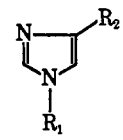
TABLE I

IMIDAZOLYL DERIVATIVES



No.	R_1	R_2	Mp, °C	Yield, %	Solvent of recrystn	Formula[c]
1	CPh_3	CHO	197–199	80	EtOH	$C_{23}H_{18}N_2O$
2	CPh_3	$CHOHCH_2NO_2$	182–183	88	MeOH	$C_{24}H_{21}N_3O_3$
3	CPh_3	$CHOHCH(CH_3)NO_2$	195–197	68	EtOH	$C_{25}H_{23}N_3O_3$
6	CPh_3	CH_2OH	234–236	80	Dioxane	$C_{23}H_{20}N_2O$
7	CPh_3	c-$CHOCH_2$	194–196	100	EtOH	$C_{24}H_{20}N_2O$
4 (salt)	H	$CHOHCH_2NH_2 \cdot 2HCl$[a]	214–216	65	MeOH–Et_2O	$C_5H_{11}Cl_2N_3O$
	H	$CHOHCH_2NH_2 \cdot$ dipicrate[a]	224–226		H_2O	$C_{17}H_{17}N_9O_{16}$
8 (salt)	H	$CHOHCH_2NHCH_3 \cdot$ fumarate[d]	185–187 dec	35	MeOH	$C_{10}H_{13}N_3O_5$
	H	$CHOHCH_2NHCH_3 \cdot$ dipicrate	209–211 dec		H_2O	$C_{18}H_{17}N_9O_{15}$
9 (salt)	H	$CHOHCH_2NHCH(CH_3)_2 \cdot$ difumarate	162–164 dec	65	MeOH	$C_{16}H_{23}N_3O_9$
	H	$CHOHCH_2NHCH(CH_3)_2 \cdot$ dipicrate	190–192 dec		H_2O	$C_{20}H_{21}N_9O_{15}$
5 (salt)	H	$CHOHCH(CH_3)NH_2 \cdot 2HCl$	216–218 dec	25	MeOH–Et_2O	$C_6H_{13}Cl_2N_3O$
	H	$CHOHCH(CH_3)NH_2 \cdot$ dipicrate	204–206 dec		H_2O	$C_{18}H_{17}N_9O_{15}$
10 (salt)	H	$CHOHCH_2N(CH_3)_2 \cdot 2HCl$[b]	173–175	55	MeOH–Et_2O	$C_7H_{15}Cl_2N_3O$
	H	$CHOHCH_2N(CH_3)_2 \cdot$ dipicrate	237–239 dec		H_2O	$C_{19}H_{19}N_9O_{15}$

[a] Ref 2. [b] Slightly hygroscopic. [c] All compds analyzed satisfactorily (±0.4%) for C, H, N. [d] Prepd in a sealed tube at 120° in dioxane.

4-(*N*-Triphenylmethyl)imidazolylmethanol (6).—Compd **1** (2 g, 0.006 mole) was added in portions to a stirred slurry of 0.3 g of LAH in 50 ml of THF. The mixt was refluxed for 2 hr and then allowed to cool, 5 ml of H_2O was added, and the mixt was worked up as usual; yield, 1.6 g (see Table I).

4-(*N*-Triphenylmethyl)imidazolyl]oxirane (7).—The procedures of Corey and Chaykowsky[5] and Duncan, *et al.*,[6] were used. To 3.36 g (0.07 mole) of NaH (50% in paraffin oil) was added 30 ml of DMSO under N_2. The mixt was stirred at 65–70° for 45–60 min and, after cooling, 30 ml of THF was added. The soln was chilled to 0° to −10° and a soln of trimethylsulfonium iodide (14.3 g, 0.07 mole) in 50 ml of DMSO was added dropwise. The mixt was stirred for another 5 min, and 12 g (0.035 mole) of the solid aldehyde **1** was added in portions. After 10 min the cooling bath was removed and stirring contd for 1 hr at 29°. The slurry was poured into a mixt of 500 ml of cold H_2O and 250 ml of petr ether (bp 30–60°), and allowed to stand at 4° overnight. The solid oxirane was filtered, washed (H_2O, petr ether), and air-dried. The yield was practically quant. The product was sufficiently pure for use in the following steps.

