REACTIONS OF CARBONYL ISOTHIOCYANATES WITH ENAMINES OF THE TYPE CH_3—$C(NH_2)$=CH—X

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Reactions of carbonyl isothiocyanates with enamines of the type CH_3—$C(NH_2)$=CH—X (X = CN, $COOC_2H_5$, or $COCH_3$) were investigated. The formation of products of Ad_N, S_N, and cyclization reactions is discussed on the basis of their IR, UV and mass spectra. In one case, the thermal cyclization was followed by differential thermal analysis.

Esters of β-aminocrotonic acids react with carbonyl isothiocyanates to give 1 : 1 C-adducts which can be cyclized to substituted 4-thiopyrimidines[1-4]. Goerdeler and Pohland[1] performed the cyclization by heating in 20% ammonium hydroxide whereas de Stevens[2] used reflux in tetrahydrofuran for 2 hours.

β-Dimethylaminocrotonate reacts with two equivalents of benzoyl isothiocyanate in chloroform with simultaneous liberation of hydrogen sulfide to give thiopyridine derivatives[5]. On reflux with bromonitromethane, the enamine-benzoyl isothiocyanate adduct affords an isothiazole derivative[6]. Reaction of 5-nitro-2-furoyl isothiocyanate with β-aminocrotonates leads to 5-nitro-2-furyliminoisothiazoline[7].

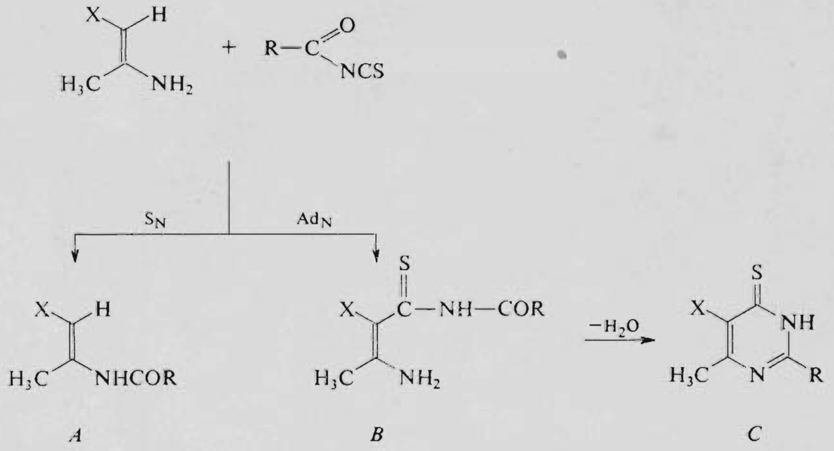
In our preceding papers[8,9] we described the utilization of carbonyl isothiocyanates for the synthesis of various heterocyclic compounds. In the present communication we investigate the reaction of carbonyl isothiocyanates with ethyl 3-amino-2-butenoate, 3-amino-2-crotononitrile and 2-amino-2-penten-4-one. We employed ethoxycarbonyl, propionyl, benzoyl, substituted benzoyl, and 2-furoyl isothiocyanates.

Carbonyl isothiocyanates reacted with 3-aminocrotononitrile in acetonitrile under formation of three kinds of products: products of nucleophilic substitution at the amino group in 3-aminocrotononitrile by the corresponding carbonyl isothiocyanate (*A*), products of an Ad_N reaction (*B*), or 1 : 1 cyclocondensation products (*C*) (Scheme 1). With ethoxycarbonyl isothiocyanate, only the addition product *IV* was isolated (Table I) whereas 2-furoyl isothiocyanate afforded both the addition and cyclization products (*VIII* and *XVI*). The compound *VIII* melted at 173°C and solidified again to form needles, melting at 262°C. Reaction of 2-furoyl isothiocyanate with 3-aminocrotonitrile in chloroform gave in 40% yield the derivative *XVI*, identical with one of the products formed in acetonitrile.

The thermal cyclization was confirmed also by the differential thermal analysis of the compound *VIII*. As seen from the thermogram (Fig. 1), during the heating a two-step weight loss was observed, the compound being stable till 143°C. Exothermic melting at 174°C indicates the cyclocondensation *VIII* → *XVI* and the weight loss ($\sim 7\%$) corresponds to loss of water during the heating. The formed derivative *XVI* decomposed at 265°C.

The other isothiocyanates studied afforded directly cyclocondensation products (*XI*, *XIV* and *XV*). Treatment of ethyl 3-aminocrotonate with ethoxycarbonyl isothiocyanate afforded only the nucleophilic addition product *VI*; in all other cases cyclocondensation products were isolated (Table I).

The infrared spectra of the prepared pyrimidinethione derivatives *IX*–*XVI* exhibit characteristic ν(N—H) vibrations in the region 3 200–3 380 cm^{-1} and ν(C=O) or ν(C=N) vibrations at 1 600–1 720 cm^{-1}. Products of the Ad_N and S_N reactions (*I*–*III*, and *IV*–*VII*) have characteristic bands due to ν(N—H) at 3 225 to 3 489 cm^{-1}, ν(C—H aliphatic) at 2 850 – 3 020 cm^{-1} and ν(C=O) at 1 670 to 1 770 cm^{-1}, the latter band being splitted in several cases.



