REACTIONS OF CARBONYL ISOTHIOCYANATES WITH CYCLIC ENAMINES

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Reactions of carbonyl isothiocyanates with cyclic enamines were investigated and the IR, UV and electron impact mass spectra of the synthesized products are discussed.

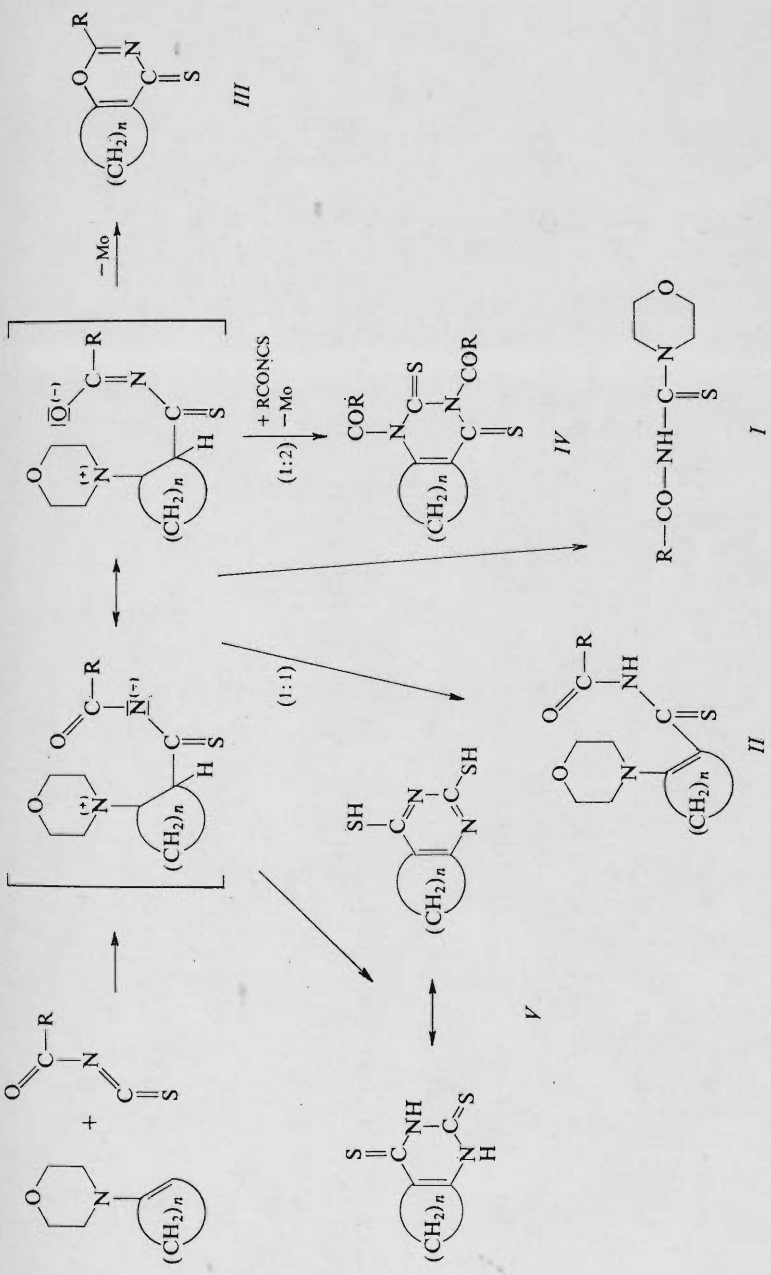
Benzoyl isothiocyanate was reported to react[1] with morpholinocyclohexene, tetrahydrobenzoxazinethione being assumed to be the product. Anilinocyclohexene cyclized with benzoyl isothiocyanate to tetrahydroquinazolinethione[2]. Ethoxycarbonyl isothiocyanate afforded with cyclic enamines the 1 : 1 adducts, which underwent cyclization with ammonia or primary amines to yield 4-thiouracil derivatives[3]. This paper deals with utilization of carbonyl isothiocyanates in preparation of heterocyclic compounds[4,5] and with the reaction of carbonyl isothiocyanates with cyclic enamines.

Starting compounds were carbethoxy isothiocyanates, propionyl isothiocyanates, unsubstituted and substituted benzoyl and 2-furoyl isothiocyanates, and morpholinocyclopentene and morpholinocyclohexene. Either 1 : 1, or 1 : 2 cycloadducts, or disproportionation products of HSCN were obtained with respect to temperature, solvent and the remaining moiety of the isothiocyanate (Scheme 1).

