FURO[2,3-*d*]THIAZOLES

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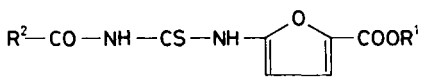
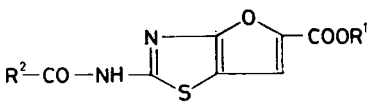
Carbonyl isothiocyanates react with 5-amino-2-furancarboxylates to give the corresponding acylthioureas which cyclize to condensed derivatives related to furo[2,3-*d*]thiazoles. Structure of these substances was corroborated by IR, mass, ^{1}H and $^{13}C\{^1H\}$NMR spectral means.

Preparation of 5- and 6-membered heterocyclic compounds starting from carbonyl isothiocyanates has already been reported[1-5]. Also the cyclization of acylthioureas to substituted thieno[3,2-*d*]- and furo[2,3-*d*]thiazoles was described[6,7].

This paper concerns the reaction of carbonyl isothiocyanates with 5-amino-2--furancarboxylates. The benzoyl-, acetyl-, and 2-furoyl isothiocyanates, proposed for this reaction were prepared from the corresponding acyl chloride and KSCN in benzene or acetone. The counterreacting esters were methyl- and butyl 5-amino--2-furancarboxylates.



I

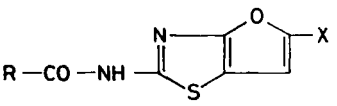


II

The reaction was carried out in benzene at room temperature and monitored by thin-layer chromatography (Table I, derivatives *Ia*–*If*). Cyclization of the prepared acylthioureas was achieved with bromine in glacial acetic acid. This cyclization probably proceeds *via* the intermediate sulfenyl bromide. The furo[2,3-*d*]thiazole derivatives were crystallized from methanol (Table II, derivatives *IIa*–*IIf*).

The ester functional group in position 5 of furo[2,3-*d*]thiazole was hydrolyzed in acid and alkaline media and the carboxylic acids *III* were decarboxylated to examine their reactivity. As found, neither hydrolysis of the acyl residue in position 2 of furo[2,3-*d*]thiazole ring, nor cleavage of the furan ring were observed. 2-Acylamido-furo[2,3-*d*]thiazole-5-carboxylic acids (Table II, derivatives *IIIa*–*IIIc*) have melting points over 200°C (with decomposition); thermogram for compound *IIIa* showed

that it is stable up to 215°C. Decomposition at 246°C occurs in one step, what indicates a simultaneous melting and decomposition. It is difficult to determine from the mass loss (31%), whether the initial decomposition starts with decarboxylation. Derivatives *IIIa–IIIc* were decarboxylated in an inert atmosphere under catalysis of copper(II) chromate in quinoline at 120°C (derivatives *IVa* and *IVb*).



III, X = COOH
IV, X = H

The IR spectra of acylthioureas (derivatives *Ia–If*, Table I) showed significant bands of C—O—C asymmetric vibration of the furan ring at 1 225–1 217 cm^{-1} and a less important band at 1 020–1 012 cm^{-1} belonging to C—O—C symmetric vibration of the furan ring. Less distinctive ν(NH) appeared at 3 310–3 243 cm^{-1} and significant ν(CO)—NH and ν(CO)—OR at 1 725 – 1 664 cm^{-1}; the latter was split with all derivatives. Compounds *IIa–IIf* (Table II) display little distinctive ν(NH) bands at 3 254–3 219 cm^{-1}, strong characteristic ν(CO) absorption bands

TABLE I
Acylthioureas *I*

Compound	R^2 / R^1	Formula / M_r	M.p., °C / Yield, %	Calculated/found	
				% N	% S
Ia	C_6H_5	$C_{14}H_{12}N_2O_4S$	169–170	9·21	10·53
	CH_3	304·2	62	9·40	10·61
Ib	C_6H_5	$C_{17}H_{18}N_2O_4S$	147–148	8·09	9·25
	C_4H_9	346·2	56	8·23	9·22
Ic	CH_3	$C_9H_{10}N_2O_4S$	212–213	11·57	13·22
	CH_3	242·2	64	11·68	13·06
Id	CH_3	$C_{12}H_{16}N_2O_4S$	115–116	9·85	11·27
	C_4H_9	284·2	52	9·98	11·34
Ie	2-furoyl	$C_{12}H_{10}N_2O_4S$	172–173	9·52	10·88
	CH_3	294·2	56	9·63	10·72
If	2-furoyl	$C_{15}H_{16}N_2O_4S$	123–124	8·33	9·52
	C_4H_9	336·2	51	8·40	9·59

at 1 722–1 666 cm^{-1} and ν(C—O—C)asymmetric (1 235–1 217 cm^{-1}) and symmetric (1 020–1 000 cm^{-1}) vibrations of furan skeleton. Position of ν(NH)bands of derivatives *IIIa–IIIc* (Table II) are difficultly readable due to overlapping by a very broad (O—H) stretching vibration band. Compounds *IIa*, *IIb*, and *IIIa* reveal, moreover, absorptions due to skeletal C=C vibrations of the aromatic system and those of C=N bonds of furo[2,3-*d*]thiazole system, which are problematic to ascribe.

