5-(3-IODOPROPARGYLOXY)PYRIMIDINES AS EFFECTIVE FUNGISTATICS

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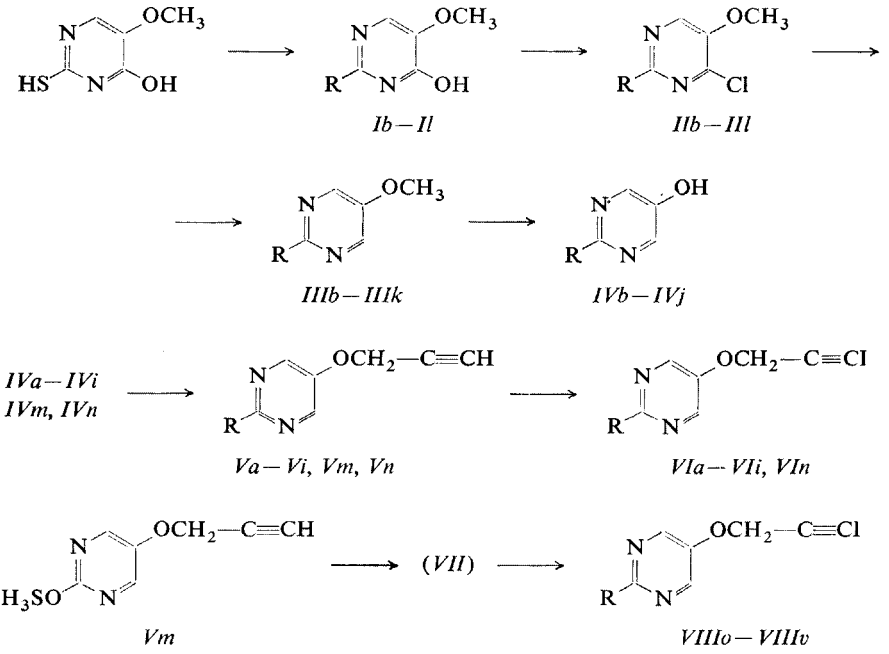
Starting from 2-mercapto-4-hydroxy-5-methoxypyrimidine, 5-(3-iodopropargyloxy)pyrimidines were prepared that were substituted in position 2 with alkylthio, allylthio, benzylthio and methylsulfonyl groups, or with alkoxy, alkenyloxy and alkinyloxy groups. Antimicrobial screening revealed for most of the substances an antifungal activity against a number of fungi and yeasts. The most effective were 2-methylthio-, 2-ethylthio-, 2-n-propylthio-, 2-n-butylthio-, 2-isobutylthio- and 2-allylthio-5-(3-iodopropargyloxy)pyrimidine (*VIb—VIf, VIh*).

During recent years, several highly effective antimycotics have been developed[1,2], such as O-(2-naphthyl)-N-methyl-N-(3-methylphenyl)thiocarbamate (tolnafta-1-(2,4-dichlorobenzyloxy)-1-(2,4-dichlorophenyl)-2-(1-imidazolyl)ethane (miconazole), diphenyl-(2-chlorophenyl)-(1-imidazolyl)methane (clotrimazole) and 2,4,5-trichlorophenyl-(3-iodopropargyl) ether (haloprogine). The last-named substance has attracted our attention because of its rather simple structure and a broad antifungal activity[3]. As a simple method of preparation of 5-hydroxypyrimidines was described here recently[4], we synthesized haloprogine analogues where the trichlorophenolic component was replaced with 5-hydroxypyrimidines differently substituted in position 2. As is well known, only the 5-hydroxypyrimidines possess properties of aromatic phenols.