Reactions of carbonyl isothiocyanates with morpholinocyclopentene and morpholinocyclohexene were carried out in chloroform. Morpholinocyclopentene furnished following 1 : 2 cycloaddition products in 40% yields: 1,3-disubstituted 1,2,3,4-tetrahydrocyclopenta[*e*]pyrimidine-2,4-dithiones *IVa*, *IVc*, *IVd*, and cyclopenteno-[*e*]pyrimidine-2,4-dithiol (*V*, $n = 3$, Table I). Chromatographic separation of the filtrate from the reaction mixture on silica gel gave N-substituted carbonylmorpholinocarbothioamides *Ia*–*If* (Scheme 1, Table I). N-Benzoylmorpholinocarbothioamide *Ia* alternatively prepared from benzoyl isothiocyanate and morpholine in acetone was identical with the compound isolated from the filtrate of the reaction mixture.

The reaction with morpholinocyclohexene was carried out in boiling chloroform. The product obtained from benzoyl isothiocyanate separated after a one-day standing, while other products had to be purified chromatographically. 2-Substituted 4*H*-cyclo-

hexa[*e*]1,3-oxazine-4-thiones *IIa–IIc* were isolated in a 30–35% yield (Scheme 1, Table I). Cyclohexeno[*e*]pyrimidine-2,4-dithiol (*V*, $n = 4$, Table I), the 1 : 2 cycloadduct *IVd* ($n = 4$, Table I, when starting from 2-furoyl isothiocyanate), and the



SCHEME 1

TABLE I

Products of reaction of carbonyl isothiocyanates with enamines

Compound *n*	R	Formula (m.w.)	M.p., °C (yield, %)	Calculated/Found				λ_1 max (log ε)		λ_2 max (log ε)
				% C	% H	% N	% S			
Ia	C_6H_5	$C_{12}H_{14}N_2O_2S$ (250)	143·5[a] (87)	—	—	—	—	280 (4·00)		340 (2·75)
Ib	4-$NO_2C_6H_4$	$C_{12}H_{13}N_3O_4S$ (295)	161·5 (75)	48·81 48·62	4·40 4·25	14·23 13·88	10·84 10·82	267 (4·42)		—
Ic	4-$CH_3OC_6H_4$	$C_{13}H_{15}N_2O_3S$ (270)	134 (90)	57·77 57·62	5·55 5·32	10·37 10·45	11·85 11·72	278 (4·44)		340 (2·94)
Id	2-Furyl-	$C_{10}H_{12}N_2O_3S$ (240)	158 (95)	50·00 49·85	5·00 5·08	11·66 11·85	13·36 13·07	270 (4·40)		350 (2·77)
Ie	C_2H_5	$C_8H_{14}N_2O_2S$ (202)	154 (68)	47·52 47·34	6·93 6·77	13·86 13·65	15·84 15·65	276 (4·05)		—
If	C_2H_5O	$C_8H_{14}N_2O_3S$ (218)	167 (63)	44·03 43·88	6·42 6·31	12·84 12·60	14·71 14·53	282 (3·98)		350 (3·62)
IIa 3	C_6H_5	$C_{17}H_{20}N_2O_2S$ (315)	145 (85)	64·76 64·55	6·34 6·18	8·88 8·65	10·16 9·98	236 (4·11)	304 (4·05)	433 (4·12)
IIe 4	C_2H_5	$C_{14}H_{22}N_2O_2S$ (282)	92[b] (79)	—	—	—	—	283 (4·02)		378 (3·92)
IIf 3	C_2H_5O	$C_{13}H_{20}N_2O_3S$ (284)	125[b] (94)	—	—	—	—	296 (3·97)	352 (3·88)	423 (4·06)
IIIa 4	C_6H_5	$C_{14}H_{13}NOS$ (243)	199[a] (55)	—	—	—	—	233 (3·43)	292 (4·35)	334 (4·16)

TABLE I
(*Continued*)

