SYNTHESIS AND PROPERTIES OF 2,5-DIMETHYL-3-FUROYLTHIOUREAS

†Adolf JURÁŠEK, Viktor BADORY, Vladimír ŽVAK and Jarmila ŠTETINOVÁ

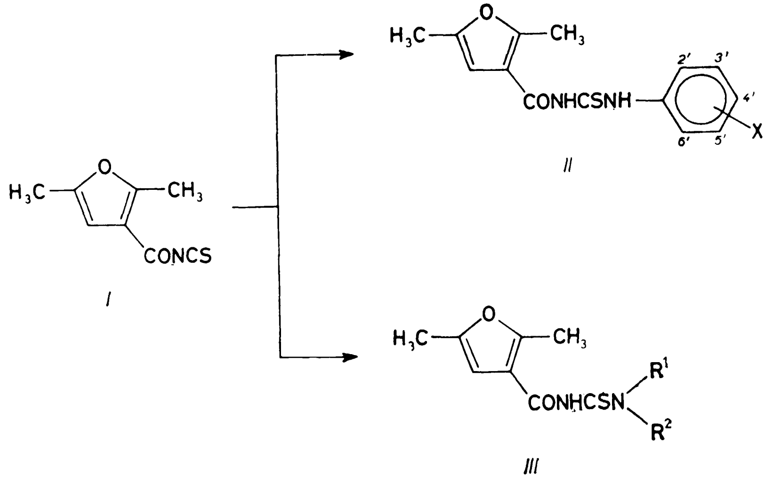
Department of Organic Chemistry, Slovak Technical University, 812 32 Bratislava

Received October 9, 1990
Accepted November 18, 1990

Addition of a series of aromatic or aliphatic amines to 2,5-dimethyl-3-furoyl isothiocyanate (*I*) afforded the corresponding N-(2,5-dimethyl-3-furoyl)-N′-aryl- or alkylthioureas *II* or *III*. Spectral data (IR, UV, ^{1}H NMR, ^{13}C NMR and mass spectra) of compounds prepared are presented.

2,5-Dimethyl-3-furancarboxamides are known to be biologically very active substances. As reported, the presence of two methyl groups in α-position at the furan ring are prerequisite for a biological effect. Especially important of the most frequented 3-substituted furamides is N-cyclohexyl-N-methoxy-2,5-dimethyl-3-furamide having low toxicity at a strong fungicide effect; therefore, it is utilized in protection of wood[1-3]. Like biological activity also revealed numerous thioureas[4,5].

Keeping this information in mind, we synthesized a series of aromatic thioureas *II* characteristic of the above-mentioned two structural features from 2,5-dimethyl-3-



