O-(2-METHYLTHIO-5-PYRIMIDINYL) THIOCARBAMATES AND THEIR ANTIMYCOTIC ACTIVITY

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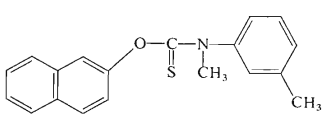
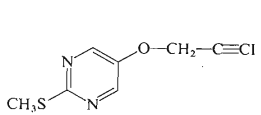
Treatment of 2-methylthio-5-pyrimidinol with thiophosgene afforded O,O-bis(2-methylthio-5-pyrimidinyl) thiocarbonate (*III*) which was converted by reaction with various substituted N-methylanilines *IIc–III* and further secondary amines to the corresponding O-(2-methylthio-5-pyrimidinyl) thiocarbamates *IVa–IVo*. The esters of N-methyl-N-arylthiocarbamoic acids *IVc–IVl* exhibit a significant antimycotic activity.

The drug Tolnaphthate (*A*), O-(2-naphthyl)-N-methyl-N-(3-tolyl) thiocarbamate, belongs to the most efficient antimycotics. In connection with pharmaceutical and chemical investigations on 2-alkylthio-5-(3-iodopropargyloxy)pyrimidines, a novel group of very efficient antimycotics has been discovered in this Laboratory[1]; the 2 methylthio derivative *B* has been subjected to clinical assays under the name Jaritin. Since both *A* and *B* contain a phenolic component, it was of interest to prepare some esters as a combination of 2-methylthio-5-pyrimidinol with various substituted thiocarbamoic acids and to test their biological activity.



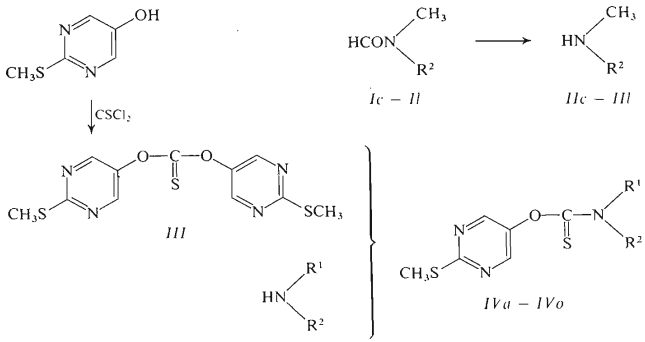
A



B

In the synthesis of the required esters, the reaction of 2-methylthio-5-pyrimidinol with thiophosgene was attempted. Instead of the expected 5-(chlorothiocarbonyloxy)-2-methylthiopyrimidine (which should serve as an acylating agent of various secondary amines), O,O bis(2-methylthio-5-pyrimidinyl) thiocarbonate (*III*) was obtained. By reaction of compound III with chloro-, methoxy-, and methyl-N-methylanilines *IIc–IIl*, dimethylamine, dibutylamine, piperidine, morpholine, and N-methylpiperazine, the compounds *IVa–IVo* were prepared with liberation of one

mol of 2-methylthio-5-pyrimidinol. In connection with the present experiments, the preparation[2,3] of dimethylthiocarbamoyl chloride from tetramethylthiuram disulfide (bis(dimethylthiocarbamoyl) disulfide) was attempted. However, we did not succeed in reproducing this preparation since the resulting dimethylthiocarbamoyl chloride decomposed to large extent during the filtration. The N-methylanilines *IIc* to *III* were obtained by reaction of the appropriate anilines with trimethyl orthoformate and hydrolysis of the primary N-methylformanilides *Ic–Il* (*cf.*[4]).



