Synthesis, properties, and reactions of heterodienes. II.* Reactions of cinnamoyl isothiocyanates with enamines and spectral study of the reaction products

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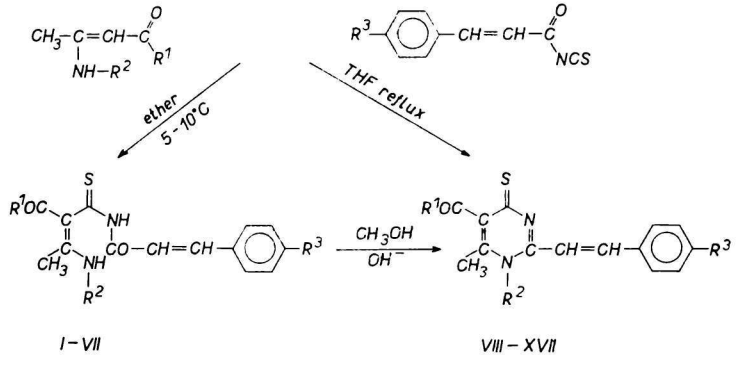
The reactions of cinnamoyl isothiocyanates with enamines of the crotone type resulting in α,β-disubstituted *N*-thiocrotonoylcinnamamides were studied. The cyclization of the mentioned derivatives to 1,2,5,6-tetrasubstituted pyrimidine-4-thiones was carried out in alkaline medium. Pyrimidinethiones were obtained also by direct heating the cinnamoyl isothiocyanates with enamines in anhydrous solvents. The structures of 17 new synthesized compounds were confirmed by infrared, ultraviolet, and nuclear magnetic resonance spectra.

Recently, acyl isothiocyanates have been frequently used for the preparation of new heterocyclic compounds of the pyrimidine, thiazole, imidazole, benzoxazine, *etc.* types because of their high reactivity [1—4]. Thus, there is a possibility to utilize these reactions for the synthesis of biologically active substances.

Goerdeler and *Gnad* [1] as well as *DeStevens et al.* [4] dealt with the synthesis and properties of pyrimidinethiones prepared from benzoyl isothiocyanates and enamines. Regarding the high biological activities of the cinnamoyl isothiocyanates [5], we decided to study the addition reactions of these compounds with enamines to obtain other types of pyrimidinethiones.



I–VII VIII–XVII

$R^1 = CH_3-$, C_2H_5O-; $R^2 = H-$, C_2H_5-, C_6H_5-; $R^3 = H-$, CH_3-, CH_3O-.

Scheme 1

* Part I: *Collect. Czech. Chem. Commun.* **37**, 3066 (1972).

Substituted cinnamoyl isothiocyanates as well as *N*-substituted 4-amino-3-penten-2--ones and *N*-substituted β-aminocrotonates were used as starting components for the synthesis of pyrimidinethiones.

Isothiocyanates were prepared from the appropriate cinnamoyl chlorides with lead thiocyanate in benzene [6]; enamines were obtained by treatment of ethyl acetoacetate and acetylacetone with ammonia and alkyl and aryl amines [7—10].

Pyrimidinethiones were synthesized by the method of *Goerdeler* [1] *via* α,β-disubstituted *N*-thiocrotonoylcinnamamides and by direct cyclization in anhydrous solvents according to DeStevens and his co-workers [4] (Scheme 1).

In the present work we describe the preparation and spectral properties of 1,2,5,6--tetrasubstituted pyrimidinethiones as well as those of the intermediates with the purpose to throw more light upon their structure and properties.

