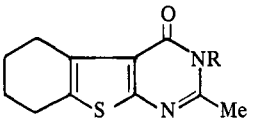
Table I



No.	R	Mp, °C	Yield, %	Formula	Anal.	LD_{50} (mice), mg/kg ip	Dose, mg/kg, po	Inhibition of carrageenin-induced edema in mice, %
1	C_6H_5	132–133	80	$C_{17}H_{16}N_2OS$	C, H, N			
2	$CH_2C_6H_5$	161–162	73	$C_{18}H_{18}N_2OS$	C, H, N	400	80	0
3	$CH_2CH_2C_6H_5$	142–143	69	$C_{19}H_{20}N_2OS$	C, H, N			
4	β-Naphthyl	194–195	80	$C_{21}H_{18}N_2OS$	C, H, N	400	80	7.2
5	p-$CH_3C_6H_4$	201	73	$C_{18}H_{18}N_2OS$	C, H, N, S	1300	160	29.8
6	p-$CH_3OC_6H_4$	195–196	75	$C_{18}H_{18}N_2O_2S$	C, H, N, S			
7	p-BrC_6H_4	238–240	58	$C_{17}H_{15}BrN_2OS$	C, H, N			
8	p-FC_6H_4	204	70	$C_{17}H_{15}FN_2OS$	C, H, N, S	400	80	19.9
9	p-ClC_6H_4	225–226	65	$C_{17}H_{15}ClN_2OS$	C, H, N, S			

The antiinflammatory activity of several of the compounds synthesized (see Table I) was assayed using the carrageenin-induced edema test[4] in mice; phenylbutazone or cortisone served as standards. For this preliminary study we chose compounds with 3 types of substituents on N at the 3 position, namely, substituted Ph (**5** and **8**), alkyl (**2**), and β-naphthyl (**4**) groups. Appreciable activity was shown by **5** and **8** which carry a p-CH_3 and a p-F substituent, respectively on the Ph ring.

Experimental Section‡

2-Amino-3-carbethoxy-4,5-tetramethylenethiophene (III) was prepd from cyclohexanone according to Gewald, *et al.*[2]

2-Amino-3-carboxy-4,5-tetramethylenethiophene (IV). 2-Amino-3-carbethoxy-4,5-tetramethylenethiophene (III, 3 g) was dissolved in 20 ml of EtOH contg 1.5 g of NaOH. The soln was refluxed on a steam bath for 5 hr and then the EtOH was removed under reduced pressure. The residue was dissolved in H_2O and crushed ice was added to the clear soln which was then acidified with HCl. IV, which pptd, was collected in pure form, mp 135–137° (70% yield). It was used for the next operation without further purification. The mass spectrum showed m/e 197.

2-Methyl-3-aryl-4-oxo-5,6-tetramethylenethieno[2,3-*d*]pyrimidines (II). A mixt of the amino acid (IV, 5 g) and Ac_2O (5 g) was refluxed for 1 hr and then kept overnight at room temp. The solid thus sepd was collected under suction and dried. Recrystn from Ac_2O afforded 4 g (72%) of V, mp 130–131°. *Anal.* ($C_{11}H_{11}NO_2S$) C, H, N, S.

Lactone V and an equimolar proportion of the amine were mixed and heated on a low flame for 15 min. On cooling a jelly-like mass was formed which on trituration with Et_2O gave cryst pyrimidones (II). Further purification by recrystn from CH_2Cl_2–C_6H_{14} afforded analytically pure samples (Table I).

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‡All compds were characterized by their satisfactory analytical and spectroscopic data.

Antitumor Activity of 2,2-Hydrazobis(3-chloro-1,4-naphthoquinone) against Walker 256 (Intramuscular) Carcinosarcoma

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In previous studies from this laboratory on potential chemotherapeutic agents, it was reported that in a series of 64 2-chloro-1,4-naphthoquinone compounds synthesized and tested for potential antimalarial activity, certain derivatives were found to possess antimalarial activity in mice experimentally infected with *Plasmodium berghei*.[1]

The biological activities of these compounds have now been studied in detail as potential antitumor agents in the 3 tumor systems, Walker 256 (intramuscular) carcinosarcoma, adenocarcinoma 755, and leukemia L-1210, by screeners under contract to the Cancer Chemotherapy National Service Center. The testing procedures employed have been described previously.[2] Among the 64 compounds one, 2,2-hydrazobis(3-chloro-1,4-naphthoquinone), was found to exhibit significant inhibition against the Walker 256 tumor in rats with confirmed activity. Table I lists

Table I. Antitumor Activity of 2,2-Hydrazobis(3-chloro-1,4-naphthoquinone) against Walker 256 (Intramuscular) Carcinosarcoma

Dose,[a] mg/kg	Survivors	Animal wt,[b] g, diff $T - C$	Tumor wt, mg, T/C	T/C, %[c]
200	6/6	−23	1.2/4.9	24
100	6/6	−22	1.3/4.9	26
50	6/6	−10	2.3/4.9	46
25	6/6	− 7.0	3.8/4.9	77

[a]Four daily doses after the third day of tumor implantation. [b]Difference between test and control animals. [c]Ratio of tumor weight of test animals to that of control animals.

the antitumor testing data for the 2,2-hydrazobis(3-chloro-1,4-naphthoquinone) compound supplied by the Cancer Chemotherapy National Service Center.

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