a, $R^1 = R^2 = CH_3$
b, $R^1 = R^2 = n\text{-}C_4H_9$
c, $R^1 = CH_3$; $R^2 = C_6H_5$
d, $R^1 = CH_3$; $R^2 = 3\text{-}ClC_6H_4$
e, $R^1 = CH_3$; $R^2 = 4\text{-}ClC_6H_4$
f, $R^1 = CH_3$; $R^2 = 3,4\text{-}Cl_2C_6H_3$
g, $R^1 = CH_3$; $R^2 = 3,5\text{-}Cl_2C_6H_3$
h, $R^1 = CH_3$; $R^2 = 3\text{-}CH_3C_6H_4$
i, $R^1 = CH_3$; $R^2 = 4\text{-}CH_3C_6H_4$
j, $R^1 = CH_3$; $R^2 = 3,4\text{-}(CH_3)_2C_6H_3$
k, $R^1 = CH_3$; $R^2 = 3,5\text{-}(CH_3)_2C_6H_3$
l, $R^1 = CH_3$; $R^2 = 4\text{-}CH_3OC_6H_4$
m, $R^1 - R^2 = -(CH_2)_5-$
n, $R^1 - R^2 = -(CH_2)_2O(CH_2)_2-$
o, $R^1 - R^2 = -(CH_2)_2N(CH_3)(CH_2)_2-$

The O-(2-methylthio-5-pyrimidyl) thiocarbamates *IVa–IVo* were assayed *in vitro* on the antifungal activity against 8 dermatophyte species. As it may be inferred from Table I, almost all the prepared substances displayed a significant antimycotic activity particularly the N-methyl-N-phenyl thiocarbamates substituted in the *meta* position by a methyl group or by a chloro atom (compounds *IVh*, *IVd*). The biological activity did not increase by introduction of an additional methyl group into the position 4 or 5 (compounds *IVj*, *IVk*). In the case of the analogous 3,5-dichloro derivative *IVg*, the antimycotic activity increased only slightly while the 3,4-dichlorophenyl derivative

was considerably less active. Replacement of the phenyl group by an alkyl residue (compounds *IVa*, *IVb*) or the presence of a nitrogen heterocycle instead of the amino group resulted in a decrease of the biological activity by 1–2 orders of ten. None of the present thiocarbamates was antimycotically more active *in vitro* than compounds *A* and *B*.

EXPERIMENTAL

N-Methylformanilides *Id–Il* and N-Methylanilines *IId–IIl*

The N-methylanilines *IId–IIl* were prepared according to the method of Roberts and coworkers[4] from the appropriate anilines by reaction with trimethyl orthoformate and the subsequent hydrolysis of N-methylformanilides *Id–Il*. *Id*, yield 62·5%, b.p. 155–156°C at 14 Torr. For C_8H_8ClNO

TABLE I

Antifungal Activity of O-(2-Methylthio-5-pyrimidinyl) Thiocarbamates *IVa–IVo in vitro*

The minimum inhibitory concentration in μg/ml. Three dermatophyte strains of various origin were assayed and an average value taken.

Compound *IV*	TM[a]	TR	TV	TSch	MG	MA	MC	EF
a	12·5	10·2	6·2	15·6	20·4	18·6	16·2	25
b	4·3	4·1	3·6	6·2	10·2	8·4	6·2	6·2
c	0·8	0·6	0·5	1·2	6·2	3·1	2·6	1·5
d	0·07	0·07	0·05	0·1	0·6	0·1	0·1	0·2
e	0·3	0·3	0·1	0·6	3·1	2·6	1·2	0·7
f	0·15	0·1	0·07	0·15	0·5	0·1	0·1	0·3
g	0·05	0·04	0·03	0·06	0·4	0·1	0·1	0·15
h	0·06	0·05	0·03	0·06	0·4	0·1	0·1	0·15
i	0·3	0·2	0·1	0·5	3·1	2·6	1·2	0·5
j	0·09	0·06	0·03	0·1	0·5	0·1	0·1	0·2
k	0·07	0·04	0·02	0·07	0'4	0·1	0·1	0·15
l	0·6	0·5	0·3	1·2	2·6	1·8	1·2	2·2
m	6·2	5·8	4·3	8·4	12·5	10·2	8·4	12·5
n	25	25	12·5	25	25	25	25	25
o	25	25	12·5	25	25	25	25	25
Tolnaphthate (*A*)	0·02	0·02	0·01	0·03	0·1	0·05	0·04	0·07
Jaritin (*B*)	0·03	0·03	0·01	0·03	0·07	0·03	0·03	0·03

[a] TM *Trichophyton mentagrophytes*, TR *Trichophyton rubrum*, TV *Trichophyton verrucosum*, TSch *Trichophyton Schoenleini*, MG *Microsporum gypseum*, MA *Microsporum Audounii*, MC *Microsporum canis*, EF *Epidermophyton floccosum*.