***N*-Substituted β-Hydroxyhistamines.**—Compd **7** (0.01 mole) was refluxed in each case for 8 hr with a mixt of 5–10 times the necessary molar amt of primary or secondary amine and enough EtOH or dioxane to keep the oxirane in soln.[6] After cooling, the reaction product was extd several times with Et_2O, and the ext was washed (H_2O) and counterextd with 1 *N* HCl (25 + 10 ml). The aq layer was heated on a steam bath for 15 min, the pptd Ph_3COH was filtered off, and H_2O was evapd *in vacuo*. The residual oil was dissolved in a small amt of abs EtOH. One part was converted to the respective picrate in EtOH.

From another portion, the dihydrochlorides were obtd on cooling, sometimes after addn of abs Et_2O. If they were hygroscopic, their soln in EtOH was made slightly alk (pH 8) with KOH in EtOH, KCl was filtered off, and a soln of excess fumaric acid in boiling MeOH was added. Recrystn from MeOH–Et_2O afforded the corresponding difumarates.

Pharmacological Methods.—Male rabbits (1.1 kg) were used; their isolated heart was suspended in Chenoweth's soln. Isuprel was used at 3×10^{-7} *M*, the drugs were used at 1×10^{-3} to 1×10^{-6} *M*. The reported changes refer to 1×10^{-6} *M* drug solns.

Potential Inhibitors of Protein Biosynthesis

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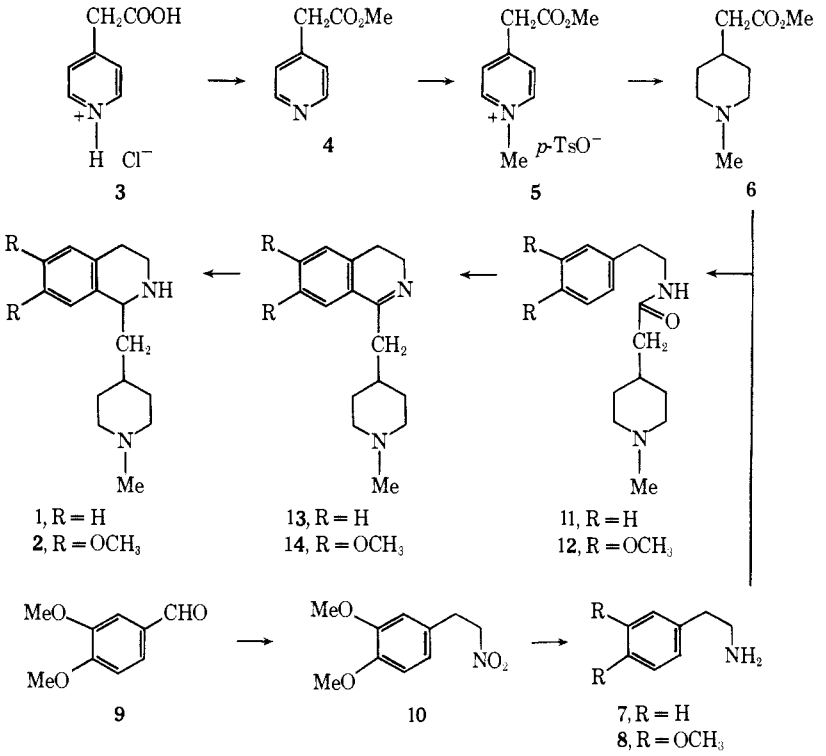
A structural basis for the inhibition of protein synthesis by emetine and cycloheximide was recently proposed, based on an analogy between the ipecac alkaloids and glutarimide antibiotics.[1,2] Based on this hypothesis, the biological activity of tubulosine was correctly predicted.[3] Compounds **1** and **2** described in this communication embody some but not all topochemical features of the proposed model.

Following esterification of **3**, the Me ester **4** was quaternized with *p*-TsOMe to give **5**. Reduction of **5** in the presence of Pt gave **6**. Homoveratrylamine (**8**) was prepared by condensation of **9** with $MeNO_2$ followed by LAH reduction of **10**.[4] Heating **7** or **8** with **6** afforded the amides (**11** or **12**). These underwent $POCl_3$-induced cyclization to **13** and **14** which afforded

(1) A. P. Grollman, *Proc. Nat. Acad. Sci. U. S.*, **56**, 1867 (1966).
(2) A. P. Grollman, in "Drug Design," Vol. 2, E. J. Ariens, Ed., Academic Press, New York, N. Y.
(3) A. P. Grollman, *Science*, **157**, 84 (1967).
(4) I. Kikkawa, *Yakugaku Zasshi*, **78**, 1006 (1958); *Chem. Abstr.*, **53**, 3260 (1959).



1 and **2** by reduction in the presence of Pt. The symmetry of the aromatic proton absorption in the nmr spectrum of **2** supports the structural assignment.

