REACTIONS OF CARBONYL ISOTHIOCYANATES WITH NUCLEOPHILIC BIFUNCTIONAL REAGENTS

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Reactions of benzoyl-, 2-furoyl-, acetyl-, and trichloroacetyl isothiocyanates with 1,2-diaminobenzene, 2-aminophenol, 5,6-diamino-1,3-dimethyluracil and 2,3-diaminopyridine were investigated. Formation of the individual products and their IR, UV and electron impact mass spectra are discussed.

Reactions of carbonyl isothiocyanates with aliphatic bifunctional nucleophiles have already been described[1] and employed for the synthesis of heterocyclic compounds related to thiazolidine, oxazolidine and imidazole[1]. The reaction course with amino--N-heterocyclic compounds is influenced by the enamine–imine tautomerism of the amino group; the properly chosen substrates react to afford products of cyclization[2,3]. The reaction products of some carbonyl isothiocyanates and aromatic or heteroaromatic diamines are the substituted mono- or diacylthioureas which were used for further reactions[4–6]. The formation of a seven-membered ring has also been described[6]. Diacylthioureas, obtained by reacting 2,3-diaminopyridine with carbonyl isothiocyanates reveal antihelmintic and fungicidal properties[7–12].

This paper is a continuation of our preceding investigation on evaluation of carbonyl isothiocyanates for the synthesis of heterocyclic compounds[13–15]; it presents results obtained when examining the reactions of carbonyl isothiocyanates with nucleophilic bifunctional reagents and refer to reactions of benzoyl-, 2-furoyl-, acetyl- and trichloroacetyl isothiocyanates with 1,2-diaminobenzene, 2-aminophenol, 1-aminothiophenol, 5,6-diamino-1,3-dimethyluracil and 2,3-diaminopyridine.

These reactions were carried out in benzene or acetone either at reflux, or at room temperature. Monoacylthioureas are the products of 1,2-dimethylaminobenzene, 2-aminophenol and 5,6-diamino-1,3-dimethyluracil at a 1 : 1 molar ratio. Their stability depends on the substituent in position 2 of the aromatic ring. The primarily formed N-(2-mercaptophenyl)-N′-acylthiourea from 2-aminothiophenol undergoes cyclocondensation to give 2-acylaminobenzothiazol.

Diacylthiourea derivatives were obtained when reacting 1,2-diaminobenzene or 2,3-diaminopyridine with benzoyl isothiocyanate or 2-furoyl isothiocyanate in a 1 : 2

