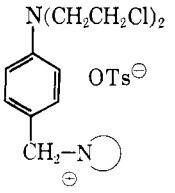
TABLE II: SCREENING DATA[a]



-N◯	Test system[b]	Dose, mg/kg	Survivors	Cures	Animal wt dif (T − C)[c]	Tumor wt Test	Tumor wt Control	T/C, %	Cell culture ED_{50}[d]	Cell culture Slope[e]
Pyridine	AA	100	0/3							
	AA	33	3/3							
	AA	10	3/3							
	WA	41	6/6	6	−56	0.0	5.0	0		
	WA	20.5	6/6	6	−29	0.0	5.0	0		
	WA	10.2	6/6	0	−25	1.1	5.0	22		
	WA	8.0	6/6	0	−17	3.0	8.0	37		
	WA	6.0	6/6	0	−5	4.5	8.0	56		
	WA	5.1	6/6	0	−17	2.5	5.0	50		
	WA	4.0	6/6	0	−7	5.9	8.0	73		
	WA	2.0	6/6	0	−2	8.5	8.0	106		
	KB								1.6	−0.56
	KB								4.3	−0.49
3-Acetylpyridine	AA	33	0/3		−13					
	AA	10	3/3		2					
	AA	3.0	3/3		6					
Ethyl isonicotinate	AA	50	3/3		3					
	AA	10	3/3		8					
	AA	3.0	3/3		20					
Quinoline	AA	33	0/3							
	AA	10	3/3							
	AA	3.0	3/3							
	WA	13	6/6	6	−59	0.0	8.9	0		
	WA	6.5	6/6	4	−40	0.9	8.9	10		
	WA	3.25	6/6	0	−19	3.0	8.9	33		
	WA	1.6	6/6	0	−15	6.9	8.9	77		
	KB								4.3	−0.33
Lepidine	AA	33	0/3							
	AA	10	3/3		−9					
	AA	3.0	3/3		1					
Isoquinoline	AA	100	0/3							
	AA	33	3/3							
	AA	10	3/3							
	AA	3.0	3/3							
	WA	41	6/6	2	−29	0.6	5.0	12		
	WA	20.5	5/6	0	−10	4.7	5.0	94		
	WA	10.2	6/6	0	−13	4.3	5.0	86		
	WA	5.1	6/6	0	−6	5.2	5.0	104		
	KB								L1.0	
	KB								1.6	−0.46

[a] Tests carried out by the CCNSC according to their normal screening protocol. [b] AA = toxicity test, WA = Walker carcinosarcoma 256, KB = cell culture. [c] T = test animal, C = control animal. [d] ED_{50} = dose (μg/ml) that inhibits growth to 50% of control growth. [e] Slope = difference in response for a tenfold difference in dose.

1-{*p*-[Bis(2-*p*-tolylsulfonyloxyethyl)amino]benzyl}pyridinium *p*-Toluenesulfonate (IV).—*p*-[Bis(2-*p*-tolylsulfonyloxyethyl)amino]benzaldehyde[6] was reduced with $NaBH_4$ as described for the preparation of I. The crude alcohol, mp 78–80°, was treated with *p*-toluenesulfonyl chloride and pyridine as described for the preparation of II to give a 66% yield of the hemihydrate of IV, mp 79–81° (from acetone).

Anal. Calcd for $C_{37}H_{40}N_2O_8S_3 \cdot 0.5H_2O$: C, 58.32; H, 5.42; N, 3.68; S, 12.63. Found: C, 58.20; H, 5.31; N, 3.65; S, 12.64.

1-{*p*-[Bis(2-*p*-tolylsulfonyloxyethyl)amino]benzyl}quinolinium *p*-toluenesulfonate was obtained in 56% yield as its hemihydrate, mp 97–99° (from acetone–dimethylformamide), in a procedure similar to the preparation of IV.

Anal. Calcd for $C_{41}H_{42}N_2O_8S_3 \cdot 0.5H_2O$: C, 60.52; H, 5.34; N, 3.45; S, 11.85. Found: C, 60.38; 60.24; H, 5.50, 5.57; N, 3.46; S, 11.55.

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2,4-Bis(arylamino)pyrimidines as Antimicrobial Agents

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Although a large number of 2,4-diaminopyrimidines with hydrogen, alkyl, or aryl substitution in the 5 and 6 positions (type A) have been synthesized and screened

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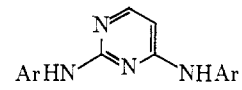
TABLE I

