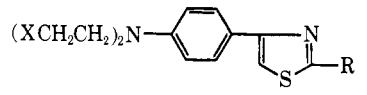
We have already reported the synthesis of a variety of Schiff bases (I) from substituted benzaldehyde N-mustards and 4-(*p*-aminophenyl)thiazoles[2,3] many of which have shown interesting activity against experimental tumor systems.



I



II

With R = CH_2OPh, R_1 = H, and R_2 = OCH_3, the Schiff base I was active against Dunning leukemia (solid) (6/6 cures at 11 mg/kg per day), L 1210 lymphoid leukemia (T/C = 146% at 15 mg/kg per day), and Walker 256 intramuscular (T/C = 4% at 33 mg/kg per day).[3] With R = CH_2Ph, R_1 = CH_3, and R_2 = OCH_3, I had good activity against L 1210 lymphoid leukemia and Walker carcinosarcoma 256 (im).[3] The most active in this series (I) against L 1210 lymphoid leukemia (2 out of 6 cures at 25 mg/kg per day and T/C = 129% at 3 mg/kg per day) had R = R_1 = CH_3 and R_2 = OCH_3.

The structure–activity study of these compounds having shown the importance of aminophenylthiazoles for the anticancer activity, we decided to synthesize a series of N-mustards (II, X = Cl) from these active aminophenylthiazoles.

Chemistry.—4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]-phenyl}-2-substituted thiazoles (II, X = OH) were prepared by suspending the requisite aminophenylthiazole in aq AcOH and treating with ethylene oxide (yields 45–55%). But we could not isolate the desired product when the substituent in position 2 of the thiazole was Ph. Accordingly, another method was tried wherein a suspension of ω-chloro-*p*-aminoacetophenone in aq AcOH was treated with $(CH_2)_2O$ to furnish the corresponding bis(2-hydroxyethyl) compd in 55% yield which on condensation with the appropriate thioamide in dry EtOH afforded all the bis(2-hydroxyethyl)thiazoles (II, X = OH) as cryst solids (Table I).

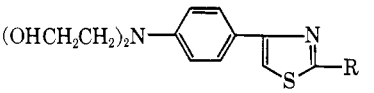
(1) Government of India Research Scholar.

(2) S. S. Sabnis, *Indian J. Chem.*, **5**, 619 (1967).

(3) J. D. Modi, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **13**, 935 (1970).

TABLE I

4-{*p*-[*N*,*N*-BIS(2-HYDROXYETHYL)AMINO]PHENYL}THIAZOLES



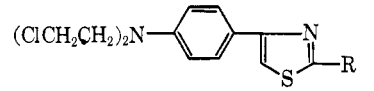
No.	R	Yield,[a,b] %	Mp, °C (uncor)	Formula[c]
1	CH_3	55	132–134	$C_{14}H_{18}N_2O_2S$[d]
2	$C_6H_5CH_2$	48	127–128	$C_{20}H_{22}N_2O_2S$
3	$C_6H_5OCH_2$	57	138–139	$C_{20}H_{22}N_2O_3S$
4	p-$CH_3C_6H_4OCH_2$	53	128–129	$C_{21}H_{24}N_2O_3S$
5	o-$CH_3C_6H_4OCH_2$	52	158–160	$C_{21}H_{24}N_2O_3S$
6	C_6H_5	50	85–87	$C_{19}H_{20}N_2O_2S$
7	p-$CH_3C_6H_4$	52	129–130	$C_{20}H_{22}N_2O_2S$[d]
8	p-$CH_3OC_6H_4$	50	120–122	$C_{20}H_{22}N_2O_3S$
9	p-ClC_6H_4	55	151–153	$C_{19}H_{19}ClN_2O_2S$

[a] The yields reported are the results of single experiment and are based on ω-chloro-4-[*N*,*N*-bis(2-hydroxyethyl)amino]acetophenone. [b] Recrystd from EtOH–H_2O. [c] All compds were anal. for N, S and were within 0.4% of theor values. [d] *Anal.* C, H.

The identity of compds prepared by both the methods was established by mmp and ir spectra. The corresponding N-mustards (II, X = Cl) were obtained by the use of $POCl_3$[4] in 30–35% yields (Table II).