Compounds **1** and **2** were found to have minimal effects on protein synthesis when tested at 10^{-3} *M* in crude lysates prepared from rabbit reticulocytes.[5] By comparison, emetine inhibits protein synthesis by 50% in these preparations at 3×10^{-6} *M*. It would appear that the topochemical requirements in the area of the tertiary N and adjacent C atoms of the proposed model[1,2] cannot be ignored in the synthesis of further compounds to test the validity of this proposal.

Experimental Section[6]

***N*-Phenethyl-α-[4-(1-methylpiperidyl)]acetamide** (11).—Dry HCl was passed into a soln (−60°) of 87 g of **3** in 400 ml of dry MeOH for 12 hr. Solv and HCl were removed *in vacuo* at room temp. The residue was mixed with 400 ml of H_2O and 100 ml of $CHCl_3$ and treated with 60 g of Na_2CO_3 at 4°. The mixt was extd with 2 more 100-ml portions of $CHCl_3$ The exts were combined, dried (Na_2SO_4), filtd, and evapd to give, after distn, 53 g (70%) of **4**: bp 113–115° (10 mm) [lit.[9] bp 114.5° (10 mm)]. This was mixed with 93 g of *p*-TsOMe and heated (90°) for 6 hr. The cooled (20°) mixt was washed with Et_2O. The Et_2O washes were evapd, and the residual oil was reheated. In this way, 90 g (80%) of Et_2O-insol quaternary salt (**5**) was obtd. Redn at 4.2 kg/cm² and 25° in the presence of 1.5 g of PtO_2 and 250 ml of EtOH gave, after filtn and removal of solv *in vacuuo* at room temp, a residue which was mixed with 400 ml of H_2O and 100 ml of $CHCl_3$ and treated with 60 g of Na_2CO_3 at 4°. The mixt was extd with 2 more 100-ml portions of $CHCl_3$. The combined exts were dried (Na_2SO_4), filtd, and evapd to give, after distn, 38 g (80%) of **6**: ir (film) 1735 cm⁻¹ (C=O, ester). To 17 g of **6** was added 12.2 g of freshly dist **7**. The mixt was heated (190°) in an oil bath for 16 hr by which time the 1735 cm⁻¹ band (film) appeared as a very weak shoulder on the principal absorption band at 1635 cm⁻¹ (C=O, amide). On cooling, the solid recrystd from Et_2O to give 18.2 g (70%) of 11: mp 99–100°; nmr ($CDCl_3$) δ 7.23 (s, 5 H, C_6H_5), 6.02 (broad m, 1 H, NH), 3.53 (4 line pattern, 2 H, CH_2N), 3.00–2.50 (m, 4 H, CH_2Ph and CH_2CO), 2.23 (s, 3 H, CH_3N), and 2.17–0.8 ppm (m, 9 H, piperidine ring protons). *Anal.* ($C_{16}H_{24}N_2O$) C, H, N.

***N*-(3,4-Dimethoxyphenethyl)-α-[4-(1-methylpiperidyl)]acetamide** (12).—To 17 g of **6** was added 18.3 g of **8** prepared as described by Kikkawa.[4] Treatment and work-up as described in the prepn of 11 afforded 19.1 g (60%) of **12** from Me_2CO–petr ether (30–60°): mp 102–103°; ir ($CHCl_3$) 1660 cm⁻¹ (C=O, amide); nmr ($CDCl_3$) δ 6.76, 6.73 (unsymm 2 line pattern, 3 H, C_6H_3), 5.90 (broad m, 1 H, NH), 3.86 (s, 6 H, $2CH_3O$), 3.53 (4 line pattern, 2 H, CH_2N), 3.00–2.50 (m, 4 H, CH_2Ph and CH_2CO), 2.23 (s, 3 H, CH_3N), and 2.17–0.9 ppm (m, 9 H, piperidine ring protons). *Anal.* ($C_{18}H_{28}N_2O_3$) C, H, N.

