

### The Tumor-inhibiting Activities of Arylnaphthoquinones

In the course of testing various synthetic compounds obtained in our laboratory against the Ehrlich ascites tumor, we discovered that compounds belonging to arylthionaphthoquinone series show tumor-inhibiting activities and especially 2-benzylthio- and 3-bromo-2-phenylthio-naphthoquinones give fairly good results as compared with such compounds as nitrogen mustard N-oxide or 8-azaguanine.

As regards the relationship between chemical structure and biological activity, it was revealed that their 1,4-dihydro or 2,3-diarylthio derivatives markedly lose the activity.

In the following are summarized these data, details of which will be published elsewhere.

**Test method**—Mice received an intraperitoneal injection of 0.05 cc. each of ascites (containing about  $10^7$  tumor cells). Several animals served as a control and the remaining animals were injected intraperitoneally with suspension in normal saline of different doses of the compound to be tested (usually 2 animals per dose). The injections were carried out once a day on 5 successive days, starting from the day of transplantation. One day after the last injection the animals were killed, the volume of ascites was measured, and the number of tumor cells in ascites counted.

Actually, however, the effectiveness of a compound was evaluated mainly by the minimum dose completely suppressing the ascites production.

1,4-Naphthoquinones	Dose (mg./kg./day)	Change in body wt. (g.)	Vol. of ascites (cc.)	No. of tumor cells ( $\times 10^6$ )	Remark
1,4-Naphthoquinone	{ 50	—	—	—	died (1)
	{ 50	—	—	—	died (1)
2-Methylthio-	{ 50	—	—	—	died (2)
	{ 50	—	—	—	died (1)
2-Butylthio-	{ 50	-3	0	0	died (4)
	{ 50	-2.5	0	0	
	{ 25	-2.5	0	0	
	{ 25	—	—	—	
	{ 10	+1.5	0.6	48	
	{ 10	-2.5	0	0	
	{ 5	0	2.6	—	
2-Allylthio-	{ 50	—	—	—	died (2)
	{ 50	—	—	—	died (1)
2-Carboxymethylthio-	{ 50	—	—	—	died (2)
	{ 50	—	—	—	died (1)
2- $\alpha, \beta$ -Dicarboxyethylthio-	{ 50	-3.5	0	0	
	{ 50	-4.5	0	0	
	{ 25	-1	0	0	
	{ 25	+0.5	0	0	
	{ 10	+2	2.2	—	
	{ 10	+0.5	0.75	—	
2-Benzylthio-	{ 50	-2	0	0	
	{ 50	-3	0	0	
	{ 25	-0.5	0	0	
	{ 25	-1.5	0	0	
	{ 10	0	0	0	
	{ 10	+2	0	0	
	{ 5	-3	0	0	
	{ 5	+2.5	0	0	
	{ 2.5	-1.5	0.6	—	
	{ 2.5	-1.5	0.1	—	
{ 1	0	1.6	—		
{ 1	+2.5	0.85	111		

2-Phenylthio-	50	-2.5	0	0	
	50	-1.5	0	0	
	25	-1	0	0	
	25	-1	0	0	
	10	+0.5	0	0	
	10	-1.5	0	0	
	5	+1	1.4	189	
2-(4'-Chlorophenyl)thio-	5	-2	0.3	66	
	50	-2	0	0	
	50	-4	0	0	
	25	-2	0	0	
	25	-2	0	0	
	10	0	0	0	
	10	+1	0.05	—	
2-(4'-Nitrophenyl)thio-	5	-2.5	0.15	36	
	5	+3	1.75	262	
	50	—	0.35	8.7	
	50	—	1.1	22	
2-(4'-Methylphenyl)thio-	50	-3.5	0	0	
	50	-3.5	0	0	
	25	-4.5	0	0	
	25	-5	0	0	
	10	-4.5	0.15	—	
	10	-3	0	0	
	5	+1	1.8	234	
2-(4'-Aminophenyl)thio- hydrochloride	5	+3	4.2	462	
	50	+0.5	3.65	—	
2-(4'-Acetaminophenyl)thio-	50	—	1.5	—	
	50	—	0	0	
	50	—	0	0	
	25	-0.5	0	0	
	25	0.5	0	0	
	10	0	2.15	258	
2-(2'-Carboxyphenyl)thio-	10	-0.5	0.7	102	
	50	—	—	—	died (1)
2-Bromo-3-methylthio-	50	—	—	—	died (1)
	50	—	—	—	died (2)
2-Bromo-3-benzylthio-	50	-3	0	0	
	50	0	2.6	—	
	25	-3.5	0	0	
	25	-3.5	0	0	
	10	+0.5	1.4	—	
	10	—	—	—	
	5	+2.5	1.75	—	
2-Chloro-3-phenylthio-	5	+3.5	4.2	—	
	25	—	—	—	died (1)
2-Chloro-3-(4'-acetamino- phenyl)thio-	25	—	—	—	died (1)
	10	0	1.25	—	
	10	-0.5	0	0	
	5	+3	5.5	—	
	5	+5	1.5	—	
	50	-2.5	0	0	
2-Bromo-3-phenylthio-	50	-4	0	0	
	25	-1	0	0	
	25	0	0	0	
	10	0	0	0	
	10	0	0	0	
	5	-1.5	0	0	
	5	-1	0	0	
	2.5	-1	0.2	—	
	2.5	-2.5	0.95	223	
	50	-3	0	0	
2-Chloro-3-(4'-acetamino- phenyl)thio-	50	-1.5	0	0	
	25	-0.5	0	0	
	25	+0.5	0	0	
	10	+1	1.25	300	
	10	+2	0	0	