TABLE II

4-*p*-{[*N*,*N*-BIS(2-CHLOROETHYL)AMINO]PHENYL}THIAZOLES



No.	R	Mp, °C[a]	Formula[b]
1	CH_3	72–74	$C_{14}H_{16}Cl_2N_2S$[c]
2	$C_6H_5CH_2$	110–112	$C_{20}H_{20}Cl_2N_2S$
3	$C_6H_5OCH_2$	123–125	$C_{20}H_{20}Cl_2N_2OS$
4	p-$CH_3C_6H_4OCH_2$	112–114	$C_{21}H_{22}Cl_2N_2OS$
5	o-$CH_3C_6H_4OCH_2$	107–109	$C_{21}H_{22}Cl_2N_2OS$
6	C_6H_5	68–69	$C_{19}H_{18}Cl_2N_2S$
7	p-$CH_3C_6H_4$	108–110	$C_{20}H_{20}Cl_2N_2S$
8	p-$CH_3OC_6H_4$	105–107	$C_{20}H_{20}Cl_2N_2OS$
9	p-ClC_6H_4	138–139	$C_{19}H_{17}Cl_3N_2S$

[a] Recrystd from EtOH–H_2O except **6** which was recrystd from hexane. [b] All compounds were anal. for N and S and were within 0.4% of theor values. [c] *Anal.* C, H.

Biological Activity.—Four representative compds were screened by C.C.N.S.C. and their data are summarized in Table III. All these showed a low order of toxicity compared to our earlier Schiff bases from aminophenylthiazoles. Only **1** exhibited significant activity against Dunning leukemia (solid) and also showed high tumor inhibition in Walker carcinosarcoma 256 (im).

Experimental Section[5,6]

2-Methyl-4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}-thiazole.—Ethylene oxide (20 g) was bubbled in a suspension of 2-methyl-4-(*p*-aminophenyl)thiazole (1.9 g, 0.01 mole) in AcOH (50 ml of 4 *N*) at 0°. The mixt was stirred in ice bath for 7 hr and then left at *ca.* 10° for 4 days. It was neutralized ($NaHCO_3$) to pH 7 and cooled (ice). The granular solid was filtered off, washed (H_2O), and recrystd (EtOH–H_2O).

2-Phenyl-4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}-thiazole.—ω-Chloro-4-[*N*,*N*-bis(2-hydroxyethyl)amino] acetophenone was obtained by the action of $(CH_2)_2O$ on ω-chloro-*p*-aminoacetophenone in 4 *N* AcOH as described above. It was

(4) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).

(5) Anal. results obtained were within ±0.4% of theor values.

(6) Melting points are capillary melting points and are uncor.

TABLE III
SCREENING RESULTS OF NITROGEN MUSTARDS FROM AMINOPHENYLTHIAZOLES[a]

No.[b]	Test[c] system	Dose, mg/kg	Survivors	Cures	Animal[d] wt diff, g ($T - C$)	Tumor[e] wt, g, or survival[f] days, T/C	T/C, %
1	3 LE	400.0	4/4		−1.0	10.0/9.0	111
		200.0	4/4		−0.1	8.8/9.0	97
		100.0	4/4		−0.5	9.5/9.0	105
	AA	100.0	3/3				
		33.0	3/3				
		10.0	3/3				
		3.0	3/3				
	DL	200.0	7/7	3	−22.0	27.7/15.0	184
		100.0	7/7		−09.0	19/15	126
		50.0	7/7		−02.0	17/15	113
		25.0	7/7		−02.0	16/15	106
	5 WM	400.0	6/6		−10.0	0.5/3.8	13
2	3 LE	400.0	6/6		1.3	8.8/9.4	93
		200.0	6/6		0.7	8.7/9.4	92
		100.0	6/6		1.2	8.8/9.4	93
	AA	330.0	3/3				
		100.0	3/3				
		33.0	3/3				
		10.0	3/3				
	5 WM	330.0	6/6		−5.0	3.9/6.1	63
3	3 LE	400.0	4/4		0.9	8.3/9.1	91
		200.0	4/4		−0.4	8.8/9.1	96
		100.0	4/4		−1.0	9.3/9.1	102
	AA	330.0	3/3				
		100.0	3/3				
		33.0	3/3				
		10.0	3/3				
	5 WM	330.0	6/6		1.0	3.5/7.3	47
5	3 LE	400.0	4/4		−1.8	8.8/8.4	104
		200.0	4/4		−1.3	9.5/8.4	113
		100.0	4/4		0.7	8.5/8.4	101

