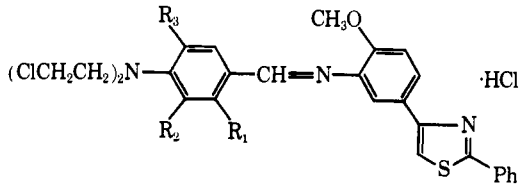
As an extension of this work the preparation and study of some new Schiff bases from *m*-aminophenylthiazoles appeared worthwhile.

The earlier work on Schiff bases with different substituted benzaldehyde nitrogen mustards having shown that compounds derived from 4-[*N*,*N*-bis(2-chloroethyl)amino]-*m*-anisaldehyde are in general significantly more active against L-1210 lymphoid leukemia,[3,4] we first prepared and studied the corresponding Schiff base from 4-[(3-amino-4-methoxy)phenyl]-2-phenylthiazole. The compound was submitted for antitumor screening to the Cancer Chemotherapy National Service Center, and was found to display considerable activity against leukemia L-1210 even at a low dosage. It has passed the sequential screen as well as the confirmation tests.[5] It also produces a high degree of inhibition in Walker carcinosarcoma 256 (intramuscular). Furthermore, it had a lower order of toxicity compared to the other nitrogen mustard derivatives reported earlier.

A few more Schiff bases from other substituted benzaldehyde nitrogen mustards have also been synthesized. All the compounds could be obtained readily by heating 2-phenyl-4-[(3-amino-4-methoxy)phenyl]thiazole·HCl with the appropriate aldehyde in EtOH. The requisite aldehyde mustards were prepared by the hydroxyethylation of the anilines with ethylene oxide[6] and treating the resultant products with $POCl_3$ and DMF.[7] All the Schiff bases prepared are shown in Table I along

TABLE I

SCHIFF BASES FROM 2-PHENYL-4-[(3-AMINO-4-METHOXY)PHENYL]THIAZOLE



No.	R_1	R_2	R_3	Yield,[a] %	Mp, °C[b]	Formula[c]
1	H	H	H	68	215–218	$C_{27}H_{26}Cl_2N_2OS \cdot HCl$
2	Me	H	H	72	185–188	$C_{28}H_{27}Cl_2N_2OS \cdot HCl$
3	F	H	H	65	156–157	$C_{27}H_{24}Cl_2FN_2OS \cdot HCl$
4	H	OMe	H	71	146–147	$C_{28}H_{27}Cl_2N_2O_2S \cdot HCl$[d]
5	OMe	H	H	68	205–207	$C_{28}H_{27}Cl_2N_2O_2S \cdot HCl$
6	H	OEt	H	70	224–226	$C_{29}H_{29}Cl_2N_2O_2S \cdot HCl$
7	OMe	H	OMe	65	190–192	$C_{29}H_{29}Cl_2N_2O_3S \cdot HCl$

[a] Recrystd from EtOH. [b] Melting points are capillary melting points and are uncorr. [c] All comps were analyzed for N, S. Analytical results obtd were within ±0.4% of theoretical values. [d] *Anal.* Calcd: C, 58.28; H, 4.69. Found: C, 58.01; H, 4.70.

with their analytical data while the antitumor screening results on **4** are given in Table II.

TABLE II

ANTITUMOR ACTIVITY[a] OF SCHIFF BASE **4**

Test[b] system	Dose, mg/kg	Survivors	Animal wt diff (*T* − *C*)	Tumor wt,[c] g, or survival days[d] *T*/*C*	*T*/*C* %
L1210	80.0	5/6	−5.7	6.5/9.3	
	40.0	6/6	−4.4	9.5/9.3	102
	20.0	6/6	−3.5	15.5/9.3	166
	10.0	6/6	−2.3	14.4/9.3	154
	5.0	6/6	−1.2	12.5/9.3	134
	3.30	6/6	−2.0	11.8/9.1	129
	2.20	6/6	−1.4	11.8/9.1	129
	1.40	6/6	−0.3	9.0/8.7	103
	0.96	6/6	−1.4	9.3/8.7	106
AA	330	0/3	0		
	110	0/3	0		
	36.0	3/3	3		
	12.0	3/3	14		
WM	45.0	5/6	−29	0.7/8.7	8

[a] For test procedures see *Cancer Chemother. Rep.*, **25**, 1 (1962). [b] L1210 = L1210 lymphoid leukemia, AA = toxicity WM = Walker 256 (intramuscular). [c] Tumor wt for WM. [d] Survival days for L1210.