The required 5-hydroxypyrimidines were prepared from 2-mercapto-4-hydroxy-5--methoxypyrimidine which was first alkylated with the corresponding dialkyl sulfate or with an alkyl halogenide. The 2-alkylthio-4-hydroxy-5-methoxypyrimidines *Ib—Il* thus obtained were then converted with phosphorus oxidochloride to the 4-chloro derivatives *IIb—IIl*, which were then dehalogenated by boiling with powdered zinc to the pyrimidines *IIIb—IIIk*. The last reaction step was a demethylation of the 5-methoxy group under the action of aqueous ammonia in an autoclave at 180°C. This procedure was used before when preparing 2-methylthio-5-hydroxypyrimidine[4]. 2-Benzylthio-5-methoxypyrimidine (*IIIi*) could not be cleaved in this way either by prolonging the reaction period or by raising the temperature to 200°C. Only after 7 h of boiling in a glycol solution of potassium hydroxide[5] was the desired compound obtained. The reagents usually employed for splitting of alkylphenyl ethers, such as hydrogen bromide, hydrogen chloride, aluminium chloride and pyridine hydrochlo-

ride, were not found to be applicable as they destroyed the pyrimidine nucleus. Since higher 2-alkylthio-5-methoxypyrimidines are insoluble in aqueous ammonia several attempts were made to split them by heating with high-boiling amines, such as benzylamine, cyclohexylamine, dodecylamine, 2-aminotridecane, ethanolamine, to 160°C. However, the results were not satisfactory. After 1 h of heating to 160°C, the content of *IVb* in the reaction mixture was estimated colorimetrically according to Johnson and Savidge[6]. At best the conversion (in ethanolamine) was 6%. Because of the chlorine in the side chain, 2-chlorocrotylthio-5-methoxypyrimidine (*IIIl*) cannot be obtained by dehalogenation of the 4-chloro derivative and hence it had to be prepared by alkylation of 2-mercapto-5-methoxypyrimidine with 1,3-dichloro-2-butene.



a, R = H
b, R = CH_3S
c, R = C_2H_5S
d, R = n-C_3H_7S
e, R = n-C_4H_9S
f, R = i-C_4H_9S
g, R = n-$C_6H_{13}S$
h, R = CH_2=CH—CH_2S
i, R = $C_6H_5CH_2S$
j, R = n-$C_{12}H_{25}S$
k, R = n-$C_{14}H_{29}S$

l, R = CH_3—CCl=CH—CH_2S
m, R = CH_3SO
n, R = CH_3SO_2
o, R = CH_3O
p, R = C_2H_5O
q, R = CH_2=CH—CH_2—O
r, R = $HOCH_2CH_2O$
s, R = IC≡C—CH_2O
t, R = CH_3—CHOH—CH_2O
u, R = $HOCH_2$—C≡C—CH_2O
v, R = $HOCH_2$—CH=CH—CH_2O

Oxidation of 2-methylthio-5-hydroxypyrimidine (*IIIb*) with hydrogen peroxide yields either 2-methylsulfinyl- or 2-methylsulfonyl- 5-hydroxypyrimidine[7] (*IVm*, *IVn*). Under otherwise identical conditions it depends only on the amount of hydrogen peroxide used. At a molar ratio of *IIIb* to hydrogen peroxide equal to 1 : 1–1·5, a sulfoxide is formed which contains a small amount of the starting compound; at a ratio of 1 : 2–2·5, a sulfone with a minor amount of sulfoxide is obtained. Oxidation of *IIIb* with sodium hypochlorite under identical conditions as in the case of 2-methylthio-5-methoxypyrimidine[8] yields relatively pure sulfone *IVb* but, because of its solubility in water, its isolation from the reaction mixture containing a considerable amount of sodium chloride is more laborious.

TABLE I

Antifungal Activity of 5-(3-Iodopropargyloxy)pyrimidines *in vitro*

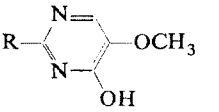
The minimum inhibitory concentration in μg/ml. A minus sign indicates that no growth inhibition was found even at a concentration of 50 μg/ml.