TABLE I

Data characteristic for the synthesized compounds

Compound	R^1 Z	Formula (m.w.)	M.p., °C (yield, %)	Calculated/Found			
				% C	% H	% N	% S
Ia	phenyl NH	$C_{14}H_{13}N_3OS$ (271)	168—169[a] (88)	—	—	—	—
Ib	2-furyl NH	$C_{12}H_{11}N_3O_2S$ (261)	142—143 (90)	55·17 55·03	4·21 4·13	16·09 16·09	12·28 12·12
Ic	CH_3 NH	$C_9H_{11}N_3OS$ (209)	186—187 (87)	51·67 51·48	5·26 5·16	20·09 20·04	15·34 15·50
Id	CCl_3 NH	$C_9H_8Cl_3N_3OS$ (312·5)	135—136·5 (93)	34·56 34·42	2·56 2·48	13·44 13·21	10·26[b] 10·48
IIa	phenyl O	$C_{14}H_{12}N_2O_2S$ (272)	209—211 (90)	61·76 61·51	4·41 4·29	10·31 10·33	11·76 11·48
IIb	2-furyl O	$C_{12}H_{10}N_2O_3S$ (262)	206—208 (83)	54·96 55·05	3·82 3·76	10·69 10·87	12·21 12·30
IIc	CH_3 O	$C_9H_{10}N_2O_2S$ (210)	161—163 (69)	51·43 51·55	4·76 4·88	13·33 13·50	15·24 15·35
IId	CCl_3 O	$C_9H_7Cl_3N_2O_2S$ (313·5)	180—182 (83)	34·45 34·35	2·23 2·35	8·93 8·71	10·21[c] 10·41
IIIa	phenyl S	$C_{14}H_{12}N_2OS_2$ (288)	133—135 (42)	58·33 58·51	4·17 4·29	9·72 9·89	22·22 22·39
IIIb	2-furyl S	$C_{12}H_{10}N_2O_2S_2$ (278)	106—109 (65)	51·80 51·65	3·60 3·48	10·07 9·89	23·02 22·86
IIIc	CH_3 S	$C_9H_{10}N_2OS_2$ (226)	121[d] (54)	47·79 47·58	4·42 4·29	12·38 12·50	28·37 28·12
IVa	phenyl —	$C_{14}H_{15}N_5O_3S$ (333)	258—260 (75)	50·45 50·32	4·50 4·61	21·04 21·16	9·64 9·44
IVb	2-furyl —	$C_{12}H_{13}N_5O_4S$ (323)	226—228 (81)	44·58 44·39	4·02 3·89	21·68 21·64	9·91 10·14
IVc	CH_3 —	$C_9H_{13}N_5O_3S$ (271)	246—249 (72)	39·85 39·68	4·80 4·65	25·83 25·64	11·81 11·56
Va	phenyl —	$C_{21}H_{17}N_5O_2S_2$ (435)	175—177 (84)	57·93 57·79	3·91 3·82	16·09 16·21	14·71 14·86
Vb	2-furyl —	$C_{17}H_{13}N_5O_4S_2$ (415)	178·5—179·[d] (54)	—	—	—	—
VIa	phenyl —	$C_{22}H_{18}N_4O_2S_2$ (434)	185—187 (93)	60·83 60·92	4·15 4·23	12·90 13·11	14·95 14·98

TABLE I
(*Continued*)

Compound	R^1 Z	Formula (m.w.)	M.p., °C (yield, %)	Calculated/Found			
				% C	% H	% N	% S
VIb	2-furyl	$C_{18}H_{14}N_4O_4S_2$	184[j]	52·17	3·38	13·53	15·46
	—	(414)	(58)	52·02	3·19	13·28	15·21
VIIa	phenyl	$C_{14}H_{10}N_2OS$	188[e]	—	—	—	—
	S	(254)	(10)				
VIIb	2-furyl	$C_{12}H_8N_2O_2S$	168—170	59·02	3·28	11·47	13·11
	S	(244)	(12)	58·92	3·37	11·54	12·92
VIIc	CH_3	$C_9H_8N_2OS$	191—192[f]	—	—	—	—
	S	(192)	(15)				
VIId	CCl_3	$C_9H_5Cl_3N_2OS$	148—149·5	36·49	1·69	9·46	10·83[g]
	S	(296)	(46)	36·28	1·48	9·51	10·68
VIIe	phenyl	$C_{14}H_{11}N_3O$	241—242·5[h]	—	—	—	—
	N	(237)	(51)				
VIIf	2-furyl	$C_{12}H_9N_3O_2$	310[i,j]	—	—	—	—
	NH	(227)	(40)				

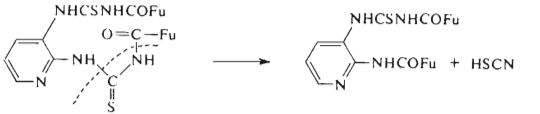
[a] M.p. 149—150°C (ref.[4]); [b] calculated: 34·03% Cl; found: 33·81% Cl; [c] calculated: 33·92% Cl; found: 33·75% Cl; [d] m.p. 174°C (ref.[8]); [e] m.p. 186°C (ref.[19]); [f] m.p. 187—188°C (ref.[18]); [g] calculated: 35·93% Cl; found: 35·68% Cl; [h] m.p. 242°C (ref.[4]); [i] m.p. 318—320°C (ref.[20]); [j] decomp.

ratio. Cyclocondensation of N-(2-aminophenyl)-N′-benzoyl-, or 2-furoylthiourea was carried out under a 1 to 3 h-reflux in the presence of HgO.