2-Bromo-3-(4'-nitrophenyl)-thio-	{ 50	+2	0.6	—	
	{ 50	+1	2.5	—	
2-Methyl-3-phenylthio-	{ 50	—	—	—	died (5)
	{ 50	-2.5	0	0	
	{ 25	+0.5	0	0	
	{ 25	0	0	0	
	{ 25	-0.5	0	0	
	{ 25	-2	0	0	
	{ 10	+0.5	0.15	—	
	{ 10	+0.5	1.7	—	
2-Amino-3-phenylthio-	{ 50	-1.5	0.2	92	
	{ 50	—	—	—	died (5)
2-Methylthio-3-anilino-	{ 50	+2	3	390	
	{ 50	0	1.75	350	
2,3-Dimethylthio-	{ 50	—	—	—	died (1)
	{ 50	—	—	—	died (1)
2,3-Diphenylthio-	{ 50	+2	2.5	—	
	{ 50	+0.5	1.7	—	
2-Phenylthio-3-(4'-chlorophenyl)thio-	{ 50	-0.5	2.65	—	
	{ 50	+2.5	3.3	—	
2-Phenylthio-3-(4'-methylphenyl)thio-	{ 50	-1.5	0	0	
	{ 50	+1.5	1	—	
2-Chloro-3-phenylthio-7-sulfonic acid	{ 50	+0.5	0	0	
	{ 50	-0.5	0.2	—	
	{ 25	0	0	0	
	{ 25	+0.5	0	0	
	{ 25	-1	0	0	
2-Phenylthio-1,4-dihydroxynaphthalene	{ 50	—	—	—	died (1)
	{ 50	—	—	—	died (1)
2-(4'-Methylphenyl)thio-	{ 50	-2	0.5	5	
	{ 50	-0.5	2.5	—	
2-Bromo-3-phenylthio-	{ 50	-2	0.5	5	
	{ 50	-5	0	0	
	{ 25	+5.5	3	—	
2-Phenylthio-1,4-diacetoxynaphthalene	{ 25	-0.5	0.3	—	
	{ 50	-2	0.5	5	
	{ 50	-5	0	0	
	{ 25	+5.5	3	—	
Nitrogen mustard N-oxide	{ 25	-0.5	0.8	5	
	{ 25	-1	0	0	
	{ 10	+3.5	2.2	264	
	{ 10	0	0.2	—	
	{ 50	-3	0	0	died (5)
8-Azaguanine	{ 100	+1	0	0	
	{ 100	0	0	0	
	{ 50	-2.5	0.25	30	
	{ 50	+2.5	0.55	82.5	
	{ 25	+1	1.55	202	
	{ 25	+0.5	0.35	—	

Faculty of Pharmacy  
University of Chiba  
Inohana, Chiba

July 21, 1956

Komei Miyaki (宮木 高明)  
Saburo Ugami (鷗上 三郎)  
Nisaburo Ikeda (池田仁三郎)  
Kazuo Kuretani (樽谷 和男)