Compound	TM[a]	TR	TV	MG	EF	CA	CT	CN	TC
VIa	2·5	1·2	1·2	2·5	1·2	1·2	1·2	0·6	1·2
VIb	0·6	0·6	0·3	0·6	0·6	0·6	0·6	0·3	0·3
VIc	0·6	0·6	0·3	0·6	0·6	0·6	0·6	0·3	0·3
VId	0·6	0·6	0·3	0·6	0·6	0·3	0·6	0·1	0·3
VIe	0·6	0·6	0·3	0·6	0·6	0·3	0·3	0·05	0·1
VIf	0·6	0·6	0·3	0·6	0·6	0·3	0·3	0·05	0·1
VIg	1·2	1·2	1·2	2·5	1·2	5·0	1·2	2·5	2·5
VIh	0·6	0·6	0·6	0·6	0·6	0·6	0·6	0·3	0·3
VIi	2·5	2·5	1·2	2·5	1·2	10·0	10·0	5·0	10·0
VIn	—	—	—	—	—	—	—	—	—
VIIIo	2·5	1·2	1·2	2·5	1·2	5·0	5·0	1·2	2·5
VIIIp	2·5	1·2	2·5	1·2	1·2	2·5	5·0	1·2	5·0
VIIIq	0·6	0·6	0·6	0·6	0·6	1·2	0·6	0·6	0·6
VIIIr	2·5	2·5	2·5	2·5	2·5	5·0	5·0	2·5	
VIIIs	0·6	0·6	0·6	0·6	0·6	2·5	2·5	1·2	
VIIIt	2·5	2·5	2·5	2·5	2·5	5·0	5·0	2·5	
VIIIu	1·2	1·2	1·2	1·2	1·2	5·0	5·0	1·2	
VIIIv	1·2	1·2	1·2	1·2	1·2	5·0	5·0	1·2	
Tolnaftate	0·3	0·6	0·3	0·6	0·3	—	—	—	—
Clotrimazole	0·6	0·6	0·6	0·6	0·6	5·0	5·0	2·5	5·0
Haloprogine	0·6	0·6	0·6	0·6	0·6	1·2	0·6	0·6	1·2

[a] TM *Trichophyton mentagrophytes*, TR *Trichophyton rubrum*, TV *Trichophyton verrucosum*, MG *Microsporum gypseum*, EF *Epidermophyton floccosum*, CA *Candida albicans*, CT *Candida tropicalis*, CN *Cryptococcus neoformans*, TC *Trichosporon cutaneum*.

TABLE II

1-Alkylthio-4-hydroxy-5-methoxypyrimidines (*I*)



Compound yield, %	Formula (m.w.)	M.p., °C	Calculated/Found			
			% C	% H	% N	% S
Id	$C_8H_{12}N_2O_2S$	143–144	47·97	6·04	13·99	16·01
77·2	(200·3)		47·96	6·14	14·24	16·13
Ie	$C_9H_{14}N_2O_2S$	121–122	50·49	6·55	13·08	
74·5	(214·2)		50·47	6·48	13·17	
If	$C_9H_{14}N_2O_2S$	151	50·49	6·55	13·08	14·96
82·5	(214·2)		50·64	6·12	13·40	14·88
Ig	$C_{11}H_{18}N_2O_2S$	98	54·51	7·48	11·56	13·23
87	(242·3)		54·51	7·62	11·87	13·35
Ih	$C_8H_{10}N_2O_2S$	132–133	48·48	5·12	14·13	16·20
68·5	(198·3)		48·16	5·25	13·85	16·01
Ii	$C_{12}H_{12}N_2O_2S$	186–188	58·06	4·83	11·28	
59·1	(248·2)		58·34	4·92	11·30	
Ij	$C_{17}H_{30}N_2O_2S$	105	62·53	9·26	8·58	9·82
84·8	(326·5)		62·97	9·53	8·85	10·26
Ik	$C_{19}H_{34}N_2O_2S$	108	64·36	9·66	7·90	9·04
83·7	(354·6)		64·36	9·70	7·58	9·29
Il	$C_9H_{11}ClN_2O_2S$	164	43·81	4·49	11·36	[a]
76·5	(246·7)		43·82	4·66	11·49	

[a] Calculated: 14·37% Cl; found: 14·43% Cl.