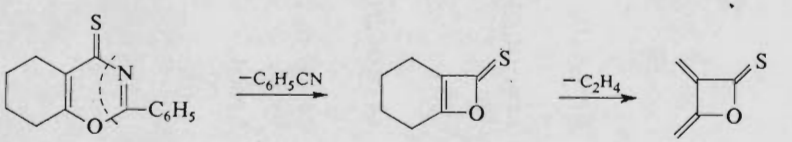
Compound *n*	R	Formula (m.w.)	M.p., °C (yield, %)	Calculated/Found % C	% H	% N	% S	λ_1 max (log ε)		λ_2 max (log ε)	
IIIb	4-$NO_2C_6H_4$	$C_{14}H_{12}N_2O_3S$	192	58·33	4·17	9·72	11·10	296		—	
4		(288)	(35)	58·10	4·02	9·52	10·85	(4·53)			
IIIc	4-$CH_3OC_6H_4$	$C_{15}H_{15}NO_2S$	165	65·93	5·49	5·12	11·72	233	257	330	
4		(273)	(30)	65·72	5·27	5·08	11·60	(3·93)	(3·90)	(4·46)	
IVa	C_6H_5	$C_{21}H_{16}N_2O_2S_2$	189	64·28	4·08	7·14	16·36	285	325	409	
3		(392)	(30)	64·13	4·15	7·25	16·45	(4·30)	(4·45)	(4·20)	
IVc	4-$CH_3OC_6H_4$	$C_{23}H_{20}N_2O_4S_2$	203	61·06	4·42	6·19	14·19	273	295	353	418
3		(452)	(42)	60·88	4·28	5·98	14·38	(4·42)	(4·41)	(4·08)	(3·14)
IVd	2-Furyl	$C_{17}H_{12}N_2O_4S_2$	196	54·84	3·23	7·52	17·24	284	330	405	
3		(372)	(37)	54·71	3·08	7·28	16·95	(4·24)	(4·52)	(4·07)	
IVd	2-Furyl	$C_{18}H_{14}N_2O_4S_2$	195	55·96	3·63	7·25	16·61	286	328	402	
4		(386)	(40)	55·72	3·48	7·38	16·62	(4·26)	(4·56)	(4·08)	
V		$C_7H_8N_2S_2$	304[c]	—	—	—	—	240	288		
3		(184)	(30)[d]					(4·11)	(3·88)		
V		$C_8H_{10}N_2S_2$	340[e]	—	—	—	—	290	350		
4		(198)	(20)					(4·30)	(4·16)		

[a] M.p. *Ia* 145°C, m.p. *IIIa* 198—199 (ref.[1]); [b] m.p. *IIe* 86—87°C, m.p. *IIf* 198—199°C (ref.[3]); [c] m.p. *V*, $n = 3$, 300°C (ref.[8]) 250°C (ref.[9]); [d] for benzoyl isothiocyanate 23%, for 4-methoxybenzoyl isothiocyanate 30%; [e] m.p. *V*, $n = 4$, 338°C (ref.[9]), 348°C (ref.[10]).

corresponding carbonylmorpholinodithioamides were present in further fractions in 63–95% yield. A two-step synthesis with morpholinocyclopentene was proceeded in a non-polar solvent. Isolated were the 1 : 1 adducts (N-substituted 2-morpholinocyclopentene carbothioamides *IIa*, *IIe*, *IIf*, Table I) in a 79–94% yield; attempts to cyclize the obtained adducts in acid or basic media failed.

The IR spectra of N-substituted carbonylmorpholinocarbothioamides *Ia–If* (Table I) displayed ν(NH) absorption bands at 3 235–3 260 cm^{-1}, ν(CH arom.) at 3 010–3 090 cm^{-1}, ν(CH aliph.) at 2 920–2 990 cm^{-1}, ν(CO) at 1 680–1 690 cm^{-1}, and ν(C—O—C) at 1 110–1 120 cm^{-1}; those of 1 : 2 cycloadducts (Table I, derivatives *IV*, *IVc*, *IVd*) revealed a strong absorption band ν(CO) at 1 640–1 645 cm^{-1}. A relatively low wave number of this band can be rationalized by the amide grouping. IR spectra of derivatives *IIIa–IIIc* (Table I) showed vibrations ν(C=N) at 1 640–1 645 cm^{-1}, those characterizing ν(C=S) and ν(C—SH) were of low intensity with derivatives *V*, $n = 3, 4$. The UV spectra of *Ia–If* (Table I) had significant absorption maxima at 267–280 and 340–350 nm. The first absorption band can be assigned to conjugation of that moiety of the molecule, which originated from the corresponding isothiocyanates, and the second band to $\pi^* \leftarrow \pi$ transitions associated with the electron-transmitting transitions. The 1 : 2 cycloadducts has three significant maxima in the 273–295, 325–353, and 405–418 nm regions. This group, *i.e.* compounds *IVa*, *IVc*, *IVd*, is characterized by a bathochromic shift and a hyperchromic effect when compared with derivative *V*. The UV spectra of compounds *IIa*, *IIc* exhibited three maxima in the 230, 290 and 330 nm regions, excepting the nitro derivative *IIIb*, which showed but one maximum at 296 nm attributable to a quinoid structure formed by the electron-accepting effect of the nitro group.

Electron impact mass spectrum of *Ia* had prominent peaks at m/z 250 ($M^{+\cdot}$, 12%), 105 ($C_7H_5O^{(+)}$, base peak), 163 (M—C_4H_9NO), 87 (morpholine, 52%), that of *IIIa* at m/z 140 (M—C_6H_5CN, base peak, and 112 (M—C_6H_5CN—C_2H_4, 33%, retro Diels–Alder reaction); peaks of ions at lower m/z values well indicated the presence of benzene ring (Scheme 2). The peaks of molecular radical ions of substances *IVa* and *IVd* (m/z 292 and 372, resp.) were of minimum intensity (0·3 and 0·4%, resp.). Further fragmentation pathway proceeded through a retro Diesel–Alder reaction followed by a cleavage of a benzoyl, or a furoyl group.