The IR spectra of acylthioureas *I*, *II*, *III* and *IV* showed ν(NH) at 3 130—3 380, $\nu(CH_{arom.})$ at 3 010—3 033, and ν(CO) at 1 641—1 816 cm^{-1}; the latter was overlapped by the band associated with the uracil backbone (1 570—1 695 cm^{-1}, derivative *IV*). The characteristic bands of the HN—C=S grouping appeared at 1 117 to 1 173 cm^{-1}.

The UV spectra of derivatives *Ia* and *VIa* (Table I) displayed two significant absorption bands. The first at 236 nm ($\log \varepsilon = 3{\cdot}39$), or at 239 nm ($\log \varepsilon = 3{\cdot}57$) can be ascribed to a $\pi^* \rightarrow \pi$ transition of the benzoyl grouping; the second band at 295 nm (*Ia*), or 285 nm (*VIa*) might be due to the charge-transmitting transition in a 1,2-diaminobenzene grouping.

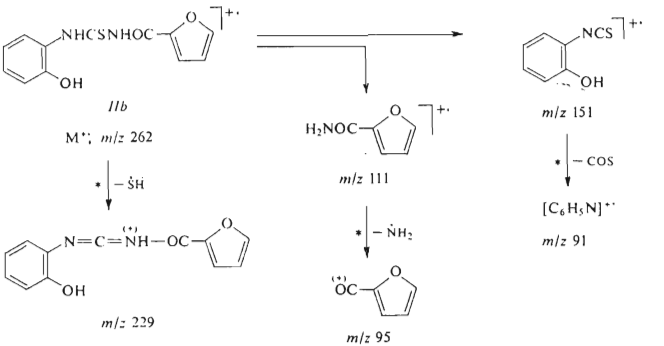
Derivative *Vb* (Table I) was subjected to a differential thermoanalysis. The thermogram showed a mass loss in two stages: the compound is up to 182°C stable; further heating leads to a 14% loss of mass corresponding to the cleavage of HSCN. This loss indicates a probable N,N'-transacylation of the diacylthiourea. A total decomposition of *Vb* (Scheme 1) is taking place at 229°C. Mass spectra of the synthesized



Vb, Fu = 2-furyl

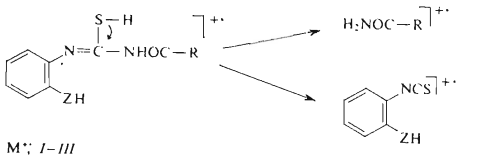
SCHEME 1

compounds backed the structural assignment. Thus, Fig. 1 depicts the mass spectra of compounds *Ia*, *IIb*, *IVc*, *VIa*, *VIId*. Fragmentation pattern of the molecular ion *IIb* is seen in Scheme 2.



SCHEME 2

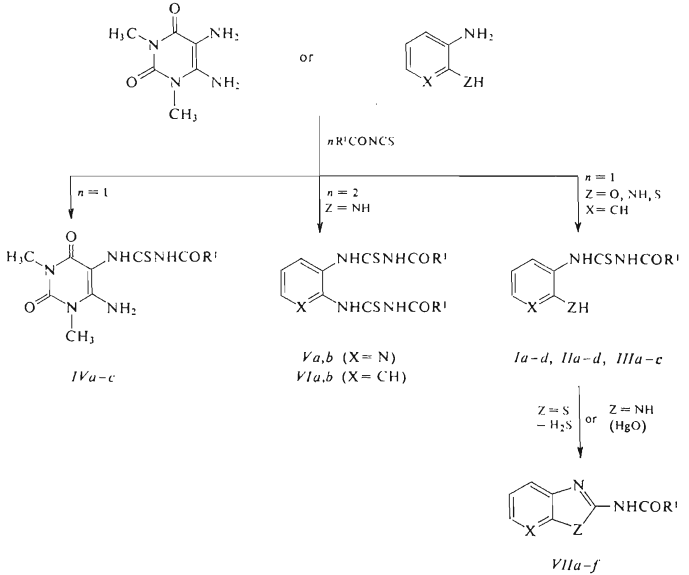
Molecular ions in the mass spectra are pronounced only feebly; *e.g.* the relative intensity of that of *IId* is less than 1%. The main fragmentation pathway of compounds *I*, *II* and *III* goes through ions of *ortho*-substituted phenyl isothiocyanates and corresponding carboxylic acid amides resulting from a hydrogen transfer (Scheme 3)