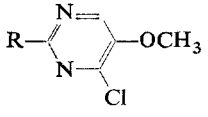
These 5-hydroxypyrimidines *IVa–IVi* and *IVm* and *IVn* were left to react with propargyl bromide in acetone or dimethylformamide solution to convert them to 5-propargyloxypyrimidines *Va–Vi*, *Vm* and *Vn*. With the exception of 2-methylthio- and 2-methylsulfonyl-5-propargyloxypyrimidine all the compounds were oily and were thus processed only in the crude state. The last reaction step, iodination, was carried out with iodine in a methanol solution of sodium hydroxide. Iodination proceeded always smoothly and produced fine yields. The result of iodination of 2-methylsulfinyl-5-propargyloxypyrimidine (*Vm*) was interesting since under the effect of a methanol solution of sodium hydroxide, it was alcoholyzed, giving rise to 2-me-

thoxy-5-(3-iodopropargyloxy)pyrimidine (*VIIIo*). If the iodination was done in an ethanol medium, the corresponding 2-ethoxy derivative *VIIIp* was obtained. The other 2-alkoxy-, 2-alkenyloxy- and 2-alkinyloxy-5-(3-iodopropargyloxy)pyrimidines *VIIIq* to *VIIIv* were prepared in the same way. The intermediate 2-alkoxy-, 2-alkenyloxy- and 2-alkinyloxy-5-propargyloxypyrimidines *VII* were not isolated but, after cooling the reaction mixture, they were iodinated to the 5-(3-iodopropargyloxy) derivatives.

The prepared compounds were tested *in vitro* for their antifungal activity against dermatophytes and against yeasts and yeast-like microorganisms[9]. The results indicate

TABLE III

2-Alkylthio-4-chloro-5-methoxypyrimidines (*II*)



Compound yield, %	Formula (m.w.)	M.p., °C b.p., °C/Torr	Calculated/Found % C	% H	% Cl	% N	% S
IIc	$C_7H_9ClN_2OS$	71	41·09	4·42	17·32	13·69	15·61
53	(204·7)	50% ethanol	40·92	4·36	17·44	13·80	15·76
IId	$C_8H_{11}ClN_2OS$	119/0·4	43·93	5·07	16·21	12·81	14·66
73·5	(218·7)		44·17	5·20	16·19	13·29	14·72
IIe	$C_9H_{13}ClN_2OS$	150/4	46·48	5·59	15·24	12·05	
91	(232·6)		46·10	5·67	14·99	11·96	
IIf	$C_9H_{13}ClN_2OS$	35	46·48	5·59	15·24	12·05	
86·5	(232·6)	120/0·6	46·31	5·81	15·44	12·33	
IIg	$C_{11}H_{17}ClN_2OS$	140/0·2	50·65	6·57	13·59	10·74	12·29
80	(260·8)		50·81	6·64	13·34	10·31	12·29
IIh	$C_8H_9ClN_2OS$	30	44·38	4·17	16·36	12·92	
82·2	(216·7)	ethanol	44·40	4·24	16·49	12·84	
IIi	$C_{12}H_{11}ClN_2OS$	62—64	53·90	4·13	13·30	10·50	
96	(266·7)	60% ethanol	53·37	4·30	13·52	10·27	
IIj	$C_{17}H_{29}ClN_2OS$	45	59·19	8·47	10·27	8·12	
97	(344·9)	tetrachlor-methane	59·32	8·67	10·08	8·03	
IIk	$C_{19}H_{33}ClN_2OS$	52—53	61·18	8·92	9·50	7·51	
99	(373·0)	ethanol	60·93	8·95	9·26	7·68	
IIl	$C_9H_{10}Cl_2N_2OS$	35	40·76	3·80	26·74	10·56	
87	(265·2)	60% ethanol	40·77	3·90	26·33	10·89	