1-[(1-Methyl-4-piperidyl)methyl]-1,2,3,4-tetrahydroisoquinoline (1).—To 13 g of 11 in 100 ml of C_6H_6 was added 20 ml of $POCl_3$ and 5 g of P_2O_5 in 50 ml of C_6H_6. The mixt was allowed to reflux for 4 hr and was then decanted. The gummy residue dissolved in 100 ml of H_2O. The soln was extd with Et_2O, alkalized with solid NaOH, and extd with $CHCl_3$. The ext was dried (Na_2SO_4), treated with C, filtd, and evapd to give 9 g of oil (**13**) [ir (film) 1635 (C=O, amide) absent, 1625 cm⁻¹ (C=N)]. Redn of this oil at 28° and 2.8 kg/cm² in the presence of 0.5 g of PtO_2 in 50 ml of MeOH gave, after filtn and evapn of solv *in vacuo*, an oil (1) [ir (film) 3260 (NH), 1625 cm⁻¹ (C=N) absent]. This was dissolved in Et_2O and treated with dry HCl to give 8 g (50%) of salt (1·2HCl) after recrystn from MeOH–Me_2CO: mp 246–248°; nmr (D_2O) δ 7.35 (s, 4 H, C_6H_4), 4.0–2.5 (m, 12 H, $PhCH_2CH_2$, PhCH, CH_2NCH_2, NCH_3) and 2.5–1.0 ppm (m, 7 H, $CH_2CH(CH_2)CH_2$). *Anal.* ($C_{16}H_{26}Cl_2N_2$) C, H, N.

1-[(1′-Methyl-4′-piperidyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2).—Treatment of 16 g of **12** as in the prepn of **13** gave 10 g of oil (**14**) [ir (film) 1660 (C=O, amide) absent, 1620 (C=N) and 1606 cm⁻¹ (C=C, Ph)]. Redn as in the prepn of 1 afforded an oil (**2**) [ir (film) 3325 (NH), 1620 (C=N) absent, 1606 cm⁻¹ (C=C, Ph)] and subsequently, a gum

(5) These assays were performed by procedures described by C. R. Maxwell and M. Rabinovitz, *Biochem. Biophys. Res. Commun.*, **35**, 79 (1969).

(6) Melting points were determined in a Thomas-Hoover Uni-Melt capillary mp apparatus and are uncor. Where anal. are indicated by symbols of the elements, determinations by Weiler and Strauss, Oxford, England, were within ±0.4% of the theor vals. Perkin-Elmer Model 421 and Varian A60-A spectrometers were used to determine ir and nmr spectra. Assignments of ir[7] and nmr[8] bands, believed accurate to within ±5 cm⁻¹ and ±1 Hz, resp, were made by analogy with reported vals.

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1964.

(8) N. S. Bacca, L. F. Johnson, and J. N. Shoollery, "NMR Spectra Catalog," Vol. 1, Varian Associates Analytical Instruments Division, Palo Alto, Calif., 1962; N. S. Bacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, *ibid.*, Vol. 2, 1963.

(9) A. R. Katritzky, *J. Chem. Soc.*, 2586 (1955).

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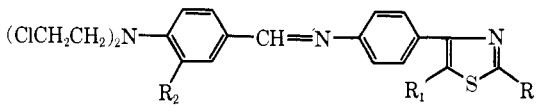
We have already reported the synthesis of a variety of Schiff bases (I) from substituted benzaldehyde N-mustards and 4-(*p*-aminophenyl)thiazoles[2,3] many of which have shown interesting activity against experimental tumor systems.



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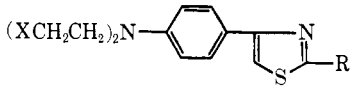


II

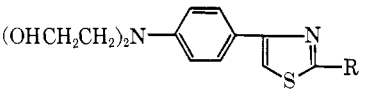
With R = CH_2OPh, R_1 = H, and R_2 = OCH_3, the Schiff base I was active against Dunning leukemia (solid) (6/6 cures at 11 mg/kg per day), L 1210 lymphoid leukemia (T/C = 146% at 15 mg/kg per day), and Walker 256 intramuscular (T/C = 4% at 33 mg/kg per day).[3] With R = CH_2Ph, R_1 = CH_3, and R_2 = 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

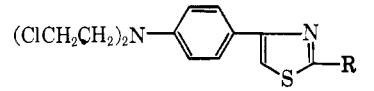


No.	R	Yield,[a,b] %	Mp, °C (uncor)	Formula[c]
1	CH_3	55	132–134	$C_{14}H_{18}N_2O_2S$[d]
2	$C_6H_5CH_2$	48	127–128	$C_{20}H_{22}N_2O_2S$
3	$C_6H_5OCH_2$	57	138–139	$C_{20}H_{22}N_2O_3S$
4	p-$CH_3C_6H_4OCH_2$	53	128–129	$C_{21}H_{24}N_2O_3S$
5	o-$CH_3C_6H_4OCH_2$	52	158–160	$C_{21}H_{24}N_2O_3S$
6	C_6H_5	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.