The UV spectra of derivatives *Ia–If* (Table I) showed two significant absorptions: that at about 230 nm can be assigned to $\pi^* \leftarrow \pi$ or $\pi^* \leftarrow n$ transitions of acyl groupings (acetyl, benzoyl, 2-furoyl). Absorption at 307 ± 2 nm might be due to charge-transfer transitions in the system acyl isothiocyanate + 5-amino-2-furancarboxylate. The series of compounds *IIa–IIf* (Table II) displayed again two considerable

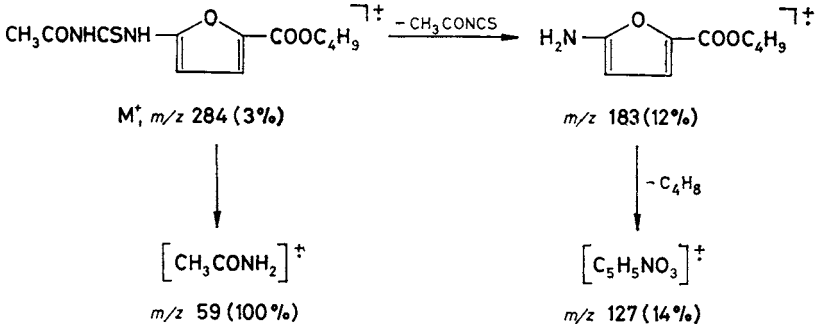
TABLE II
Substituted furo[2,3-*d*]thiazoles *II* and *III*

Compound	R^2 / R^1	Formula / M_r	M.p., °C / Yield, %	Calculated/found % N	Calculated/found % S
IIa	C_6H_5	$C_{14}H_{10}N_2O_4S$	273–275	9·27	10·60
	CH_3	302·3	47	9·36	10·62
IIb	C_6H_5	$C_{17}H_{16}N_2O_4S$	177–178	8·14	9·30
	C_4H_9	344·4	51	8·29	9·35
IIc	CH_3	$C_9H_8N_2O_4S$	270[a]	11·67	13·33
	CH_3	240·2	56	11·78	13·34
IId	CH_3	$C_{12}H_{14}N_2O_4S$	156–157	9·93	11·35
	C_4H_9	282·3	59	9·86	11·44
IIe	2-furoyl	$C_{12}H_8N_2O_5S$	271–273	9·59	10·96
	CH_3	292·3	57	9·66	11·08
IIf	2-furoyl	$C_{15}H_{14}N_2O_5S$	189–190	8·38	9·58
	C_4H_9	334·3	60	8·34	9·62
IIIa	C_6H_5	$C_{13}H_8N_2O_4S$	250[a,b]	9·72	11·11
	H	288·3	86	9·59	11·05
IIIb	CH_3	$C_8H_6N_2O_4S$	230[a]	12·39	14·16
	H	226·2	90	12·47	14·19
IIIc	2-furoyl	$C_{11}H_6N_2O_5S$	260[a]	10·07	11·51
	H	278·2	89	10·21	11·44

[a] Decomposition; [b] ref.[6] >250°C.

absorptions at 237–250 nm and 322–341 nm. Cyclization resulted in bathochromic and hyperchromic shifts: *Ia* → *IIa* (λ_{max} 305 → 355 nm, log ε 3·26 → 3·50). Hydrolysis of the respective esters to the corresponding carboxylic acids (derivatives *IIIa–IIIc* Table II) had no significant effect on the shift of absorption bands.