(Table I) that the compounds exhibit a pronounced antifungal activity which culminates with 5(3-iodopropargyloxy)pyrimidines substituted in position 2 with methylthio to butylthio groups. The 2-alkoxy derivatives are less efficient with the exception of 2-allyloxy-5-(3-iodopropargyloxy)pyrimidine (*VIIIq*) which has practically the same efficiency as its thio analogue *VIh*.

EXPERIMENTAL

2-Ethylthio-4-hydroxy-5-methoxypyrimidine (*Ic*)

2-Mercapto-4-hydroxy-5-methoxypyrimidine[10] (3·62 g) was dissolved in boiling 15% NaOH (120 ml) and, after cooling, further sodium hydroxide was added (150 ml) whereupon diethyl sulfate was added dropwise under stirring (35·3 g). The mixture was heated to 86°C and after 3 h acidified with hydrochloric acid (70 ml). A product precipitated on cooling, was filtered, washed with water and dried. The yield was 33·8 g (79%), m.p. 140°C (water.) For $C_7H_{10}N_2O_2S$ (186·2) calculated: 45·14% C, 5·41% H, 15·04% N, 17·28% S; found: 45·27% C, 5·59% H, 15·16% N, 17·11% S.

2-Alkylthio-4-hydroxy-5-methoxypyrimidines (*Id—Il*)

A solution of 2-mercapto-4-hydroxy-5-methoxypyrimidine[10] (0·2 mol) in ethanol (500 ml) was combined at 40—50°C with a solution of 9·2 g Na in 150 ml ethanol, whereupon 0·2 mol of the corresponding alkyl bromide (for *Id—Ih*) or alkyl chloride (for *Ii—Il*) was added. The mixture was refluxed for 3—4 h, the inorganic salts were filtered, the filtrate was evaporated *in vacuo*, the residue was dissolved in water and, after bleaching with charcoal, it was acidified with dilute hydrochloric acid to pH 4—5. The product was filtered, washed with water and recrystallized from ethanol. The yields, the melting points and the results of elementary analyses are shown in Table II.

2-Alkylthio-4-chloro-5-methoxypyrimidines (*IIc—IIl*)

The corresponding 2-alkylthio-4-hydroxy-5-methoxypyrimidine (0·1 mol) was heated to boiling with phosphorus oxidochloride (60 ml). After dissolving, the excess oxidochloride was distilled *in vacuo* and the residue poured into a mixture of ice and water. The product was extracted with chloroform and the chloroform extract was dried with calcium chloride and evaporated. If the residue was liquid, it was distilled *in vacuo*. The yields, melting points and the results of elementary analyses are shown in Table III.

2-Alkylthio-5-methoxypyrimidines (*IIIc—IIIk*)

A mixture of 2-alkylthio-4-chloro-5-methoxypyrimidine (0·1 mol), powdered zinc (120 g), water (500 ml) and ethanol (500—600 ml) was heated under stirring for 6 h to boiling while ammonia was added in parts (12—14 ml). The zinc was then filtered, washed with hot ethanol and the combined filtrates were evaporated *in vacuo* to 1/4—1/5 their original volume. The residue was

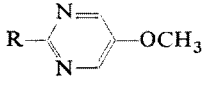
extracted with chloroform (3 × 40 ml), the extract was dried with calcium chloride and evaporated. If the residue was liquid, it was purified by rectification *in vacuo*; if it was solid it was recrystallized. The yields, melting points and the results of elementary analyses are shown in Table IV.