Table 1

The synthesized α,β-disubstituted *N*-thiocrotonoylcinnamamides

Compound	R^1, R^2, R^3	Formula	*M*	Calculated/found % N	Calculated/found % S	Yield [%]	M.p. [°C]
I	C_2H_5O H H	$C_{16}H_{18}N_2O_3S$	318.38	8.79 8.86	10.06 9.92	41.1 red needles	116—118 benzene—petroleum ether
II	C_2H_5O H CH_3O	$C_{17}H_{20}N_2O_4S$	348.39	8.04 8.13	9.20 9.28	63.8 red plates	121—123 acetone—petroleum ether
III	C_2H_5O H CH_3	$C_{17}H_{20}N_2O_3S$	332.39	8.42 8.50	9.64 9.58	51.6 dark-orange crystals	139—141 acetone—petroleum ether
IV	CH_3 H H	$C_{15}H_{16}N_2O_2S$	288.37	9.71 9.62	11.11 11.25	56.7 dark-red plates	123—125 acetone—petroleum ether
V	CH_3 H CH_3O	$C_{16}H_{18}N_2O_3S$	318.38	8.79 8.71	10.06 9.98	63.1 dark-red crystals	123—126 acetone—petroleum ether
VI	CH_3 H CH_3	$C_{16}H_{18}N_2O_2S$	302.38	9.26 9.31	10.60 10.68	44.8 dark-red crystals	129—131 acetone—petroleum ether
VII	CH_3 C_2H_5 H	$C_{17}H_{20}N_2O_2S$	316.39	8.85 8.79	10.13 10.04	85.5 dark-red crystals	117—119 chloroform—petroleum ether

Experimental

The starting cinnamoyl isothiocyanate (m.p. 41—43°C), 4-methylcinnamoyl isothiocyanate (m.p. 46—47°C), 4-methoxycinnamoyl isothiocyanate (m.p. 47—48°C), and their preparation were described in our previous work [6].

The starting enamines, *i.e.* 4-amino-3-penten-2-one (b.p. 114°C/15 torr), 4-ethylamino--3-penten-2-one (b.p. 210—215°C), 4-phenylamino-3-penten-2-one (m.p. 51—53°C), ethyl β-aminocrotonate (b.p. 105°C/15 torr), and ethyl β-ethylaminocrotonate (b.p. 128—130°C/2 torr) were prepared according to [7—10].

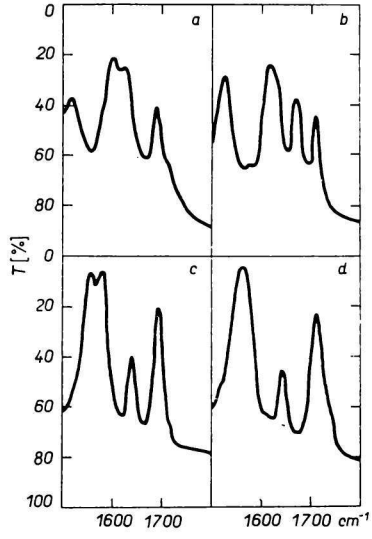


Fig. 1. Infrared absorption spectra.
a) α-acetyl-β-amino-*N*-thiocrotonoylcinnamamide (*IV*); *b*) α-carbethoxy-β-amino-*N*-thiocrotonoyl--*p*-methylcinnamamide (*III*); *c*) 5-acetyl-6-methyl--2-styrylpyrimidine-4-thione (*XI*); *d*) 5-carbethoxy--6-methyl-2-(4-methylstyryl)pyrimidine-4-thione (*X*).

Infrared spectra of the synthesized compounds were recorded with an UR-20 (Zeiss, Jena) spectrophotometer in the range of 800—3600 cm^{-1} using KBr pellets (a sample size of 0.4—0.6 mg with 500 mg KBr). The apparatus was calibrated with polystyrene foil.

Ultraviolet spectra of α,β-disubstituted *N*-thiocrotonoylcinnamamides and pyrimidinethiones in methanol (concentration 3×10^{-5} mol l^{-1}) were taken on a Perkin—Elmer 402 recording spectrophotometer at 20 ± 2°C using 10-mm cells.

Nuclear magnetic resonance spectra were measured on a Tesla BS 487 A spectrometer at 80 MHz in deuteriodimethyl sulfoxide. Hexamethyldisiloxane (HMDS) was used as internal standard.

Characterization of the synthesized compounds is in Tables 1—6.

α,β-Disubstituted N-thiocrotonoylcinnamamides (I—VII)

To the appropriate cinnamoyl isothiocyanate (0.013 mole) dissolved in anhydrous ether (10—15 ml), enamine (0.013 mole) was added dropwise at 5—10°C under stirring. After 30 minutes' stirring, an orange or red very fine precipitate was formed, which was filtered and dissolved in a small amount of polar solvent. When petroleum ether was added, the α,β-disubstituted *N*-thiocrotonoylcinnamamide crystallized.