2,4-BIS(ARYLAMINO)PYRIMIDINES



Compd	Ar	Yield, % (crude)	Reaction time, min	Mp, °C[a]	Solvent of recrystn	Formula	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found	% nitrogen Calcd	% nitrogen Found
I	*p*-$NO_2C_6H_4$	95	30	300	Dimethylformamide	$C_{16}H_{12}N_6O_4$	54.82	54.91	3.40	3.43	23.86	23.56
II	*p*-ClC_6H_4	95	30	225	95% ethanol	$C_{16}H_{12}N_4Cl_2$	58.06	58.40	3.62	3.93	16.91	16.76
III	*m*-ClC_6H_4	90	30	179–180	90% ethanol	$C_{16}H_{12}N_4Cl_2$	58.06	57.98	3.62	3.65	16.91	16.80
IV	*o*-ClC_6H_4	90	30	247	HCl–aq ethanol	$C_{16}H_{12}N_4Cl_2 \cdot HCl$	52.24	52.43	3.53	3.56	15.23	14.91
V	*p*-OHC_6H_4	52	60	210	1 *N* HCl	$C_{16}H_{12}N_4O_2 \cdot HCl$	58.09	57.72	4.53	4.33	16.91	16.78
VI	*p*-$OCH_3C_6H_4$	90	30	155–156	50% ethanol	$C_{18}H_{18}N_4O_2$	67.04	67.06	5.59	5.90	17.39	17.76
VII	*p*-$CH_3C_6H_4$	95	30	160–162	60% ethanol	$C_{18}H_{18}N_4$	74.49	73.99	6.20	6.34	19.36	19.50
VIII	*p*-$COCH_3C_6H_4$	85	60	230	Aq acetone	$C_{20}H_{18}N_4O_2$	69.07	68.85	5.20	5.26	16.18	16.10
IX	*p*-$SO_2NH_2C_6H_4$	57	60	300	1 *N* HCl	$C_{16}H_{18}N_6O_4S_2 \cdot HCl$	42.06	41.88	3.07	3.20	18.04	17.95

[a] All melting points are determined in capillary tubes and are uncorrected.

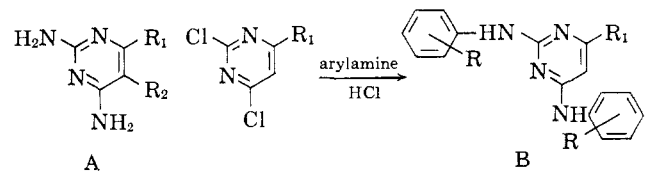
TABLE II

ANTIMICROBIAL ACTIVITY OF 2,4-BIS(ARYLAMINO)PYRIMIDINE

Compd	Concn for 50% inhibition of growth, μg/ml — *S. faecalis*	*E. coli* B	*C. albicans*
I	0.46	0.60	0.62
II	0.80	0.88	0.84
III	0.90	1.10	0.82
IV	2.20	1.24	1.14
V	39.20	64.00	62.00
VI	5.60	6.80	8.00
VII	1.30	1.10	0.90
VIII	*a*	*a*	6.60
IX	3.40	1.60	1.50
6-Azauracil	12.00	7.20	*b*
Neomycin	*b*	1.30	1.10

[a] No inhibition at saturating concentration. [b] Little or no activity.

for their possible chemotherapeutic value,[2] only a few 2,4-bis(arylamino)pyrimidines[3] are known. In our previous communications[4,5] we have shown that 2,4-bis(arylamino)-6-hydroxypyrimidines (type B, R_1 = OH) possess high antibacterial activity. Encouraged by this observation we have further synthesized a number of compounds of type B where R_1 = H. As expected, these compounds have been found to inhibit the growth of many gram-positive and gram-negative bacteria, as well as yeasts at very low concentrations. In this communication, however, we are reporting the activity of these compounds (type B, R_1 = H) against one gram-positive and one gram-negative bacterium and one pathogenic strain of yeast. The activity of these synthetic pyrimidines has been compared with



A B

that of two known antimicrobial agents, 6-azauracil and neomycin, with respect to inhibition of growth.

2,4-Bis(arylamino)pyrimidines (type B, R_1 = H) were synthesized by the acid-catalyzed condensation of 2,4-dichloropyrimidine with appropriate aromatic amines as described by Banks.[3a]

Experimental Section

2,4-Bis(*p*-chloroanilino)pyrimidine (II).—2,4-Dichloropyrimidine (1.5 g, 0.01 mole) was added to a solution of *p*-chloroaniline (2.6 g, 0.02 mole) in dilute HCl (0.2 ml of concentrated HCl in 30 ml of water) and slowly heated to reflux on a sand bath with shaking. Crystals began to appear within a few minutes of refluxing. The refluxing was discontinued after 30 min, and the reaction mixture was kept overnight in a refrigerator. The crystalline product was filtered off and washed with cold water. This compound could be readily recrystallized from 95% ethanol. The yield was almost quantitative.

The other compounds listed in Table I were synthesized by the same general method as described for II. As indicated in Table I the time of refluxing had to be extended in certain cases and some compounds were recrystallized as the hydrochlorides since they could not be satisfactorily crystallized in their basic form. All compounds were dried *in vacuo* at 100° for 20 hr before analysis.

Inhibition of Growth of Microorganisms.—All compounds were tested for their antimicrobial activity against *Streptococcus faecalis*, *Escherichia coli* B, and a pathogenic strain of yeast, *Candida albicans*. The concentrations of synthetic compounds necessary for 50% inhibition of growth were determined turbidimetrically by serial-dilution technique in test tubes using liquid growth medium[4] (shown in Table II).

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