2-Chlorocrotylthio-5-methoxypyrimidine (*IIIl*)

2-Mercapto-5-methoxypyrimidine[10] (7·1 g) was dissolved in a warm solution of 1·15 g Na in 40 ml ethanol, the solution combined with 1,3-dichloro-2-butene and the mixture was boiled for 5 h. After cooling, it was diluted with water (120 ml) and the precipitated oil was extracted with chloroform. The oily residue after evaporation of the chloroform was rectified *in vacuo*. The yield was 4 g (34·7%), b.p. 140°C/0·1 Torr. For $C_9H_{11}ClN_2OS$ (230·7) calculated: 46·86% C, 4·80% H, 12·15% N, 13·90% S; found: 46·92% C, 4·76% H, 12·60% N, 14·01% S.

TABLE IV

2-Alkylthio-5-methoxypyrimidines (*III*)



Compound yield, %	Formula (m.w.)	M.p., °C b.p., °C/Torr solvent	Calculated/Found % C	% H	% N	% S
IIIc	$C_7H_{10}N_2OS$	86/0·4	49·38	5·92	16·46	18·84
59·6	(170·2)		49·17	5·91	16·80	18·96
IIId	$C_8H_{12}N_2OS$	34	52·14	6·56	15·20	17·40
74	(184·3)	100/0·6	52·02	6·73	15·32	17·32
IIIe	$C_9H_{14}N_2OS$	130/4	54·53	7·12	14·14	16·18
59·5	(198·2)		54·52	7·38	14·46	16·06
IIIf	$C_9H_{14}N_2OS$	120/0·6	54·53	7·12	14·14	16·18
73·2	(198·2)		53·89	7·02	13·86	15·93
IIIg	$C_{11}H_{18}N_2OS$	120/0·3	58·35	8·01	12·36	14·11
68·8	(226·3)		58·57	8·09	12·23	14·25
IIIh	$C_8H_{10}N_2OS$	140/20	52·72	5·53	15·37	
51·6	(182·3)		52·81	5·51	15·03	
IIIi	$C_{12}H_{12}N_2OS$	47—48	62·06	5·21	12·04	13·75
70·8	(232·2)	methanol	61·56	5·34	12·14	13·61
IIIj	$C_{17}H_{30}N_2OS$	45	65·75	9·74	9·02	10·32
76·3	(310·5)	methanol	65·61	9·62	8·71	9·97
IIIk	$C_{19}H_{34}N_2OS$	53—54	67·40	10·12	8·27	
66·6	(338·6)	tetra-chloro-methane	67·75	10·52	7·87	

2-Alkylthio-5-hydroxypyrimidines (*IVc—IVh*)

The corresponding 2-alkylthio-5-methoxypyrimidine (3 g) was heated with 9 ml ammonia in an rotating autoclave to 180—190°C. After cooling and filtration, the solution was freed of ammonia, by boiling and neutralized with diluted hydrochloric acid to pH 3—4. The precipitated product was filtered and crystallized from water. The yields, melting points and the results of elementary analyses are shown in Table V.

2-Benzylthio-5-hydroxypyrimidine (*IVi*)

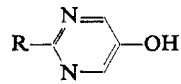
A mixture of 2-benzylthio-5-methoxypyrimidine (6 g), glycol (60 ml) and powdery NaOH (6 g) was refluxed for 7 h. After cooling, it was acidified with hydrochloric acid to pH 3—4 and evaporated *in vacuo* to dryness. The yield was 1 g (17·5%), m.p. 170°C (25% ethanol). For $C_{11}H_{10}N_2OS$ (218·3) calculated: 60·52% C, 4·62% H, 12·83% N; found: 59·79% C, 4·64% H, 12·56% N.

2-Methylsulfinyl-5-hydroxypyrimidine (*IVm*)

7 ml of 30% hydrogen peroxide was added dropwise to a boiling solution of 2-methylthio-5-hydroxypyrimidine (7·1 g) in 30 ml water. After cooling, a product separated, was filtered and dried. The yield was 4·1 g (47·8%), m.p. 148—149°C (water). For $C_5H_6N_2O_2S$ (158·2) calculated: 37·92% C, 3·79% H, 17·71% N, 20·27% S; found: 37·84% C, 3·94% H, 17·53% N, 20·52% S.