IIIa $M^{+\cdot}$ 243
rel. int. 65%

m/z 140
rel. int. 100%

m/z 112
rel. int. 33%

SCHEME 2

Base peaks of cyclopenteno- and cyclohexeno[*e*]pyrimidine-2,4-dithiol at *m/z* 184 and 198 were ascribable to molecular radical ions; further fragmentation pattern was triggered by the loss of —SH, —SCN, HSCN and H_2SCN species.

EXPERIMENTAL

Isothiocyanates employed in this study were prepared according to[6], cyclic enamines were synthesized by reacting cyclic ketones with morpholine under catalysis of *p*-toluenesulfonic acid in toluene, water being removed by azeotropic distillation[7].

The IR spectra were measured with a UR-20 (Zeiss, Jena) apparatus (1 mg/300 mg KBr), the UV spectra with a UV-VIS (Zeiss, Jena) spectrophotometer (methanol, $3-5 \cdot 10^{-5}$ mol l^{-1}, cell width 10 mm). Electron impact mass spectra were recorded with an MS 902 S (AEI, Manchester) instrument (ionization chamber temperature 150°C, ionizing electron energy 70 eV, trap current 100 μA).

Reactions of Carbonyl Isothiocyanates with Morpholinocyclopentene

The proper isothiocyanate (10 mmol) was dropwise added at 0°C to a stirred solution of morpholinocyclopentene (0·6 g, 5 mmol) in chloroform (15 ml) and stirred for 3 h. The precipitate was filtered off, washed with chloroform, transferred to water–pyridine (30 and 5 ml, resp.) and heated to boiling point temperature. The undissolved residue was filtered off, dried and crystallized from dimethylformamide (derivatives *IVa*, *IVc*, *IVd*, Table I). The filtrate acidified with 10% hydrochloric acid to pH 4 was left to stand for 3 to 4 h, during which yellow compound *V*, $n = 3$ crystallized. The filtrate remaining from the reaction mixture was separated by chromatography on a silica gel column into compounds *Ia—If* (Table I) with chloroform–benzene–ether (3 : 2 : 1) as eluent.

Reactions of Carbonyl Isothiocyanates with Morpholinocyclohexene

The respective carbonyl isothiocyanate (10 mmol) was added in one instalment into a solution of the enamine (0·7 g, 5 mmol) in chloroform (15 ml), refluxed on a steam bath for 30 min and allowed to stand for one day. Derivative *IIIa*, which was crystallized from dimethylformamide, separated when benzoyl isothiocyanate was the starting compound. Substance *Ia* (Table I) crystallized from the concentrated filtrate to which ether was added. Reaction mixture of other carbonyl isothiocyanates were chromatographically purified on a silica gel column with chloroform–benzene–ether (3 : 2 : 1 — derivatives *IIb*, *IIc*, Table I). Derivative *V*, $n = 4$ (Table I) was obtained from the filtrate after acidification with 10% hydrochloric acid to pH 4. Further products *Ib—Id* were obtained in an analogous way as with morpholinocyclopentene. The reaction with carbethoxy and propionyl isothiocyanates was carried out in ether (60 ml) with stirring (4 h) at room temperature. Yellow crystals, recrystallized from ethanol (derivatives *IIc*, *IIf*, Table I) were obtained after a 12 h standing.

A Two-step Reaction of Morpholinocyclopentene with Benzoyl Isothiocyanates

A solution of benzoyl isothiocyanate (1·62 g, 10 mmol) in light petroleum was added to a stirred solution of morpholinocyclopentene (1·53 g, 10 mmol) in light petroleum (30 ml) at room temperature. Compound *IIa*, which separated during 30 min was suction-filtered and crystallized from methanol. Yield 2·64 g (83%). *a*) Compound *IIa* (1 g) was dissolved in methanol (30 ml),

glacial acetic acid (1 ml) was added and the mixture refluxed for 1 h. The cooled mixture was neutralized and concentrated under diminished pressure. The unreacted *IIa* was recovered from the residue. *b*) Solid NaOH (0·1 g) was added to compound *IIa* (1 g) dissolved in methanol (30 ml), and the mixture was refluxed for 1 h and worked up as sub *a*). The chromatographic work-up of the residue afforded only compound *IIa*.

N-Benzoylmorpholinocarbothioamide (*Ia*)

Morpholine (2·17 g, 25 mmol) was added during 2 h to the solution of benzoyl isothiocyanate (3·24 g, 20 mmol) in acetone (10 ml). The mixture was allowed to stand for a short time and then poured into a two-fold excess of dilute hydrochloric acid (1 : 1). The separated *Ia* was filtered off and crystallized from methanol. Yield 3·75 g (75%), m.p. 143·5°C.

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