Experimental Section

2-Phenyl-4-[(3-amino-4-methoxy)phenyl]thiazole·HCl.—A mixt of 2.0 g (0.01 mole) of 2-chloro-3-amino-4-methoxyacetophenone,[8] 1.5 (0.011 mole) of thiobenzamide, and 8 ml of abs EtOH was refluxed. The solid pptd from the mixt after about 0.5 hr was filtered, washed with Et_2O, and dried, 2.45 g (80%). It was of anal. purity, mp 248° dec. *Anal.* ($C_{16}H_{14}N_2S \cdot HCl$) N, S.

2-Phenyl-4-[3-({4-[*N*,*N*-bis(2-chloroethyl)amino]-3-methoxybenzylidene}amino)-4-methoxyphenyl]thiazole·HCl (4).—To a soln of 2-phenyl-4-[(3-amino-4-methoxy)phenyl]thiazole·HCl (3.0 g, 0.01 mole) in 10 ml of EtOH was added a soln of 4-[*N*,*N*-bis(2-chloroethyl)amino]-*m*-anisaldehyde (2.76 g, 0.01 mole) in 5 ml of EtOH. The soln was heated on a steam bath for a short time and allowed to stand at room temp for 1 hr. The solid that sepd was filtd, washed (EtOH, Et_2O), and crystd (EtOH). All the Schiff bases were prepared by this procedure.

Acknowledgments.—We are greatly indebted to Dr. H. B. Wood, Chief, Drug Development Branch, Cancer Chemotherapy National Service Center, for his cooperation and for making the screening data available and to Mr. M. T. Jaokar for microanalyses. We are grateful to Dr. N. K. Dutta, Director, Haffkine Institute, Bombay, for providing facilities to carry out the present work. One of us (J. D. M.) wishes to thank the Ministry of Education, Government of India, for the award of a fellowship.

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Some Halogenated Acetyl Derivatives and Their Antitumor Activity[1,2]

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Received August 17, 1970

There is evidence that physiologically active compounds containing the dichloroacetyl group are poten-

(1) This work was supported by grants from the New York City Cancer Committee of the American Cancer Society, Inc., and the Pythian Sisters, State of New York.

(2) Parts of this work were first presented at the Meeting in Miniature of the New York Association of the American Chemical Society Student Affiliates at Manhattan College, Manhattan, N. Y., April 1966, and St. Francis College, Brooklyn, N. Y., May 1970.

tial antitumor agents.[3-5] Also, incorporation of F into physiologically active compounds occasionally increases activity.[6,7]

We are describing the preparation of dichloroacetyl and trifluoroacetyl derivatives of compounds which have been of interest in experimental cancer chemotherapy.[8-13]

Experimental Section

***N*-5-Dichloroacetamidouracil** (1).—Dichloroacetic anhydride (50 g, 0.2084 mole) was added dropwise to 5-aminouracil (1.5 g, 0.0393 mole). After the reaction had subsided, the mixt was heated for 1 hr, and poured into ice-H_2O with stirring. The yellow-white ppt was collected, washed with cold H_2O (600 ml) and then with hot EtOH (400 ml), and dried on a clay plate at 110° for 3 days. The yield of white powdery ppt was 5.4 g (58%), mp 292.5-293° dec. Ir spectra were as expected. *Anal.* ($C_6H_5Cl_2N_3O_3$) C, H, Cl, N.

***N*-5-Trifluoroacetamidouracil** (2).—Prepared as **1** using $(CF_3CO)_2O$ (20 g, 0.0952 mole). The yield of light yellow powdery ppt was 7.4 g (88.0%), mp 338-339° dec. Ir spectra were as expected. *Anal.* ($C_6H_4F_3N_3O_3$) C, H, F, N.

Methyl *N*-Trifluoroacetamidoanthranilate (3).—Methyl anthranilate, purified by vac distn (5 g, 0.0331 mole), and $(CF_3CO)_2O$ (21 g, 0.0952 mole) were refluxed for 5 hr. The mixt was cooled and poured into PhH (20 ml). The PhH layer was poured into H_2O (100 ml), sepd, and washed with H_2O until neutral. After drying ($CaCl_2$) for 2 days, the PhH soln was distd leaving a white ppt in the distg flask. The ppt was dried on a clay plate and stored under N_2. The yield of white needles was 4.3 g (55.2%), mp 62.5-64.0°. Ir spectra were as expected. *Anal.* ($C_{10}H_8F_3NO_3$) C, H, F, N.