M⁺·; *I–III*

SCHEME 3

A like fragmentation of molecular ions was encountered with derivatives *IV* (Table I). Derivative *IVc*, *e.g.*, afforded a very intense species at *m/z* 212 (Fig. 1) as a result of a cleavage of acetamide molecule from the molecular ion. A subsequent loss of CH_3NCO from the uracil ring furnished the ion at *m/z* 155. Cleavage of CH_3. .CONCS from the molecular ion involving a hydrogen transfer leads, on the other hand, to the diamine fragment at *m/z* 170.



IVa–c

Va,b (X = N)
VIa,b (X = CH)

Ia–d, *IIa–d*, *IIIa–c*

VIIa–f

Diacylthioureas *V* and *VI* (Table I) did not reveal molecular ion peaks in their mass spectra. The species with the highest mass belongs to an ion formed from the molecular ion by a loss of RCONCS. Derivative *VIa*, *e.g.*, loses C_6H_5CONCS to give an ion at *m/z* 271 (Fig. 1). Further fragmentation traces that of this mono-substituted derivative *Ia*.

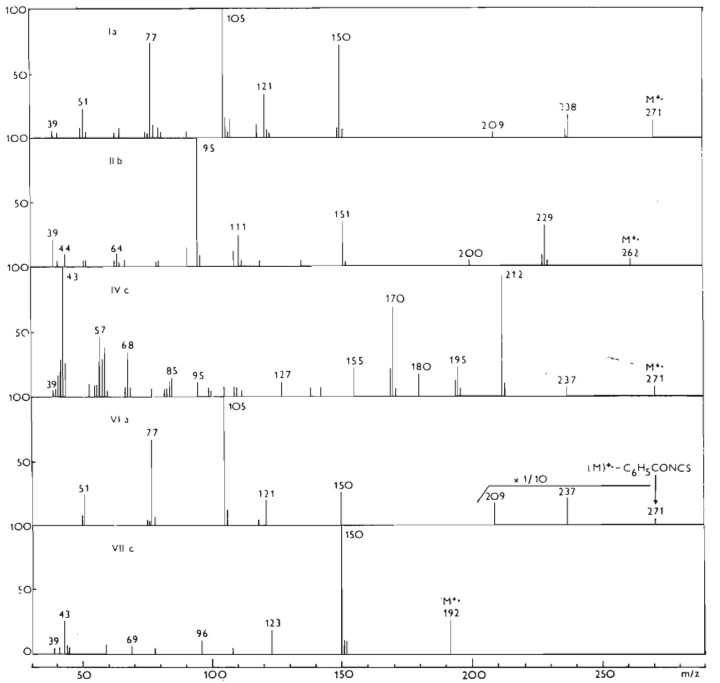


FIG. 1

Mass spectra of N-(2-aminophenyl)-N′-benzoylthiourea (*Ia*); N-(2-hydroxyphenyl)-N-*s*-furoyl-thiourea (*IIb*); N-(6-amino-1,3-dimethyluracilyl)-N′-acetylthiourea (*IVc*); N,N′-dibenzoylthiourea (*VIa*); 2-N-acetylaminobenzothiazol (*VIIc*)

