

Table I. Minimal Antifungal Activity of Substituted Quinolines (millimoles per liter)

Compd	X	Y	Z	<i>A. niger</i>		<i>T. viride</i>		<i>A. oryzae</i>		<i>M. verrucaria</i>		<i>T. mentagrophytes</i>	
				S ^a	C	S	C	S	C	S	C	S	C
Ia	H	H	H	7.0	NA ^b	3.9	NA	NA		5.4	NA	2.3	7.8
Ib	F	F	H	4.3	NA	1.8	2.4	NA		3.6	NA	1.8	2.4
Ic	Cl	Cl	H	NA		NA		NA		NA		NA	
Id	Br	Br	H	NA		NA		NA		NA		NA	
Ie	I	I	H	NA		NA		NA		NA		NA	
IIa	H	H	NO ₂	4.6	NA	2.2	NA	5.2	NA	NA		2.0	NA
IIb	F	F	NO ₂	0.29	NA	0.11	4.6	0.57	NA	0.23	0.29	0.11	0.11
IIc	Cl	Cl	NO ₂	NA		NA		NA		NA		NA	
IId	Br	Br	NO ₂	NA		NA		NA		NA		NA	
IIe	I	I	NO ₂	NA		NA		NA		NA		NA	
IIf	CH ₃ O	CH ₃ O	NO ₂	NA		NA		NA		NA		NA	
IIIa	H	H	NH ₂	6.3	NA	3.8	3.8	NA		4.2	5.2	2.1	3.5
IIIb	F	F	NH ₂	NA		1.1	NA	NA		1.1	NA	0.83	NA
IIIc	Cl	Cl	NH ₂	NA		0.094	NA	NA		0.094	2.1	0.26	0.28
IIId	Br	Br	NH ₂	NA		1.0	NA	NA		2.6	NA	0.33	2.0
IIIe	I	I	NH ₂	NA		1.5	NA	NA		NA		0.15	0.25
IIIf	CH ₃ O	CH ₃ O	NH ₂	NA		1.7	1.7	NA		3.3	3.3	0.11	0.11

^aS = fungistatic, C = fungicidal. ^bNA = not active below 1000 ppm, highest level tested.

The mixt was poured onto ice, and 31 g (95%) of product was obtd by filtration, washing with H₂O, and drying at 70° overnight: mp 168–171°. An analytical sample was crystd from MeOH-DMF: mp 170–172°. *Anal.* (C₉H₄L₂N₂O₂) C, H, I, N.

8-Amino-5,7-diiodoquinoline (IIIe) was prepd in 41% yield from IIe in a manner similar to that for the prepn of IIb: mp 120–132° dec. An analytical sample was prepd by several recrystns from MeOH; mp 143–144° dec. *Anal.* (C₉H₆L₂N₂) C, H, I, N.

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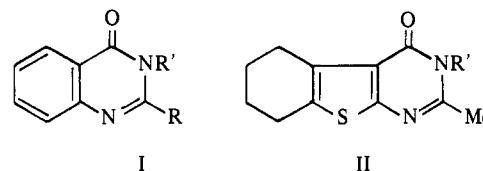
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Heterocyclic Compounds. 4.† Synthesis and Antiinflammatory Activity of Some Substituted Thienopyrimidones

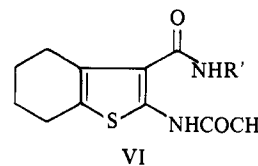
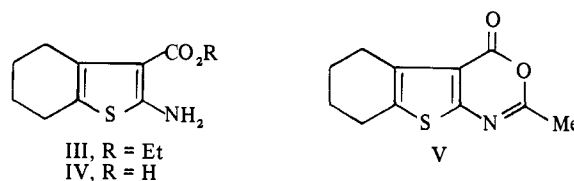
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Substituted quinazolines (I) have attracted attention because of their biological activity.¹ This communication describes the preparation of a number of derivatives of 2-

methyl-3-aryl-4-oxo-5,6-tetramethylenethieno[2,3-*d*]-pyrimidines (II) which are closely related to I.



The thienopyrimidones II described here were prepared from 2-amino-3-carbethoxy-4,5-tetramethylenethiophenes (III) which are easily made.² Alkaline hydrolysis of III afforded the *o*-aminocarboxylic acid IV in 70% yield. Refluxing IV with Ac₂O provided the lactone V³ which on heating with equiv proportions of appropriate arylamines gave the 3-aryl substituted pyrimidones of the general structure II (Table I). It was observed that the yields of the



pyrimidones (II) were good when aniline or a para-substituted aniline was used as the amine component; the ortho- or meta-substituted anilines gave mixtures of the cyclic compounds II and the open chain amides VI.

†Part 3 was submitted for publication.

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 ₆ H ₅	132-133	80	C ₁₇ H ₁₆ N ₂ OS	C, H, N			
2	CH ₂ C ₆ H ₅	161-162	73	C ₁₈ H ₁₈ N ₂ OS	C, H, N	400	80	0
3	CH ₂ CH ₂ C ₆ H ₅	142-143	69	C ₁₉ H ₂₀ N ₂ OS	C, H, N			
4	β-Naphthyl	194-195	80	C ₂₁ H ₁₈ N ₂ OS	C, H, N	400	80	7.2
5	<i>p</i> -CH ₃ C ₆ H ₄	201	73	C ₁₈ H ₁₈ N ₂ OS	C, H, N, S	1300	160	29.8
6	<i>p</i> -CH ₃ OC ₆ H ₄	195-196	75	C ₁₈ H ₁₈ N ₂ O ₂ S	C, H, N, S			
7	<i>p</i> -BrC ₆ H ₄	238-240	58	C ₁₇ H ₁₅ BrN ₂ OS	C, H, N			
8	<i>p</i> -FC ₆ H ₄	204	70	C ₁₇ H ₁₅ FN ₂ OS	C, H, N, S	400	80	19.9
9	<i>p</i> -ClC ₆ H ₄	225-226	65	C ₁₇ H ₁₅ ClN ₂ OS	C, H, N, S			

The antiinflammatory activity of several of the compounds synthesized (see Table I) was assayed using the carrageenin-induced edema test⁴ 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*-CH₃ 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 H₂O 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 Ac₂O (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 Ac₂O afforded 4 g (72%) of V, mp 130-131°. *Anal.* (C₁₁H₁₁NO₂S) 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 Et₂O gave cryst pyrimidones (II). Further purification by recrystn from CH₂Cl₂-C₆H₁₄ 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) Carcinoma

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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) carcinoma, 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) Carcinoma

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

^aFour daily doses after the third day of tumor implantation. ^bDifference between test and control animals. ^cRatio 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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