TABLE V

2-Alkylthio-5-hydroxypyrimidines (*IV*)



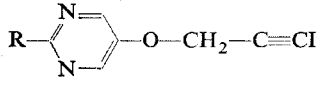
Compound yield, %	Formula (m.w.)	M.p., °C	Calculated/Found			
			% C	% H	% N	% S
IVc	$C_6H_8N_2OS$	120	46·13	5·16	17·94	20·53
33·2	(156·2)		45·90	5·19	18·29	20·31
IVd	$C_7H_{10}N_2OS$	102	49·38	5·92	16·46	18·84
48·6	(170·2)		49·34	5·95	16·39	19·01
IVe	$C_8H_{12}N_2OS$	114	52·16	6·57	15·22	
49	(184·2)		51·71	6·55	14·94	
IVf	$C_8H_{12}N_2OS$	128	52·16	6·57	15·22	17·40
58·7	(184·2)		51·84	6·53	15·09	17·38
IVg	$C_{10}H_{16}N_2OS$	101	56·56	7·59	13·19	15·10
26·7	(212·3)		56·39	7·68	12·97	14·91
IVh	$C_7H_8N_2OS$	100	49·97	4·79	16·65	19·06
45·6	(168·2)		50·00	4·91	16·57	18·87

2-R-5-(3-Iodopropargyloxy)pyrimidines (*VIa*—*VIi*, *VIn*)

Anhydrous potassium carbonate (0·555 mol) and propargyl bromide (0·555 mol) were added consecutively under stirring to a solution of the corresponding 5-hydroxypyrimidine *IVa*—*IVi*, *IVn* (0·517 mol) in acetone (1 200 ml). The mixture was then refluxed for 8—15 h. The reaction course was followed by thin-layer chromatography (Silufol) using benzene. After cooling, the inorganic salts were filtered, the filtrate was evaporated and the residue dissolved in ether (1 500 ml). The ether solution was extracted with 10% NaOH (3 × 100 ml), water and then dried with magnesium sulfate. After distillation of ether, the residue (crude propargyloxypyrimidine *Va*—*Vi*, *Vn*) was iodinated.

TABLE VI

2-R-5-(2-Iodopropargyloxy)pyrimidines (*VI*)



Compound yield, %	Formula (m.w.)	M.p., °C	Calculated/Found				
			% C	% H	% I	% N	% S
VIa	$C_7H_5IN_2O$	159	32·33	1·94	48·80	10·77	—
7	(260·0)	[a]	32·64	2·10	48·78	10·97	
VIb	$C_8H_7IN_2OS$	142	31·38	2·30	41·45	9·15	10·49
94	(306·1)	80% ethanol	31·51	2·38	41·47	9·36	10·85
VIc	$C_9H_9IN_2OS$	110	33·76	2·83	39·64	8·75	10·01
71	(320·2)	80% methanol	34·02	2·77	39·57	8·79	10·13
VId	$C_{10}H_{11}IN_2OS$	93	35·94	3·32	37·97	8·38	9·59
64·5	(338·1)	60% methanol	36·09	3·25	37·91	8·28	9·52
VIe	$C_{11}H_{13}IN_2OS$	78	37·94	3·76	36·44	8·04	9·21
63	(348·2)	methanol	38·46	3·90	36·76	7·92	9·63
VIf	$C_{11}H_{13}IN_2OS$	76	37·94	3·76	36·44	8·04	9·21
71·7	(348·2)	50% ethanol	38·17	3·82	36·05	8·28	9·11
VIg	$C_{13}H_{17}IN_2OS$	66	41·50	4·55	33·73	7·44	8·52
71·7	(376·3)	50% methanol	41·72	4·45	33·54	7·43	8·73
VIh	$C_{10}H_9IN_2OS$	111	36·16	2·73	38·20	8·43	9·65
59	(332·2)	70% methanol	36·33	2·82	38·03	8·57	9·69
VIi	$C_{14}H_{11}IN_2OS$	110	43·99	2·90	33·20	7·33	8·39
47	(382·2)	methanol	44·09	2·90	32·62	7·63	8·46
VIn	$C_8H_7IN_2O_3S$	154	28·49	2·08	37·53	8·28	9·48
61	(338·1)	benzene	28·56	1·97	37·60	8·39	9·42