X = —CN; —$COOC_2H_5$; —$COCH_3$
R = C_2H_5O; C_2H_5; C_6H_5; 4-NO_2—C_6H_4—; 4-CH_3—C_6H_4—; 2-furyl-

SCHEME 1

Ultraviolet spectra of the cyclocondensation products *IX*–*XVI* (Table I) display one marked maximum in the region 295–310 nm which is only little affected by substituent at the aromatic nucleus or by substitution of phenyl by furyl or ethyl groups. The products of nucleophilic substitution *I*–*III* have strong maxima of

TABLE I

Products of the reaction RCONCS + CH_3—$C(NH_2)$=CH—X

Compound Reaction	R X	Formula (mol.w.)	M.p., °C (yield, %)	Calculated/Found				$\lambda_{1\,max}$ (log ε)		$\lambda_{2\,max}$ (log ε)
				% C	% H	% N	% S			
I	OC_2H_5	$C_7H_{10}N_2O_2$	242	54·54	6·49	18·18	—	259		302
A	CN	(154)	(38)	54·28	6·25	18·43		(4·01)		(4·60)
II	C_2H_5	$C_7H_{10}N_2O$	240	60·86	7·24	20·28	—	258		300
A	CN	(138)	(41)	60·75	7·12	19·94		(4·37)		(3·86)
III	4-$NO_2C_6H_4$	$C_{11}H_9N_3O_3$	292	57·14	3·89	18·28	—	257		302
A	CN	(231)	(20)	57·02	3·65	18·32		(4·42)		(3·90)
IV	OC_2H_5	$C_8H_{11}N_3O_2S$	140	45·07	5·16	19·72	15·02	251	285	332
B	CN	(213)	(41)	45·18	5·02	19·97	15·26	(4·28)	(4·15)	(4·43)
V	OC_2H_5	$C_{10}H_{16}N_2O_4S$	138[a]	—	—	—	—		349	384
B	$COOC_2H_5$	(260)	(58)						(3·86)	(4·34)
VI	OC_2H_5	$C_9H_{14}N_2O_3S$	114	46·95	6·08	12·17	13·91		288	312
B	$COCH_3$	(230)	(67)	46·72	6·19	12·22	14·19		(4·35)	(4·19)
VII	C_2H_5	$C_{10}H_{16}N_2O_3S$	117	49·18	6·55	11·47	13·11		283	
B	$COOC_2H_5$	(244)	(46)	49·02	6·38	11·25	12·91		(4·23)	
VIII	2-Furyl	$C_{10}H_9N_3O_2S$	173	51·06	3·83	17·87	14·62		364	
B	CN	(235)	(51)	50·92	3·65	17·70	13·54		(4·09)	
IX	C_2H_5	$C_{10}H_{14}N_2O_2S$	155	53·09	6·19	12·39	14·15		298	338
C	$COOC_2H_5$	(226)	(34)	52·88	6·02	12·18	14·02		(4·08)	(3·83)
X	C_2H_5	$C_8H_{11}N_3OS$	137	48·73	5·58	21·32	16·24		304	
C	$COCH_3$	(197)	(62)	48·61	5·22	21·06	16·32		(4·02)	

XI *C*	C_6H_5 CN	$C_{12}H_9N_3S$ (227)	224[b] (55)	—	—	—	—	273 (4·28)	310 (4·25)	358 (3·55)
XII *C*	C_6H_5 $COOC_2H_5$	$C_{14}H_{14}N_2O_2S$ (274)	127—130[c] (66)	—	—	—	—	259 (4·27)	309 (4·16)	
XIII	C_6H_5 $COCH_3$	$C_{13}H_{12}N_2OS$ (244)	125 (78)	63·94 63·79	4·91 4·80	11·40 11·19	13·11 12·93	256 (4·18)	307 (4·36)	
XIV *C*	4-CH_3O—C_6H_4 CN	$C_{13}H_{11}N_3OS$ (257)	101 (48)	60·70 60·55	4·28 4·07	16·32 16·38	12·45 12·22	295 (4·48)	385 (3·25)	
XV *C*	4-NO_2—C_6H_4 CN	$C_{12}H_8N_4O_2S$ (272)	175 (36)	52·94 52·78	2·94 2·81	20·58 20·29	11·76 11·58	243 (3·90)	305 (4·45)	390 (3·14)
XVI *C*	2-Furyl CN	$C_{10}H_7N_3OS$ (217)	262 (90)	55·30 55·06	3·22 3·12	19·35 19·60	14·74 14·57	234 (4·00)	304 (4·09)	369 (3·93)

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[a] M.p. 145°C for *V* (ref.[13]); [b] M.p. 230°C for *XI* (ref.[3]); [c] M.p. for *XII* (ref.[1]).

different intensity at 258 ± 1 nm nad 300 ± 2 nm. Products of nucleophilic addition of ethoxycarbonyl isothiocyanate with 3-aminocrotononitrile, ethyl 3-aminocrotonate and 2-amino-2-penten-4-one (*IV*–*VI*) differ in the shape and position of their UV maxima; the intensity of the bands, however, is similar.