SCHEME 1

TABLE I

Characteristic data of thioureas *IIa*—*IIIh*

Compound X, R_1, R_2	Formula (M.w.)	M.p., °C (Yield, %)	Calculated//Found		IR (cm^{-1})	
			% N	% S	γ(C—H)	$\tilde{\nu}$(C—O—C) $\tilde{\nu}$(NH—C=S)
IIa	$C_{14}H_{14}N_2O_2S$	138—138·5[a]	10·21	11·68	828	1 040
	(274·3)	(76)	10·35	11·52		1 130
IIb	$C_{15}H_{16}N_2O_3S$	108—109[a]	9·20	10·53	835	1 040
4-OCH_3	(304·4)	(94)	9·88	10·70		1 150
IIc	$C_{13}H_{14}N_2O_3S$	194—200[a]	9·62	11·02	810	1 050
2-OH	(290·9)	(77)	9·80	11·05		1 135
IId	$C_{13}H_{14}N_2O_3S$	195—198[b]	9·62	11·02	800	1 045
3-OH	(290·9)	(50)	10·10	10·80		1 130
IIe	$C_{13}H_{14}N_2O_3S$	196—197[b]	9·62	11·02	820	1 045
4-OH	(290·9)	(78)	9·85	11·05		1 140
IIf	$C_{15}H_{16}N_2O_3S$	111—112[b]	9·01	11·11	810	1 038
4-CH_3	(288·4)	(89)	9·48	10·90		1 130
IIg	$C_{16}H_{17}N_3O_3S$	178—182[b]	12·62	9·67	830	1 040
4-AcNH	(331·4)	(46)	11·96	9·69		1 135
IIh	$C_{14}H_{13}ClN_2O_2S$	131[c]	9·01	10·38	810	1 035
4-Cl	(308·8)	(88)	9·20	10·59		1 130
IIi	$C_{14}H_{13}N_3O_4S$	161·0—162·5[c]	13·16	10·04	810	1 030
4-NO_2	(319·3)	(77)	13·11	9·30		1 125
IIj	$C_{17}H_{16}N_2O_2S$	134·5—136·5[a]	8·63	9·88	850	1 045
2-Naphthyl	(324·4)	(60)	8·55	9·96		1 135
IIIa	$C_9H_{12}N_2O_2S$	102—108[b]	13·2	15·10	840	1 040
H, Me	(212·2)	(76)	12·73	15·03		1 120
IIIb	$C_{10}H_{14}N_2O_2S$	93—96[a]	12·38	14·16	850	1 040
H, Et	(226·3)	(62·5)	12·34	14·11		1 130
IIIc	$C_{11}H_{16}N_2O_2S$	88—90·5[b]	11·66	13·34	830	1 030
H, 2-Pr	(240·3)	(46)	11·71	13·40		1 120
IIId	$C_{12}H_{18}N_2O_2S$	49—53[b]	11·02	12·60	860	1 030
H, 2-Bu	(254·3)	(80)	10·97	12·67		1 115
IIIe	$C_{18}H_{30}N_2O_2S$	41—45[a]	8·28	9·47	850	1 030
H, Decyl	(338·5)	(80)	8·30	9·60		1 135
IIIf	$C_{12}H_{18}N_2O_2S$	95—96·5[c]	11·02	12·60	830	1 040
Et, Et	(254·3)	(51)	10·87	12·53		1 105
IIIg	$C_{11}H_{14}N_2O_2S$	74—75[a]	11·75	13·45	855	1 030
H, Allyl	(238·3)	(56·5)	11·73	13·38		1 145
IIIh	$C_{14}H_{20}N_2O_2S$	55—60[a]	9·98	11·43	850	1 035
H, Cyclohexyl	(280·3)	(90)	9·90	11·60		1 125

Crystallized from: [a] methanol; [b] chloroform; [c] tetrachloromethane.

-furoyl isothiocyanate (*I*) (Scheme 1). The starting isothiocyanate *I* was obtained from 2,5-dimethyl-3-furoyl chloride[6] and potassium thiocyanate in acetone purified by distillation over $KMnO_4$ in c. 80% yield. Compounds *II* (X = CH_3, OCH_3, $NHCOCH_3$) prepared in this way were attempted to cyclize with bromine in acetic acid[7] into the only free β-position of the furan ring (Scheme 1). Cyclization neither to α- (ref.[8]), nor to β-position[9] was succeeded under the given reaction conditions. Only unreacted thioureas were recovered from the reaction medium; it follows that reactivity of the β-position of the furan ring is insufficient for this electrophilic reaction (cyclization with bromine[10]) in spite of the activation effect of two methyl groups in positions 2 and 5.

The structure of products was corroborated by elemental analyses (Table I), IR, UV, ^1H and ^{13}C NMR spectral data and masss pectra (Tables I – V). The IR spectra of compounds *II* and *III* contain bands associated with the C—O—C stretching

TABLE II

^1H NMR spectra of substituted thioureas *IIa*–*IIi* (δ, ppm; *J*, Hz)