TABLE II

O-(2-Methylthio-5-pyrimidinyl) Thiocarbamates *IVa*—*IVo*

Compound *IV*[a] Yield, %	M.P., °C solvent	Formula (M.w.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
a	100—101	$C_8H_{11}N_3OS_2$	41·90	4·84	—	18·32	27·96
60	voda	(229·3)	42·05	4·79	—	18·74	27·71
b	183—196/0·8[b]	$C_{14}H_{23}N_3OS_2$	53·64	7·39	—	13·40	20·46
64		(313·5)	54·45	7·70	—	13·25	20·38
c	157·5—158·5	$C_{13}H_{13}N_3OS_2$	53·58	4·50	—	14·42	22·01
68 (1·5)	ethanol	(291·4)	53·78	4·79	—	14·68	21·80
d	90—95	$C_{13}H_{12}ClN_3OS_2$	47·92	3·71	10·88	12·90	19·68
25 (1·5)	ethanol	(325·8)	48·31	3·92	10·89	12·92	19·87
e	144·5—145	$C_{13}H_{12}ClN_3OS_2$	47·92	3·71	10·88	12·90	19·68
65·5 (0·75)	70% ethanol	(325·8)	48·04	3·80	10·90	12·93	19·81
f	122·5—123	$C_{13}H_{11}Cl_2N_3OS_2$	43·34	3·08	19·68	11·66	17·80
33 (2)	90% ethanol	(360·3)	44·62	3·22	19·39	11·65	17·74
g	160—162	$C_{13}H_{11}Cl_2N_3OS_2$	43·34	3·08	19·68	11·66	17·18
14 (3·5)	ethanol	(360·3)	44·34	3·14	19·50	11·82	17·50
h	112—114	$C_{14}H_{15}N_3OS_2$	55·05	4·95	—	13·76	21·00
40 (1)	ethanol	(305·4)	55·26	5·23	—	13·88	21·12
i	109—111	$C_{14}H_{15}N_3OS$	55·05	4·95	—	13·76	21·00
72 (1·5)	ethanol	(305·4)	55·25	5·23	—	13·70	20·79
j	113·5—115	$C_{15}H_{17}N_3OS_2$	56·40	5·36	—	13·15	20·07
88 (1·5)	90% ethanol	(319·5)	57·24	5·56	—	13·49	19·02
k	147·5—149	$C_{15}H_{17}N_3OS_2$	56·40	5·36	—	13·15	20·07
44 (1)	85% ethanol	(319·5)	56·50	5·42	—	13·45	19·88
l	102·5—103	$C_{14}H_{15}N_3O_2S_2$	52·31	4·70	—	13·07	19·95
86 (1)	80% ethanol	(321·4)	52·12	4·79	—	12·82	19·92
m	70·5—71·5	$C_{11}H_{15}N_3OS_2$	49·04	5·61	—	15·60	23·81
82	60% ethanol	(269·4)	48·72	5·73	—	15·62	23·98
n	148—148·5	$C_{10}H_{13}N_3O_2S_2$	44·26	4·83	—	15·48	23·63
85·5	ethanol	(271·4)	44·07	4·72	—	15·36	23·80
o	128—129	$C_{11}H_{16}N_4OS_2$	46·45	5·67	—	19·70	22·55
67	30% methanol	(284·4)	46·81	5·55	—	19·93	22·87

[a] The refluxing time (h) is given in parentheses. [b] Boiling point.