[a] Purified by sublimation at 120°C/10 Torr.

A solution of crude 5-propargyloxypyrimidine *Va*—*Vi* and *Vn* (0·014 mol) in 100 ml methanol was combined with 10% NaOH (17·5 ml) and powdery iodine (0·018 gat). The mixture was then stirred for 1 h at 18°C, diluted with 10 ml water, in the case of *VIn* diluted with 1000 ml water and left to crystallized in a refrigerator. The precipitated product was filtered, washed with 50% methanol and dried. The yields, melting points and the results of elementary analyses are shown in Table VI.

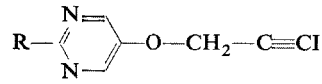
2-Alkoxy-5-(3-iodopropargyloxy)pyrimidines (*VIIIo*—*VIIIv*)

A solution of 2-methylsulfinyl-5-propargyloxypyrimidine (3·5 g) in a mixture of the corresponding alcohol (130 ml) and 10% NaOH (23 ml) was heated to 70—100°C until disappearance (according to thin-layer chromatography on Silufol in ethanol–benzene 1 : 8) of the starting product. It was then cooled to 15°C, combined with iodine powder (6 g) and stirred for 30 min. After diluting with water (200 ml) the crystalline product was filtered, washed with 50% methanol and dried. The yields, melting points and the results of elementary analyses are shown in Table VII.

The elementary analyses were done by Mrs J. Komancová, Mrs A. Slavíková, Mrs V. Šmídová, Dr M. Čech and Mr K. Havel of the analytical department of this Institute. The colorimetric estima-

TABLE VII

2-Alkoxy-5-(3-iodopropargyloxy)pyrimidines (*VIII*)



Compound yield, %	Formula (m.w.)	M.p., °C solvent	Calculated/Found			
			% C	% H	% I	% N
VIIIo	$C_8H_7IN_2O_2$	154	33·12	2·43	43·75	9·66
23	(290·1)	benzene	33·26	2·38	43·52	9·73
VIIIp	$C_9H_9IN_2O_2$	149	35·55	2·98	41·73	9·21
24·3	(304·1)	ethanol	36·11	3·07	41·67	9·25
VIIIq	$C_{10}H_9IN_2O_2$	103	37·99	2·87	40·14	8·86
71	(316·1)	methanol	37·88	2·84	40·24	8·76
VIIIr	$C_9H_9IN_2O_2$	142	33·77	2·83	39·65	8·75
54·5	(320·1)	water	33·77	2·77	39·57	9·16
VIIIs	$C_{10}H_6I_2N_2O_2$	138	27·30	1·37	57·69	6·36
62·5	(440·0)	acetone	27·89	1·52	57·00	6·44
VIIIt	$C_{10}H_{11}IN_2O_3$	115	35·97	3·32	38·00	8·38
29	(334·1)	water	35·61	3·51	37·87	8·56
VIIIu	$C_{11}H_9IN_2O_3$	135	38·39	2·63	36·88	8·14
78	(344·1)	40% methanol	38·20	2·71	36·80	7·91
VIIIv	$C_{11}H_{11}IN_2O_3$	118	38·17	3·20	36·66	8·04
20	(346·1)	water	38·20	3·11	36·52	8·09

tion of 2-methylthio-5-hydroxypyrimidine was done by Mr V. Malý of the department of physical chemistry of this Institute.

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