Compound X	2-CH_3	5-CH_3	H-4	H-2′	H-3′	$J_{2',3'}$	Other signals
IIa H	2·57 s	2·26 s	6·71 s	7·25–7·86 (m, 5 H)		—	9·44 (s, 1 H, CSNH)
IIb 4-OCH_3	2·57 s	2·27 s	6·70 s	7·65 (d, 2 H)	6·95 (d, 2 H)	9	9·59 (s, 1 H, CSNH) 3·83 (s, 3 H, CH_3O-Ph)
IIc 2-OH	2·51 s	2·25 s	6·65 s	7·04–7·86 (m, 4 H)		—	9·42 (s, 1 H, OH)
IId 3-OH	2·60 s	2·30 s	6·74 s	6·80–7·56 (m, 4 H)		—	8·57 (s, 1 H, CONH) 9·42 (s, 1 H, CSNH)
IIe 4-OH	2·58 s	2·28 s	6·72 s	7·54 (d, 2 H)	6·89 (d, 2 H)	9	
IIf 4-CH_3	2·58 s	2·27 s	6·16 s	7·53 (d, 2 H)	7·19 (d, 2 H)	8·3	2·36 (s, 3 H, CH_3-Ph) 8·64 (s, 1 H, CONH) 12·49 (s, 1 H, CSNH)
IIg 4-AcNH	2·61 s	2·30 s	6·77 s	7·74 (s, 4 H)	7·74 (s, 4 H)	—	2·61 (s, 3 H, CH_3CO)
IIh 4-Cl	2·54 s	2·24 s	6·69 s	7·38 (d, 2 H)	7·78 (d, 2 H)	9	9·62 (s, 1 H, CSNH)
IIi 4-NO_2	2·49 s	2·25 s	6·79 s	8·00 (d, 2 H)	8·21 (d, 2 H)	9	10·80 (s, 1 H, CSNH)

vibrations at 1 030 – 1 050 cm^{-1} and γ(C—H) vibrations at 800 – 860 cm^{-1}. The latter are shifted to substantially lower wave numbers when compared with other furan derivatives with one free α-position (γ(C—H) at 870 – 885 cm^{-1}, ref.[11]). The ν(NH—C=S) vibrations at 1 105 – 1 150 cm^{-1} indicate the thioureas under investigation, measured either in chloroform or in KBr, to be in a thione form. This assignment is also backed by the absence of the γ(S—H) band in the 2 550 to 2 600 cm^{-1} region, and the presence of both associated ν(NH) (at 3 110 – 3 180 cm^{-1}) and free ν(NH) (at 3 460 – 3 370 cm^{-1}) vibrations. The ν(C=O) appears at 1 640 to 1 670 cm^{-1}. The UV spectra of thioureas *IIa – IIj* (Table V) show noticeable absorption bands at 208 – 219 (the more intense) and 285 – 298 nm; derivatives *IIi* and *IIj* reveal three bands corresponding to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions.

The ^{1}H NMR spectra (Tables II and III) display signals of methyl groups attached to positions 2 and 5 of the furan ring (δ 2·47 – 2·61 (2-CH$_3$), 2·21 – 2·30 (5-CH$_3$)). The downfield shift of 2-CH$_3$ protons is due to an anisotropic effect of the carbonyl group in position 3 of the furan ring; the difference in proton shifts of methyl groups in most derivatives was within 0·25 to 0·30 ppm. The chemical shift value for the

TABLE III

^{1}H NMR spectra of substituted thioureas *IIIa – IIIh* (δ, ppm)

Compound R$_1$, R$_2$	2-CH$_3$	5-CH$_3$	CH$_3^1$	CH$_3^2$	CH$_2$	CH	CONH	CSNH	H-4
IIIa H, Me	2·50 s	2·25 s	3·13 s	—	—	—	9·25 s	10·67 s	6·63 s
IIIb H, Et	2·50 s	2·23 s	1·22 t	—	3·66 q	—	—	—	6·62 s
IIIc H, 2-Pr	2·51 s	2·25 s	1·26 d	1·26 d	—	4·46 m	9·13 s	10·70 s	6·63 s
IIId H, 2-Bu	2·50 s	2·25 s	0·92 t	1·21 d	1·73 m	4·32 m	9·15 s	10·75 s	6·62 s
IIIe H, Decyl	2·50 s	2·25 s	0·85 t	—	—	—	—	—	6·65 s
IIIf Et, Et	2·47 s	2·25 s	1·22 t	1·22 t	3·76 q	—	8·80 s	—	6·50 s
IIIg H, Allyl	2·50 s	2·25 s	—	—	3·47 – 3·85 m	—	9·32 s	10·90 s	6·65 s
IIIh H, Cyclohexyl	2·51 s	2·21 s	2·23 s	—	1·23 – 2·15 m	4·25 m	8·51 s	10·68 s	6·13 s