Table 2

The synthesized 1,2,5,6-tetrasubstituted pyrimidine-4-thiones

Compound	R^1, R^2, R^3	Formula	M	Calculated/found % N	Calculated/found % S	Yield [%]	M.p. [°C]
VIII	C_2H_5O H H	$C_{16}H_{16}N_2O_2S$	300.37	9.32 9.18	10.66 10.52	79.7 yellow crystals	224–225 ethanol
IX	C_2H_5O H CH_3O	$C_{17}H_{18}N_2O_3S$	330.38	8.47 8.56	9.70 9.60	84.5 yellow crystals	190–192 ethanol
X	C_2H_5O H CH_3	$C_{17}H_{18}N_2O_2S$	314.38	8.91 9.13	10.19 10.24	73.5 yellow crystals	177–179 ethanol
XI	CH_3 H H	$C_{15}H_{14}N_2OS$	270.36	10.36 10.45	11.86 11.75	85.2 yellow crystals	240–242 ethanol
XII	CH_3 H CH_3O	$C_{16}H_{17}H_2O_2S$	301.37	9.29 9.24	10.63 10.67	86.6 yellow crystals	210–212 ethanol
XIII	CH_3 H CH_3	$C_{16}H_{16}N_2OS$	284.37	9.83 9.91	11.15 11.31	84.8 yellow crystals	202–204 ethanol
XIV	C_2H_5O C_2H_5 H	$C_{18}H_{20}N_2O_2S$	329.40	8.50 8.92	9.73 9.94	5.05 yellow crystals	226–228 ethanol
XV	CH_3 C_2H_5 H	$C_{17}H_{18}N_2OS$	298.37	9.36 9.56	10.74 10.90	85.7 yellow crystals	217–219 ethanol
XVI	C_2H_5O C_6H_5 H	$C_{22}H_{20}N_2O_2S$	376.44	7.70 7.86	8.51 8.64	41.3 yellow crystals	253–255 acetonitrile
XVII	CH_3 C_6H_5 H	$C_{21}H_{18}N_2OS$	336.41	8.32 8.49	9.53 9.70	67.3 yellow crystals	239–242 chloroform–petroleum ether

1,2,5,6-Tetrasubstituted pyrimidine-4-thiones (VIII—XVII)

A. Sodium hydroxide (1 N) was added dropwise to the appropriate α,β-disubstituted *N*-thiocrotonoylcinnamamide (*I—VII*; 0.33 mole) dissolved in the smallest amount of methanol until the colour of the solution changed from red to yellow. Immediately after filtration and neutralization with 1 N-HCl, the yellow precipitate of the corresponding pyrimidinethione was formed which was crystallized from a suitable solvent after suction.

Compounds *VIII—XIII* were prepared by this method.

Table 3

Spectral data of α,β-disubstituted *N*-thiocrotonoylcinnamamides and 1,2,5,6-tetrasubstituted pyrimidine-4-thiones

Compound	$\tilde{\nu}$(NH—C=S) |	$\tilde{\nu}$(=N—C=S) |	$\tilde{\nu}$(C=C)	$\tilde{\nu}_1$(C=O)[a] $\tilde{\nu}_2$(C=O)[b]	$\lambda_{max\ I}$ log ε_1	$\lambda_{max\ II}$ log ε_2	$\lambda_{max\ III}$ log ε_3
I	1316; 1337	—	1620	1671	226	323	376
	1521			1692	4.15	4.49	3.80
II	1318; 1332	—	1620	1670	239	345	—
	1518			1698	4.09	4.53	—
III	1319; 1337	—	1627	1670	234	332	375
	1524			1708	4.17	4.54	3.83
IV	1361	—	1628	1690	229	323	380
	1522			—	4.10	4.57	3.36
V	1354	—	1615	1690	240	348	—
	1518			—	3.97	4.50	—
VI	1350	—	1630	1696	237	330	380
	1526			—	4.08	4.62	3.36
VII	1333	—	1630	1709	226	326	378
	1519			—	4.07	4.53	3.30
VIII	—	1302	1643	—	230	312	368
				1703	4.02	4.54	3.80
IX	—	1308	1642	—	240	330	379
				1735	4.01	4.52	4.14
X	—	1299	1643	—	236	322	376
				1712	4.09	4.59	3.92
XI	—	1358	1642	1694	232	312	371
				—	4.02	4.47	3.76
XII	—	1358	1638	1695	242	331	379
			—	—	4.13	4.52	4.13
XIII	—	1359	1642	1700	236	320	376
				—	4.14	4.59	3.93
XIV	—	1284	1628	—	230	329	—
				1721	4.01	4.55	—
XV	—	1285	1631	1694	234	329	—
				—	4.02	4.55	—
XVI	—	1309	1632	—	235	331	—
				1727	4.07	4.59	—
XVII	—	1309	1632	1701	236	333	—
				—	4.01	4.53	—