[a] For test procedures see *Cancer Chemother. Rep.*, **25**, 1 (1962). [b] Numbers refer to those from Table II. [c] AA = toxicity; 3 LE = L 1210 lymphoid leukemia; 5 WM = Walker 256 (im); DL = Dunning leukemia (solid). [d] Av wt change of test group minus av wt change of control animals in grams; T = test; C = control. [e] Tumor wt for 5 WM test system. [f] Survival days for 3 LE and DL test systems.

recrystd (C_6H_6), yield 55%, mp 121°. *Anal.* ($C_{12}H_{16}ClNO_3$) C, H, N.

A mixt of this halo ketone (2.57 g, 0.01 mole), thiobenzamide (1.5 g, 0.011 mole), and abs EtOH (15 ml) was heated at reflux temp for 3 hr. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O and decolorized. The filtrate on basifying (NH_4OH) gave the required thiazole which was recrystd (EtOH–H_2O).

All the 4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}-2-substituted thiazoles were prepared similarly.

2-Phenyl-4-{*p*-[*N*,*N*-bis(2-chloroethyl)amino]phenyl}-thiazole.—To a suspension of 2-phenyl-4-{*p*-[*N*,*N*-bis(2-hydroxyethyl)amino]phenyl}thiazole (1.7 g, 0.005 mole) in C_6H_6 (15 ml) was added $POCl_3$ (2.3 g, 0.015 mole). The mixt was heated gently at reflux temp for 1 hr. The dark red soln was cooled, and the solvent was removed *in vacuo*. The oily residue was poured onto ice and left overnight, neutralized ($NaHCO_3$), and extd (Et_2O). The Et_2O exts were washed (H_2O) and dried (Na_2SO_4), and the solvent was removed. Residue crystd (hexane) gave the desired N-mustard.

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Synthesis and Pharmacology of Some Dimethoxy-Substituted Indanamines as Potential Hypoglycemic Agents. 1-Methyl-2-*N*-(dialkylaminomethyl)-5,6-dimethoxyindans

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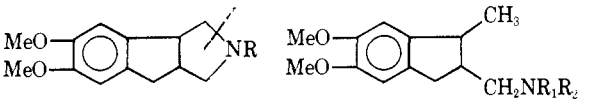
In view of reported significant oral hypoglycemic activity among hexahydroindeno[1,2-*c*]pyrroles (I) and their hypothetical degradation products, indanamines,[1] a large number of such compounds were synthesized and screened for oral hypoglycemic activity as reported earlier.[2-4] This paper is concerned with the synthesis of some dimethoxy-substituted indanamines along with the salient features of their biological activities. These compounds may be considered to have originated by the fission along the dotted lines in the indeno[1,2-*c*]pyrrole structure and subsequent alkylation at the generated basic center.



I II

Chemistry.—Ethyl 2-(3,4-dimethoxybenzyl)acetoacetate[5] was cyclized with polyphosphoric acid to ethyl 3-methyl-5,6-dimethoxyindene-2-carboxylate in 85% yield.[6] The corresponding carboxylic acid was reduced with NaHg and converted to the acid chloride; this was treated with appropriate primary or secondary amines to yield amides. The amides were converted to the desired amines by LAH reduction. The overall reaction sequence is outlined in Scheme I.

All compounds reported in Table I were prepared by a method similar to that described earlier.[1-3] They were first screened for hypoglycemic activity.[7] Blood glucose determinations were made at different intervals up to 24 hr after dosing, using tolbutamide as reference standard. Compounds **8**, **9**, and **14** showed appreciable hypoglycemic activity in both normal- and alloxan-diabetic animals.

Pharmacology.—Groups of 8 normal, healthy, male rabbits, weighing 1.5–2.0 kg were used for screening hypoglycemic activity. The animals were fasted over-

(1) S. C. Lahiri and B. Pathak, *J. Med. Chem.*, **8**, 131 (1965).
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(5) J. Koo, *J. Amer. Chem. Soc.*, **75**, 2000 (1953).
(6) J. Koo, *ibid.*, **75**, 1891 (1953).
(7) Some of these compounds also exhibited appreciable hypotensive and moderate muscle relaxant activities though they do not possess significant antimicrobial activity.