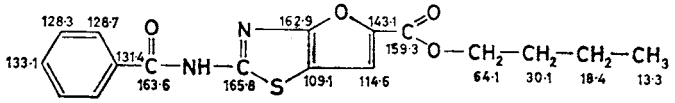
The structure of derivatives *Id* (acylthioureas, Table I), *IIb*, *IId*, *IIf* (Table II) and products of decarboxylation was further evidenced by mass spectrometry. The fundamental fragmentation pattern of the molecular radical ion of *Id* is accompanied by a hydrogen transfer (Scheme 1). The parent peak at *m/z* 95 in the spectrum



SCHEME 1

of butyl 2-furoylaminofuro[2,3-*d*]thiazole-5-carboxylate (derivative *IIf*, Table II) is due to the furoyl fragment. The loss of a neutral molecule C_4H_8 from the molecular radical ion (*m/z* 334) leads to formation of a fragment ion at *m/z* 278 (19%), which upon ejection of a hydroxyl radical afforded species of *m/z* 261 (8%). 2-Benzoylaminofuro[2,3-*d*] thiazole (derivative *IVa*) revealed the molecular radical ion peak at *m/z* 244 (10%). Peak with the benzoyl ion at *m/z* 105 is the parent one; loss of CO molecule forms the phenyl ion appearing at *m/z* 77 (76%).

^{1}H NMR spectra of compounds listed in Tables III and IV also backed the proposed structure. The $^{13}C\{^1H\}$NMR spectrum of *IIb* (Table II) displayed following signals of carbon atoms (δ, ppm): 165·8, 163·6, 162·9, 159·3, 143·1, 133·1, 131·4, 128·7, 128·3, 114·6, 109·1, 64·1, 30·1, 18·4, 13·3. Assigment of these data is shown in formula *IIb*.



II b

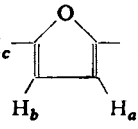
EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage. The IR spectra (1 mg of the compound per 300 mf of KBr) were measured with a Specord IR 71 (Zeiss, Jena) spectrophotometer in the 700—4 000 cm^{-1} region, the UV spectra of methanolic solutions ($3 . 10^{-5}$ mol l^{-1}) with a Specord UV VIS apparatus, the mass spectra with an MS 902 S (AEI Manchester) instrument at a 70 eV ionizing electron energy, 100 μA trap current, and 70—140°C ionizing chambre temperature. The ^{1}H NMR spectra were recorded with a Tesla BS 487 C (Brno) spectrometer operating at 80 MHz at 25°C (internal reference tetramethylsilane). The ^{13}C NMR spectra of *IIb*, *IId*, *IIIa*, and *IIIb* were run at 25 and 50°C with a Jeol FX-100 (Japan) apparatus operating at 25·05 MHz in hexadeuteriodimethyl sulfoxide containing tetramethylsilane as internal reference. The differential thermal analyses of *IIc* and *IIf* were carried out with Termoanalyser (Mettler) in stationary phase at heating gradient 6°C/min. Employed were Pt and Pt–Rh thermocouples and freshly annealed alumina. Carbonyl isothiocyanates were prepared according to[8], 5-nitro-2-furancarboxylates according to[9] and reduction to the corresponding 5-amino derivatives was proceeded according to a modified method[10] in 70% yields.

TABLE III

^{1}H NMR data of acylthioureas *I* (δ, ppm, *J*, Hz)

Compound	R^1 / R^2	$H_4{}^a$ / $H_3{}^a$	R^1	R^2
Ia	CH_3	7·07	3·82 s (3 H)	7·50—8·05 m (5 H)
	C_6H_5	7·37		
Ib	C_4H_9	7·07	0·91 t (3 H)	7·52—8·04 m (5 H)
	C_6H_5	7·35	1·20—1·75 m (4 H)	
			4·24 t (2 H)	
Ic	CH_3	7·01	2·21 s (3 H)	3·81 s (3 H)
	CH_3	7·35		
Id	C_4H_9	6·98	0·91 t (3 H)	2·16 s (3 H)
	CH_3	7·31	1·22—1·73 m (4 H)	
			4·21 t (2 H)	
Ie	CH_3	7·05	3·84 s (3 H)	6·71 q (1 H) *b*
	2-furoyl	7·35		7·88 d (1 H) *a*
				8·06 d (1 H) *c*
If	C_4H_9	7·04	0·91 t (3 H)	6·76 q (1 H) *b*
	2-furoyl	7·35	1·25—1·66 m (4 H)	7·86 d (1 H) *a*
			4·24 t (2 H)	8·07 d (1 H) *c*

[a] Doublet, J_{H_3,H_4} = 4 Hz, for *Ie* and *If*, R^2 =  .

Acylthioureas *I*

A solution of the respective carbonyl isothiocyanate (12 mmol) in benzene (10 ml) was successively added (30 min) to the stirred solution of 5-amino-2-furancarboxylate (10 mmol) in benzene (20 ml) at an ambient temperature. Stirring was continued for additional 20 min, light petroleum was added (20 ml), the separated crystals were filtered off and crystallized from benzene (Table I, derivatives *Ia*—*If*).

