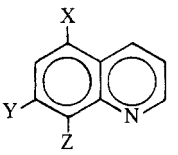
Table I. Minimal Antifungal Activity of Substituted Quinolines (millimoles per liter)



Compd	X	Y	Z	*A. niger* S[a]	*A. niger* C	*T. viride* S	*T. viride* C	*A. oryzae* S	*A. oryzae* C	*M. verrucaria* S	*M. verrucaria* C	*T. mentagrophytes* S	*T. mentagrophytes* 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_3O	CH_3O	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_3O	CH_3O	NH_2	NA		1.7	1.7	NA		3.3	3.3	0.11	0.11

[a] S = fungistatic, C = fungicidal. [b] NA = 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 H_2O, and drying at 70° overnight: mp 168–171°. An analytical sample was crystd from MeOH–DMF: mp 170–172°. *Anal.* ($C_9H_4I_2N_2O_2$) 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.* ($C_9H_6I_2N_2$) C, H, I, N.

References

(1) H. Gershon, R. Parmegiani, A. Weiner, and R. D'Ascoli, *Contrib. Boyce Thompson Inst.*, **23**, 219 (1966).
(2) H. Gershon and R. Parmegiani, *ibid.*, **24**, 33 (1968).
(3) H. Gershon, R. Parmegiani, M. W. McNeil, and Y. J. Hinds, *ibid.*, **24**, 149 (1969).
(4) G. C. Finger, F. H. Reed, and J. L. Finnerty, *J. Amer. Chem. Soc.*, **73**, 153 (1951).
(5) D. Vorländer and E. Siebert, *Ber. Deut. Chem. Ges.*, **52**, 283 (1919).
(6) C. Willgerodt and E. Arnold, *ibid.*, **34**, 3343 (1901).
(7) M. H. Palmer, *J. Chem. Soc.*, 3645 (1962).
(8) R. C. Elderfield and G. L. Krueger, *J. Org. Chem.*, **17**, 358 (1952).
(9) E. C. Hurdis, *ibid.*, **23**, 891 (1958).
(10) R. C. Elderfield and E. F. Claflin, *J. Amer. Chem. Soc.*, **74**, 2953 (1952).
(11) H. Gershon and R. Parmegiani, *Appl. Microbiol.*, **11**, 62 (1963).

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

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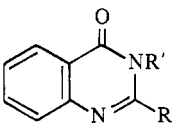
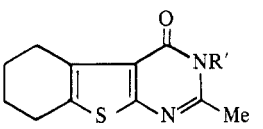
Substituted quinazolines (I) have attracted attention because of their biological activity.[1] This communication describes the preparation of a number of derivatives of 2-methyl-3-aryl-4-oxo-5,6-tetramethylenethieno[2,3-*d*]-pyrimidines (II) which are closely related to I.

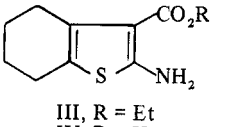


I

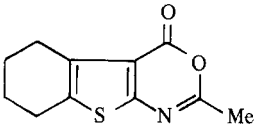


II

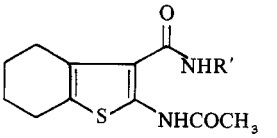
The thienopyrimidones II described here were prepared from 2-amino-3-carbethoxy-4,5-tetramethylenethiophenes (III) which are easily made.[2] Alkaline hydrolysis of III afforded the *o*-aminocarboxylic acid IV in 70% yield. Refluxing IV with Ac_2O provided the lactone V[3] which on heating with equiv 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



III, R = Et
IV, R = H



V

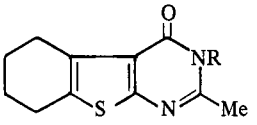


VI

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_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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References

(1) D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, p 162.
(2) K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).
(3) (a) M. T. Bogert and H. A. Seil, *J. Amer. Chem. Soc.*, **27**, 1305 (1905); (b) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).
(4) C. V. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

‡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.

References

(1) B. Prescott, *J. Med. Chem.*, **12**, 181 (1969).
(2) *Cancer Chemother. Rep.*, **25**, 1 (1962).