EXPERIMENTAL

Melting points were measured with a Kofler micro hot-stage. The IR spectra of KBr discs were measured in the 700—4 000 cm^{-1} spectral range with a Specord IR 71 (Zeiss, Jena) apparatus. The electronic vibrational spectra of dioxane solutions were recorded with a Specord UV VIS spectrophotometer (Zeiss, Jena) in $2{\cdot}5-6 . 10^{-5}$ mol/l concentrations. The electron impact mass spectra were recorded with an AEI (Manchester) MS 902 S instrument using a direct inlet system at a 70 eV electron energy, 100 μA trap current and 70—170°C ionization chamber temperature. Thermoanalyser 2 (Mettler) was used for differential thermal analysis; analyzed was a 7 mg-sample at a 7 l/h nitrogen flow rate. Carbonyl isothiocyanates were prepared according to[16], 2-furoyl isothiocyanates according to[17] in a 30% yield. Yields, melting points and analytical data of the derivatives synthesized are listed in Table I.

Reactions of Carbonyl Isothiocyanates with 1,2-Diaminobenzene, or 2-Aminophenol

A solution of the respective carbonyl isothiocyanate (10 mmol) in benzene (10 ml) was dropwise added to the nucleophile (10 mmol) in benzene (25 ml) under stirring and exclusion of the atmospheric moisture. Stirring was continued for 1—3 h, the solid filtered off and crystallized from chloroform or ethanol (derivatives *Ia—Id*, *IIa—IId*, Table I).

Reaction of Carbonyl Isothiocyanates with 2-Aminophenol

The respective carbonyl isothiocyanate (10 mmol) in benzene (10 ml) was added to a stirred solution of 2-aminophenol (1·25 g, 10 mmol) in benzene (15 ml) at 6—10°C. Stirring was then continued for 30 min. Crystals separated within several days were suction-filtered and the concentrated filtrate was left to give the second crop of crystals (derivatives *IIIa—IIIc*, Table I).

Reaction of Carbonyl Isothiocyanates with 5,6-Diamino-1,3-dimethyluracil

The respective carbonyl isothiocyanate (5 mmol) in acetone (10 ml) was dropwise added to a suspension of 5,6-diamino-1,3-dimethyluracil (0·85 g, 5 mmol) in acetone (10 ml). The mixture was refluxed under stirring for 30 min, the products were filtered off, washed with acetone, air-dried and recrystallized from acetone or pyridine (derivatives *IVa—IVd*, Table I).

Reactions of 2-Furoyl Isothiocyanate (*in situ*) and Benzoyl Isothiocyanate with 1,2-Diaminobenzene and 2,3-Diaminopyridine

a) 2-Furoyl chloride (4·2 g, 33 mmol) was added to a suspension of KSCN (3·5 g) in acetone (15 ml) at 10°C and stirred for 15 min. The solid diamine (7·5 mmol) was added in one instalment and the mixture was stirred for 3 h at an ambient temperature. The solid was filtered off, washed with acetone, suspended in water (180 ml, filtered and repeatedly washed with acetone. The air-dried product was crystallized from acetone (derivatives *Vb*, *VIb*, Table I).

b) The solid diamine (1·09 g, 10 mmol) was at once added to a solution of benzoyl isothiocyanate (3·26 g, 20 mmol) at 10°C and stirred for 1 h. The product was filtered off, washed with cold acetone and recrystallized from the proper solvent (derivatives *Va*, *VIa*, Table I).

Desulfuration of N-(2-Aminophenyl)-N'-benzoyl- or 2-Furoylthioureas

A mixture of the respective thiourea (2·5 mmol) and HgO (0·5—1·5 g) in dioxane (20—30 ml), or chloroform was refluxed for 1 to 3 h. The separated HgS was hot-filtered and washed with

hot dioxane or chloroform. The solvent was evaporated under reduced pressure and the residue crystallized from dioxane–hexane (derivatives *VIIe*, *VIIf*, Table I).

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