a) $\tilde{\nu}_1$(C=O) = acetyl and cinnamoyl, respectively,
b) $\tilde{\nu}_2$(C=O) = carboxyethyl.

B. The mixture of cinnamoyl isothiocyanate (0.028 mole) and enamine (0.028 mole) dissolved in ether or tetrahydrofuran (30—50 ml) was refluxed for several hours. The formed yellow precipitate was crystallized from a suitable solvent after suction.

Compounds *XIV*—*XVII* were prepared by this method.

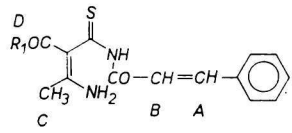
Results and discussion

Pyrimidinethiones were synthesized in most cases *via* α,β-disubstituted *N*-thiocrotonoylcinnamamides which were formed easier in the case of the enamines with ketone group (derivative *IV*) than in the case of the similar derivatives with ester group (derivative *I*). This is probably due to the disturbing mesomeric interaction of the ester ethoxy group with the enamine conjugation system. We failed to isolate the unstable addition products formed in the case of *N*-alkyl derivatives of enamines.

Pyrimidinethiones were prepared by cyclization of *N*-thiocrotonoylcinnamamides in alkaline medium at laboratory temperature as well as by direct cyclization of enamines with isothiocyanates in anhydrous organic solvents. The cyclization product precipitated during the reaction directly from the medium.

Table 4

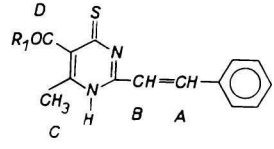
The n.m.r. spectral data (τ) of α,β-disubstituted *N*-thiocrotonoylcinnamamides



Compound	R¹	*A*	*B*	*C*	*D*
I	C_2H_5O	2.19	2.78	7.63	5.86
IV	CH_3	2.05	2.72	7.85	7.82

Table 5

The n.m.r. spectral data (τ) of 1,2,5,6-tetrasubstituted pyrimidine-4-thiones

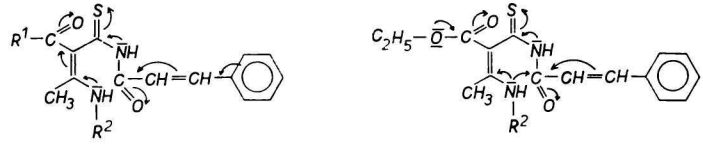


Compound	R¹	*A*	*B*	*C*	*D*
VIII	C_2H_5O	1.84	2.69	7.60	5.50
IX	CH_3	1.77	2.60	7.64	7.29

Pyrimidinethiones were intensively yellow coloured and little soluble in organic solvents.

Two absorption bands belonging to —NH—C=S and =N—C=S groups, respectively were typical for the infrared spectra of *N*-thiocrotonoylcinnamamides *I*—*VII* and pyrimidinethiones *XIII*—*XVIII*. In the case of *N*-thiocrotonoylcinnamamides these two intensive bands appeared at 1522 ± 5 and 1345 ± 15 cm^{-1}. In the spectra of pyrimidinethiones with the =N—C=S group the first band was absent while the second one of high intensity was shifted to higher wavenumbers in the region 1290 ± 20 cm^{-1}. These facts are in good agreement with the results of our previous works concerning the study of i.r. spectra of thiocarbonyl compounds with the thione group on the secondary, tertiary, and imide nitrogen atom (—NH—C=S, >N—C=S, =N—C=S) [11—13].