Hexestrol Bistrifluoroacetate (4).—Hexestrol (5 g, 0.0092 mole) was dissolved in pure PhH (20 ml). $(CF_3CO)_2O$ (18.5 g, 0.0880 mole) was added over a 15-min period. After 2 hr the soln was poured into cold H_2O (200 ml). The PhH layer was sepd, washed with H_2O until neutral and dried ($CaCl_2$) for 24 hr, and most of the PhH was vac distd at room temp. The solid which pptd in the distg flask had mp 101-107°. It was redissolved in 20 ml of PhH and 75% of the soln was again vac distd. The ppt was filtered, dried on a clay plate, and kept in a sealed tube under N_2. The yield of fine white crystals was 2.0 g (47%), mp 109.5-110°. The compd undergoes 4 to 6 color changes within a week (white-lavender-light brown-orange-brown-purple). Ir spectra were as expected. *Anal.* ($C_{22}H_{18}F_6O_4$) C, H, F.

Stilbestrol Bistrifluoroacetate (5).—This was prepd similarly using stilbestrol (2.5 g, 0.0093 mole). The yield of white crystals was 1.4 g (46.1%), mp 11-113°. Ir spectra were as expected. *Anal.* ($C_{22}H_{16}F_6O_4$) C, H, F, N.

***p*-Aminobenzoic Acid *N*-Trifluoroacetate** (6).—*p*-Aminobenzoic acid (5 g, 0.0365 mole) was treated with $(CF_3CO)_2O$ (20 g, 0.0952 mole) as for 1. The brown-white reaction mixt was poured into ice-H_2O. The product was washed with cold H_2O (1 l.), and dried in a vac dessicator. The yield of white powdery ppt was 7.0 g (86.4%), mp 282° dec. *Anal.* ($C_9H_6F_3NO_3$) C, H, F, N.

Pentaerythritol Tetratrifluoroacetate (7).—$(CF_3CO)_2O$ (34 g, 0.1619 mole) was added to pentaerythritol (5 g, 0.0367 mole) and the mixt was heated gently on a hot plate. The soln obtained was allowed to stand, coned, and allowed to stand again. A white powder sepd, mp 47-48°. The product was recrystd from $CHCl_3$ giving monoclinic cryst, yield 13.6 g (71%), mp 47-48°. *Anal.* ($C_{13}H_8F_{12}O_8$) C, H, F.

Pentaerythritol Tetradichloroacetate (8) was prepd as above by treating $(CHCl_2CO)_2O$ (42.5 g, 0.1771 mole) with pentaerythritol (5 g, 0.0367 mole). The yield was 6 g (33.5%), mp 103-108°. *Anal.* ($C_{13}H_{12}Cl_8O_8$) C, H, Cl.

Inositol hexadichloroacetate (9) **and hexestrol dichloroacetate** (10) have been described before.[3]

Biological Results.—The procedure used was the established technique of the Sloan-Kettering Institute[14-17] except that injections began 48 hr after implantation instead of after 24 hr. The vehicles used were Planters' peanut oil or trioctanoin.[18] The mice were sacrificed the 8th day after implantation. Results found are shown in Table I. Carcinostatic activity was obtained with **1**, **2**, **3**, **4**, **5**, and combinations of **2** and **9** at the specified dosages.

TABLE I

WEIGHT CHANGE AND TUMOR DIAMETER CHANGE IN S-180 AT DIFFERENT DOSAGES OF CHEMICALS TESTED

Run	Compd	Dosage, mg/kg per day	Average tumor diam, cm, $T/C \times 100$	Weight change, g, $T/C \times 100$	Survivors
1	1	250	42.5	30.7	5/5
2		500	64.9	52.0	5/5
3	2	5	81.0	98.0	5/5
4		25	92.0	79.0	5/5
5		500	91.0	72.0	5/5
6	3	75	78.6	54.5	5/5
7	4	75	66.1	76.7	5/5
8		125	65.3	54.4	5/5
9		250	74.4	97.6	5/5
10	5	75	66.8	81.4	5/5
11	6	250	214.0	186.0	5/5
12	7	250	92.0	98.0	5/5
13	8	250	89.0	100.0	5/5
14	2 and 9	75 and 250	77.0	48.3	5/5
15	1 and 9	250 and 250	77.1	83.6	5/5
16	1 and 10	250 and 250	95.6	45.8	5/5

Acknowledgments.—The authors wish to thank Dr. George S. Tarnowski, Dr. H. Christine Reilly, and Dr. C. Chester Stock for helpful discussions and communications. We also wish to thank Dr. Hyman Guthwin of the Biological Sciences Department of H. H. Lehman College for his technical assistance and supervision. We also gratefully acknowledge the assistance of the student members of the Lehman College Cancer Research Project who aided us in the biological screening of our compounds.

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(17) The sarcoma 180 was obtained from Dr. George S. Tarnowski, Sloan-Kettering Institute, Rye, N. Y.
(18) In the case of **2** DMSO served as solvent.