TABLE IV

^{13}C NMR spectra of some substituted thioureas *II* (δ, ppm)

Compound X	2-CH$_3$	5-CH$_3$	C-2	C-3	C-4	C-5	C=O	C=S	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
IIa	14·02	13·12	160·09	115·65	105·13	151·65	165·03	179·71	139·17	124·49	129·49	126·96	129·49	124·49
H	q	q	s	s	d	s	s	s	s	d	d	d	d	d
IIf	13·90	13·13	159·31	114·35	103·30	151·26	163·60	178·67	136·57	129·42	124·10	135·27	124·10	129·42
4-CH$_3$	q	q	s	s	d	s	s	s	s	d	d	s	d	d
IId	13·77	12·80	158·40	114·74	105·19	149·70	163·99	177·37	125·85	118·31	123·32	126·31	115·06	148·79
2-OH	q	q	s	s	d	s	s	s	s	d	d	d	d	s
IIh	14·04	13·12	160·22	115·52	105·13	151·65	165·16	179·97	131·76	126·18	129·92	138·00	129·92	126·18
4-Cl	q	q	s	s	d	s	s	s	s	d	d	s	d	d
IIi	14·03	13·12	158·13	114·22	103·31	151·65	163·99	178·67	143·59	178·67	124·49	145·14	124·49	123·06
4-NO$_2$	q	q	s	s	d	s	s	s	s	d	d	s	d	d
IIj	13·90	13·12	161·66	114·44	130·30	151·39	163·86	178·54	121·50—135·27					
2-Naphthyl	q	q	s	s	d	s	s	s	m					

Solvents: CDCl$_3$ + TMS: *IIc*, *IIj*; (CD$_3$)$_2$CO + TMS: *IIi*; (CD$_3$)$_2$SO + HMDS: *IIa*, *IId*, *IIh*.

H-4 proton of compounds *II* was found to be 6·65 – 6·79 excepting for derivative *IIf* (4-CH_3) and the naphthyl substituted *IIj* for which these shifts are δ 6·16 and 6·15, respectively. Singlet of the H-4 proton with thioureas *III* appears in a narrow range (δ 6·62 – 6·65) with exception of derivative *IIIf* (δ 6·50) and *IIIh* (δ 6·13). Chemical shifts of protons H-2 and H-3 of the benzene ring with *para*-substituted derivatives occur as doublets with coupling constant 9 Hz. Coupling constant for the afore-mentioned derivative *IIf* was 8·3 Hz.

Table IV lists the ^{13}C NMR chemical shifts evidencing structures of compounds synthesized. Signals for methyls in positions 2 and 5 of the furan ring appear at δ 13·77 – 14·04 and 12·8 – 13·13, respectively, as quartets, those for C-4 and C-3 at 103·30 – 105·19 (doublet) and 114·22 – 115·65 (singlet), respectively. The carbonyl group resonates at a lower value (δ 163·60 – 165·16) than the thione one (δ 177·37 to 179·97), thus evidencing such an arrangement. The C-2′ and C-3′ carbon signals

TABLE V

UV and mass spectra of some substituted thioureas *II*

Compound X	λ_{max}, nm (log ε, m^2 mol^{-1})	*m/z* (%)[a]
IIa H	208 (3·28), 294 (3·14)	274, $M^{+\cdot}$ (50), 139 (18), 123 (100), 93 (14), 81 (16), 77 (11), 65 (8), 53 (13), 43 (35), 28 (19)
IIb 4-OCH_3	214 (3·28), 288 (3·20)	304, $M^{+\cdot}$ (44), 165 (81), 150 (15), 139 (17), 123 (100), 108 (14), 81 (19), 53 (17), 43 (24), 28 (22)
IIc 2-OH	214 (3·15), 288 (3·00)	290, $M^{+\cdot}$, (20), 231 (9), 151 (18), 139 (11), 123 (100), 109 (18), 81 (19), 53 (17), 43 (39), 28 (21)
IIe 4-OH	219 (3·25), 290 (3·08)	290, $M^{+\cdot}$ (10), 257 (39), 151 (21), 139 (16), 123 (100), 109 (15), 81 (17), 53 (16), 43 (27), 28 (24)
IIf 4-CH_3	211 (3·20), 292 (3·08)	288, $M^{+\cdot}$ (45), 149 (18), 139 (36), 123 (100), 107 (18), 94 (16), 81 (23), 53 (18), 43 (52), 28 (23)
IIh 4-Cl	208 (3·35), 290 (3·25)	308, $M^{+\cdot}$ (27), 169 (5), 149 (7), 139 (19), 123 (100), 109 (8), 81 (13), 53 (12), 43 (34), 28 (31)
IIi 4-NO_2	218 (3·24), 298 (3·19), 341 (3·08)	319, $M^{+\cdot}$ (13), 138 (100), 123 (10), 108 (41), 92 (45), 80 (18), 65 (100), 52 (15), 39 (33), 28 (16)
IIj 2-Naphthyl	217 (3·44), 247 (3·00), 285 (3·01)	124, $M^{+\cdot}$ (28), 185 (29), 165 (53), 43 (19), 139 (17), 123 (100), 81 (18), 53 (15), 43 (40), 28 (26)