With the *N*-thiocrotonoylcinnamamides when $R^1 = -CH_3$ (ketone), both carbonyl groups absorbed in the same region. Consequently, they had the same electron nature (Fig. 1*a*, Scheme 2*a*).



b

Scheme 2

On the spectra of the same derivatives with $R^1 = -OC_2H_5$ (ester), two absorption bands belonging to carbonyl groups were observed at ~1670 and 1700 cm^{-1}. It can be explained by the fact that the disturbing interference of the mesomeric effect of ethoxy group to the original conjugated system enabled the lone-electron pair on the nitrogen atom to interact more significantly with the carbonyl group of the cinnamoyl residue (Feld effect; Fig. 1*b*, Scheme 2*b*). Due to this interaction, there is one ester carbonyl group ($\tilde{\nu}$(C=O) 1700 cm^{-1}) and an amide carbonyl group. This is demonstrated also by the i.r. spectra of the cyclic derivatives (*VII*—*XVII*) where the amide carbonyl group was absent (Fig. 1*c*, *d*).

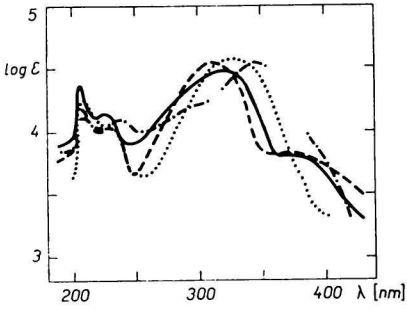
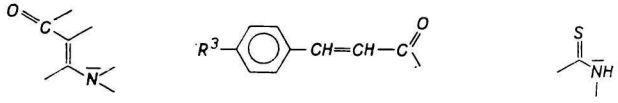


Fig. 2. Ultraviolet absorption spectra.
——— α-carbethoxy-β-amino-*N*-thiocrotonoylcinnamamide (*I*);
— — — 5-carbethoxy-6-methyl-2-styrylpyrimidine-4-thione (*VIII*);
— — . α-carbethoxy-β-amino-*N*-thiocrotonoyl-*p*-methoxycinnamamide (*II*);
5-carbethoxy-1-ethyl-6-methyl-2-styrylpyrimidine-4-thione (*XIV*).

The u.v. spectra of *N*-thiocrotonoylcinnamamides (*I*—*VII*) showed three absorption bands in the investigated region. These bands could be assigned to the $\pi \rightarrow \pi^*$ transition states of the following chromophoric systems (Scheme 3).



$\lambda_{max\,I} \sim 240$ nm	$\lambda_{max\,II} \sim 350$ nm	$\lambda_{max\,III} \sim 377$ nm
N,O conjugation	C,O conjugation	N,S conjugation

Scheme 3

The most significant second band at 350 nm was very sensitive to the effect of the substituents because these were in direct conjugation with the appropriate chromophoric system (Table 3). The third absorption band was a shoulder of lower intensity. With the derivatives *II* and *V*, this band was overlapped because of the significant bathochromic shift of the second absorption band caused by the strong auxochrome groups (methoxy; Fig. 2).

There were observed certain changes on the u.v. spectra of pyrimidinethiones (*VIII*—*XVII*) when compared with those of the above-mentioned compounds. The derivatives *XIV*—*XVII* substituted on the nitrogen atom showed only two absorption bands. The third band at 380 nm was absent because in the cyclic form there could be no N,S conjugation.

Owing to the low solubility of *N*-thiocrotonoylcinnamamides and mainly pyrimidinethiones in chloroform, the n.m.r. spectra of some representative compounds (*I*, *IV*, *VIII*, *XI*) were measured in deuteriodimethyl sulfoxide. In consequence of the deshielding effect of the formed quinoid system, the resonance signals of pyrimidinethiones were shifted to lower field when compared with those of *N*-thiocrotonoylcinnamamides. The obtained τ values presented in Tables 5 and 6 are in agreement with the other physicochemical data as well as with the results of the elementary analyses of the studied compounds.

The elemental analyses were performed at the Department of Organic Chemistry, Faculty of Natural Sciences, Komenský University, Bratislava.

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