(169·6) calculated: 56·66% C, 4·75% H, 20·90% Cl, 8·26% N; found: 57·08% C, 4·98% H, 20·64% Cl, 8·38% N. *Ig*, yield 77·5%, m.p. 81·5—82·5°C. For $C_8H_7Cl_2NO$ (204·1) calculated: 47·09% C, 3·46% H, 34·75% Cl, 6·86% N; found: 47·41% C, 3·53% H, 34·64% Cl, 7·00% N. *Ii*, yield 82%, b.p. 144°C at 18 Torr (reported[5], b.p. 273—277°C. *Ij*, yield 78·5%, b.p. 120—124°C at 3 Torr. For $C_{10}H_{13}NO$ (163·2) calculated: 73·59% C, 8·03% H, 8·58% N; found: 73·05% C, 8·20% H, 8·32% N. *Ik*, yield 55%, b.p. 129—135°C at 16—18 Torr. For $C_{10}H_{13}NO$ (163·2) calculated: 73·59% C, 8·03% H, 8·58% N; found: 73·30% C, 8·44% H, 8·65% N. *Il*, yield 40%, b.p. 117—118°C at 1·2 Torr (reported[6], b.p. 155—157°C at 17 Torr). *IId*, yield 73%, b.p. 126°C at 20 Torr (reported[7], b.p. 234·5—235·5°C at 764 Torr. *IIf*, yield 70%, b.p. 142—145°C at 13 Torr (reported[8], b.p. 140—145°C at 13 Torr), *IIg*, yield 72%, b.p. 130·5—133°C at 11 Torr (reference[9] does not state the b.p. value). *IIi*, yield 83·5%, b.p. 112°C/27 Torr (reported[5], b.p. 207—209°C at 715 Torr). *IIj*, yield 82%, b.p. 112°C at 12 Torr (reported[10], b.p. 170°C at 110 Torr). *IIk*, yield 46%, b.p. 120°C at 20 Torr (reported[11], b.p. 110—111°C at 15—16 Torr). *III*, yield 79%, b.p. 128—129·5°C at 15 Torr, m.p. 36·5—37°C (reported[12], b.p. 135—136°C at 19 Torr, m.p. 37°C).

O,O-Bis(2-methylthio-5-pyrimidinyl) Thiocarbonate (*III*)

At the temperature below 30°C and with stirring, a solution of 2-methylthio-5-pyrimidinol (91·0 g) in an equivalent amount of 5% aqueous sodium hydroxide (48·5 ml) was added dropwise into a solution of thiophosgene (77·0 g) in chloroform (500 ml). The mixture was briefly refluxed and cooled down. The solid was collected with suction and separately washed with water and acetone. The first filtrate was separated, the chloroform layer extracted with three 100 ml portions of water, and the extract concentrated under diminished pressure to about one third of the original volume to deposit a solid which was collected with suction and washed with acetone. The crops were combined and crystallised from tetrachloromethane. Yield 50 g (48%) of compound *III*, m.p. 168—169·5°C. For $C_{11}H_{10}N_4O_2S$ (326·4) calculated: 40·48% C, 3·09% H, 17·17% N, 29·47% S; found: 40·48% C, 3·31% H, 17·42% N, 29·54% S.

O-(2-Methylthio-5-pyrimidinyl) Thiocarbamates *IVa—IVo*

At 0°C to 10°C, compound *III* (3·26 g; 0·01 mol) was introduced in small portions with stirring into a solution of the appropriate amine *IIIa—IIIo* (0·01 mol) in acetone (20 ml). The mixture was then either stirred at room temperature (in the preparation of compounds *IVa*, *IVb*, *IVm*, *IVn*, and *IVo*) or refluxed (for hours see the first column of Table II), cooled down, and poured into water (100 ml). The precipitate was collected with suction and crystallised from the appropriate solvent. For yields, m.p. values, solvents, and elemental analyses see Table II.

The elemental analyses were performed in the Analytical Department of this Institute by Mrs J. Komancová.

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