[a] Relative abundance of $M^{+\cdot}$ and nine most intense peaks.

of the benzene ring occur as doublets. The chemical shift values for C-1′ and C-4′ (Table IV) are strongly influenced by the character of the substituent. Electron-donating substituents in *para*-position have an upfield effect, the electron-accepting ones a downfield one.

Mass spectra are in line with the mentioned structures (Table V). All spectra contain a peak of molecular radical ion and that corresponding to 2,3-dimethyl-3-furoyl fragment (*m*/*z* 123, base peak) with the exception of derivative *IIi* (4-NO_2), the relative intensity of which makes only 10%. Another peak lies at *m*/*z* 43 (CH_3CO^+), stemming from rupture of the furan ring with a methyl group in α-position.

EXPERIMENTAL

The melting points were determined on a Boëtius micro hot-stage, the IR spectra of chloroform solutions were recorded with a Perkin–Elmer, model 577, spectrophotometer, the UV spectra of methanolic solutions ($5 . 10^{-5}$ mol l^{-1}, $l = 1$ cm) with a UV VIS (Zeiss, Jena) apparatus. The ^1H and ^{13}C NMR spectra of deuteriochloroform solutions containing tetramethylsilane as an internal reference were measured with the respective Tesla BS 487 C and Jeol FX-60 instruments; measuring temperature for ^1H NMR spectra was between 25 and 80°C. The mass spectra were taken at 130°C with an AEI MS 902 S (Manchester) spectrometer at 100 μA trap current and 70 eV ionization energy.

2,5-Dimethyl-3-furoyl Isothiocyanate (*I*)

2,5-Dimethyl-3-furoyl chloride (15·8 g, 0·1 mol) was added to potassium thiocyanate (9·7 g, 0·1 mol) in acetone (100 ml) at room temperature. The mixture was refluxed for 15 min, cooled, potassium chloride was filtered off and the filtrate was concentrated to dryness under diminished pressure. The residue was dissolved in benzene (20 ml), filtered and distilled under reduced pressure. B.p. 130—132°C/2 kPa, yield 14 g (78%). For $C_8H_7NO_2S$ (181·2) calculated: 7·73% N, 17·6% S; found: 7·80% N, 17·2% S. IR ($CHCl_3$), cm^{-1}: 1 945 (NCS), 1 675 (C=O), 1 385 (CH_3), 1 060 (C—O—C). ^1H NMR spectrum ($CDCl_3$), δ: 2·5 s, 3 H (2-CH_3); 2·24 s, 3 H (2-CH_3); 2·24 s, 3 H (5-CH_3); 6·2 s, 1 H (H-4).

N-(2,5-Dimethyl-3-furoyl)-N-arylthioureas (*II*)

2,5-Dimethyl-3-furoyl isothiocyanate (2 g, 11 mmol) in ether (50 ml) was introduced into a stirred solution of the respective amine (12 mmol) in ether (200 ml) at room temperature. After 30 min, the product was filtered off and crystallized (Table I). The aliphatic thioureas *III* were obtained by the same procedure in acetone and were crystallized from methanol or ethanol (Table I).

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Translated by Z. Votický.