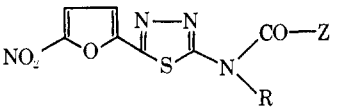
TABLE I

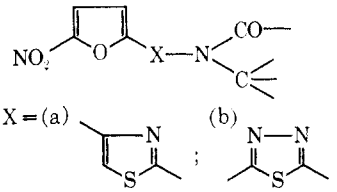
[5-(5-NITRO-2-FURYL)-1,3,4-THIADIAZOL-2-YL]AMIDES AND -UREAS



II

Compd no.	R	Z	Method	Yield, %	Mp, °C	Formula
1	H	$NHCH_2CH{=}CH_2$	*a*	65	255–257 dec	$C_{10}H_9N_5O_4S$
2	H	$NHCH_2CH(Br)CH_2Br$	*a*	22	210–213 dec	$C_{10}H_9Br_2N_5O_4S$
3	$CH_2C(Me){=}CCl_2$	$NHCH_2CH{=}CH_2$	A[b]	40	120–122	$C_{14}H_{13}Cl_2N_5O_4S$
4	$CH_2CONHCO_2Et$	$NHCH_2CH{=}CH_2$	A[c]	35	193–195[e]	$C_{15}H_{16}N_6O_7S$
5	$CH_2C(Me){=}CCl_2$	Me	B[b]	28	180–181	$C_{12}H_{10}Cl_2N_4O_4S$
6	CH_2CONH_2	Me	B[c]	63	267–268	$C_{10}H_9N_5O_5S$
7	CH_2CONEt_2	Me	B[c]	33	198–200	$C_{14}H_{17}N_5O_5S$
8	CH_2CONPr_2	Me	B[c]	47	150–153	$C_{16}H_{21}N_5O_5S$[f]
9	CH_2CONBu_2	Me	B[c]	44	115–116	$C_{18}H_{25}N_5O_5S$
10	$CH_2CONHCO_2Et$	Me	B[c,d]	17	200–201	$C_{13}H_{13}N_5O_7S$

[a] Described in Experimental Section. [b] Alkylating agent RCl. [c] Alkylating agent RBr. [d] 2 hr at 80°. [e] From EtOAc. [f] C: calcd, 48.6; found, 48.1.



5-(5-nitro-2-furyl)-1,3,4-thiadiazole[2] to give the amides or ureas II is described in the Experimental Section.

Experimental Section[3]

The physical properties of the nitrofurans prepared are collected in Table I.

1-Allyl-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (1).—A mixt of allyl isocyanate (9.3 g) and 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole[2] (21.2 g) in THF (120 ml) was stirred and refluxed 3 hr, then cooled. Solid was collected, washed with Et_2O, and recrystd from AcOH.

1-(2,3-Dibromopropyl)-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (2).—Br_2 (1.04 ml) was added slowly to a suspension of urea 1 (6.0 g) in $CHCl_3$ (200 ml) at 0°, and the mixt was then stirred 4 hr at room temp. Recrystn of the sepd solid from 96% EtOH afforded the product, after removal of some less sol material.

Method A. 3-Allyl-1-(3,3-dichloro-2-methylallyl)-1-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (3).—NaH (61% dispersion in oil, 1.965 g, 0.05 mole) was added in portions to a stirred suspension of urea 1 (14.75 g, 0.05 mole) in DMF (70 ml), followed by 1,1,3-trichloro-2-methylprop-1-ene (8.75 g, 0.055 mole). The mixt was stirred at room temp until neutral (2–4 hr), then poured into H_2O. Solid was collected and recrystd from MeOH.

Method B.—The procedure used was the same as for method A except that the nitrofuran alkylated was 2-acetamido-5-(5-nitro-2-furyl)-1,3,4-thiadiazole.[2] The products were all recrystd from 96% EtOH.

Screening Results.—The above compds were tested *in vitro* against a variety of bacteria according to procedures described previously,[4] and the most active of the compds are listed in Table II.[5] When tested against *Streptococcus pyogenes* and *Staphylococcus aureus* infections in mice by oral and subcutaneous administration,[6] the only nitrofuran to show appreciable activity was **6**. This compd has ED_{50} 5.0 mg/kg (sc) and 11.4 mg/kg (po) against *S. pyogenes*, and ED_{50} 155 mg/kg (sc) and 120 mg/kg (po) against *S. aureus* UC-76.

TABLE II

In Vitro ANTIBACTERIAL ACTIVITY OF 1–10

	Minimum inhibitory concentration, μg/ml[a]			
Compd	*Streptococcus faecalis* MGH-2	*Staphylococcus aureus* UC-76	*Staphylococcus aureus* S 18713[c]	*Shigella sonnei* C-10
1	5	1.5	2	5
2	2	1.5	1.5	5
3	>25	2.5	2.5	>25
4[b]	5	2.5	2.5	10
6	2.5	2	2.5	5
10	20	5	5	20

[a] See W. Szybalski, *Bacteriol. Proc.*, 36 (1952); W. Szybalski and V. Bryson, *J. Bacteriol.*, **64**, 489 (1952); and V. Bryson and W. Szybalski, *Science*, **116**, 45 (1952). [b] MIC against *Escherichia coli* VOGEL and *Pseudomonas aeruginosa* −28 was 10 μg/ml. [c] Penicillin-resistant strain.

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(2) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(3) Melting points are corrected, and were determined in a capillary tube. Analytical results were obtained for C, H, and N for all compounds, and unless otherwise stated were within ±0.4% of the theoretical values.

(4) W. Szybalski, *Bacteriol. Proc.*, 36 (1952); W. Szybalski and V. Bryson, *J. Bacteriol.*, **64**, 489 (1952); and V. Bryson and W. Szybalski, *Science*, **116**, 45 (1952).

(5) Compds described in the note but not listed in Table II were less active than those given in the table.

(6) For the general *in vivo* test procedures see M. W. Fisher, M. C. Manning, L. A. Gagliardi, M. R. Gaetz, and A. R. Erlandson, *Antibiot. Annu.*, **1959–1960**, 293–303 (1960); and M. W. Fisher, *Proc. Soc. Exp. Biol. Med.*, **85**, 538 (1954).

Antitumor Agents. Schiff Bases from Benzaldehyde Nitrogen Mustards and 2-Phenyl-4-[(3-amino-4-methoxy)phenyl]thiazole

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We have already reported several Schiff bases from *p*-aminophenylthiazoles and benzaldehyde nitrogen mustards as possessing good antitumor activity.[2,3]

(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).

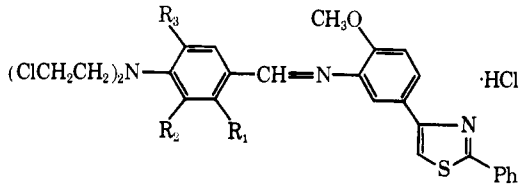
As an extension of this work the preparation and study of some new Schiff bases from *m*-aminophenylthiazoles appeared worthwhile.

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.

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(5) *Cancer Chemother. Rep.*, **25**, 1 (1962).
(6) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 1477 (1961).
(7) R. H. Wiley and G. Irick, *ibid.*, **26**, 593 (1961).
(8) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 552 (1949).

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

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

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