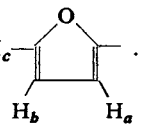
Cyclization of Acylthioureas

Suspension of the corresponding acylthiourea (1 mmol) in glacial acetic acid (10—20 ml) was slowly heated to 60°C till the solution clarifies. A solution of bromine (1 mmol) in acetic acid (2 ml) was successively added and the mixture was further stirred for 1 h at room temperature.

TABLE IV

^{1}H NMR data of substituted furo[2,3-*d*]thiazoles *II* and *III* (δ, ppm; *J*, Hz)

Compound	R^1	R^2	H_6[a]	R^1	R^2
IIa	CH_3	C_6H_5	7·55	3·79 s (3 H)	7·39—8·12 m (5 H)
IIb	C_4H_9	C_6H_5	7·55	0·88 t (3 H) 1·20—1·76 m (4 H) 4·21 t (2 H)	7·41—8·12 m (5 H)
IIc	CH_3	CH_3	7·67	3·82 s (3 H)	2·19 s (3 H)
IId	C_4H_9	CH_3	7·67	0·91 t (3 H) 1·26—1·77 m (4 H) 4·27 t (2 H)	2·21 s (3 H)
IIe	CH_3	2-furoyl	7·59	3·80 s (3 H)	6·64 q (1 H) *b* 7·55 d (1 H) *a* 7·88 d (1 H) *c*
IIf	C_4H_9	2-furoyl	7·68	0·92 t (3 H) 1·27—1·75 m (4 H) 4·25 t (2 H)	6·76 q (1 H) *b* 7·73 d (1 H) *a* 8·04 d (1 H) *c*
IIIa	—	C_6H_5	7·68	—	7·52—8·20 m (5 H)
IIIb	—	CH_3	7·52	—	2·16 s (3 H)
IIIc		2-furoyl	7·67	—	6·77 q (1 H) *b* 7·73 d (1 H) *a* 8·06 d (1 H) *c*

[a] Singlet for *IIa*, *IIf*, *IIIc*, R^2 = 

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The separated crystals were filtered off and crystallized from methanol (150 ml/1 g, derivatives *IIa—IIf*, Table II).

Hydrolysis of 2-Acylaminofuro[2,3-*d*]thiazole-5-carboxylates

a) The ester (1 g) was refluxed with NaOH (2 mol l^{-1}, 20 ml) for half an hour, cooled, neutralized with dilute (1 : 1) hydrochloric acid and the precipitated crystals were suction-filtered and crystallized from acetone (derivatives *IIIa—IIIc*, Table II).

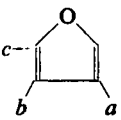
b) The ester (1 g) was refluxed with concentrated sulfuric acid (3 ml) for 2 h, the solution was poured into cold water (15 ml), the separated crystals were filtered off and crystallized from acetone. This procedure led to the same products as described under *a*).

Decarboxylation of 2-Acylaminofuro[2,3-*d*]thiazole-5-carboxylic Acids

A mixture of the acid (1 g), quinoline (10 ml), and copper(II) chromate (0·64 g) was stirred under nitrogen at room temperature for 10 min. Temperature was then raised to 120°C and kept constant until carbon dioxide evolved (1 h, CO_2 was trapped in calcium hydroxide solution). The mixture was cooled to 0°C, the product was taken with ether (250 ml), washed with HCl 0·1 mol l^{-1} and dried with Na_2SO_4. Crystals obtained after evaporation of the solvent were recrystallized from methanol.

2-*Benzoylaminofuro*[2,3-*d*]*thiazole* (IVa). M.p. 168—169°C, yield 0·74 g (74%). For $C_{12}H_8N_2O_2S$ (244·2) calculated: 11·21% N, 13·05% S; found: 11·47% N, 13·11% S. IR spectrum ($\tilde{\nu}$, cm^{-1}): 1 008, 1 222 (C—O—C), 1 660 (C=O). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 232 (3·21), 323 (3·21). ^{1}H NMR spectrum (δ, ppm): 6·95 (d, H_5), 7·72 (d, H_6), 7·54—8·18 (m, H_{arom}).

2-*Furoylaminofuro*[2,3-*d*]*thiazole* (IVb). M.p. 143—144°C, yield 0·72 g (72%). For $C_{10}H_6N_2O_3S$ (234·2) calculated: 12·06% N, 13·61% S; found: 11·97% N, 13·67% S. IR spectrum ($\tilde{\nu}$, cm^{-1}): 1 010, 1 220 (C—O—C), 1 662 (C=O). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 254 (2·98), 325 (2·98). ^{1}H NMR spectrum (δ, ppm): 6·92 (d, H_5), 7·67 (d, H_6), 6·74 (q, H_b), 7·72 (d, H_a), 7·99 (d, H_c).



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