The most abundant peaks (100% of relative intensity) in mass spectra of compounds *IV*–*VI* (Table I) are those due to the ($M^{+\cdot} - CO_2C_2H_5$) ions of m/z 140, 187, 157, respectively. Also the molecular ion peaks are relatively intense ($M^{+\cdot}$ 213 (91%), $M^{+\cdot}$ 260 (69%) and $M^{+\cdot}$ 230 (96%)). Further fragmentation proceeds by splitting off the radicals $C_2H_5^{\cdot}$, $C_2H_5O^{\cdot}$ or $CH_3^{\cdot}$. Mass spectrum of the cyclocondensation product *IX* exhibits the molecular ion $M^{+\cdot}$ 226 as the most abundant (100% of relative intensity), further fragmentation affords C_2H_4 (10%), $C_2H_5O^{\cdot}$ (69%), C_2H_5OH (41%) and CO (38%).

EXPERIMENTAL

The isothiocyanates were prepared from the corresponding acid chlorides (ethoxycarbonyl isocyanate from ethyl chloroformate) and KSCN in acetone according to Elmore and Ogle[10]. The crude products were purified by distillation under diminished pressure or crystallization. Yields and spectral properties of the isothiocyanates agree with the published values. 2-Aminocrotononitrile was prepared from acetonitrile by action of sodium powder[11], ethyl 3-amino-2-butenoate and 2-amino-2-penten-4-one were synthesized according to ref.[12].

IR spectra were measured at room temperature on a UR-20 (Karl Zeiss, Jena), instrument in KBr pellets (1 mg/300 mg KBr) or in chloroform. UV spectra were taken in methanol on a Specord UV VIS (Zeiss) spectrophotometer (10 mm cells; concentration 3—5 . 10^{-5} mol l^{-1}). Mass spectra were obtained on an AEI MS-902S instrument (direct inlet, ionization chamber temperature 150°, 70 eV, electron current 100 μA). Differential thermal analysis of the derivative *VIII* was carried out on a Thermoanalyzer 2 (Mettler) instrument; sample weight 7·5 mg, nitrogen flow rate 7 l/h, heating rate 6°C/60 s, Pt and Pr-Rh thermocouples.

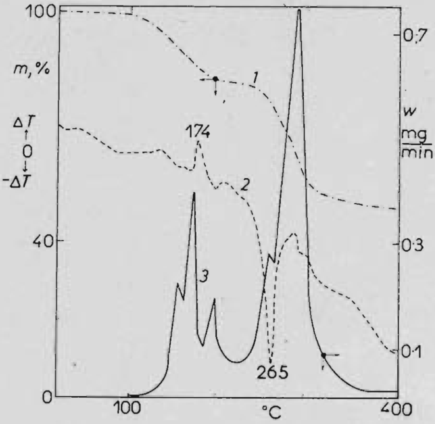

FIG. 1

TG *1*, DTA *2* and DTG *3* curves for compound *VIII*

Reaction of Carbonyl Isothiocyanates with 3-Aminocrotononitrile

A solution of the appropriate carbonyl isothiocyanate in acetonitrile was added dropwise to a solution of 3-aminocrotononitrile (0·82 g; 0·01 mol) in acetonitrile at a temperature below 5°C and the mixture was stirred for 2 h. The crystalline material was filtered and crystallized from methanol (compounds *I*—*III*, Table I). The filtrate was concentrated, affording compounds *IV*, *VIII* or *XVI* and *XV*. The reaction of benzoyl and 4-methoxybenzoyl isothiocyanates gave no precipitate and therefore ether (20 ml) was added to the reaction mixtures and after 1 day the separated crystals were collected on filter and crystallized from benzene (compounds *XI* and *XIV*).

Reaction of Carbonyl Isothiocyanates with Ethyl 3-Aminocrotonate or 2-Amino-2-penten-4-one

The appropriate carbonyl isothiocyanate (0·01 mol; neat or dissolved in acetonitrile) was added at room temperature to a solution of 0·01 mol of ethyl 3-aminocrotonate (1·3 g) or 2-amino-2-penten-4-one (0·99 g) in acetonitrile (20 ml). The mixture was refluxed for 3 h and set aside for 24 h. In cases of ethoxycarbonyl and benzoyl isothiocyanates the respective crystalline products *V* and *XIII* separated (Table I). In other experiments, the reaction mixtures were taken down and the products separated by chromatography on a silica gel column, using cyclohexane–ethyl acetate (1 : 1) (compounds *VI*, *VII*, *IX* and *X*) or benzene–acetone (2 : 1) (compound *XII*) as eluants.

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