Isothiocyanates and their synthetic producers. XIII. Preparation and spectral properties of 2,5,6-trisubstituted 5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones

P. KRISTIAN, D. KOŠČÍK, and J. BERNÁT

Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, 041 67 Košice

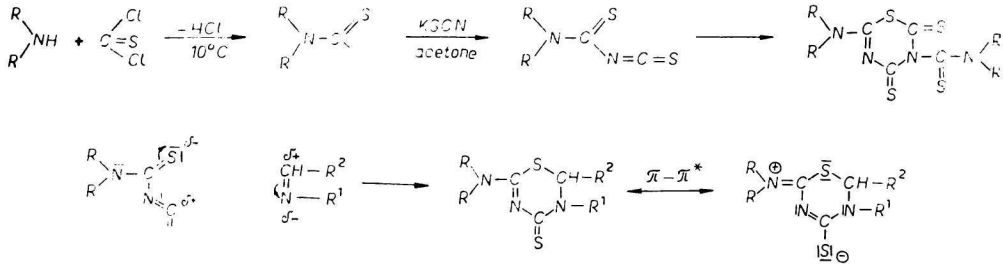
Received 22 July 1971

Accepted for publication 18 December 1971

The synthesis of ten new 2,5,6-trisubstituted thiadiazine-4-thiones by cyclization of thiocarbamoyl isothiocyanates with aldimines is described. Infrared, ultraviolet, and nuclear magnetic resonance spectra of the compounds mentioned as well as of their intermediates are studied. Two absorption bands are typical for thiadiazinethiones; one in the range of 1550 cm^{-1} ($\tilde{\nu}$(C=N)) and the other in the range of 1300 cm^{-1} ($\tilde{\nu}$(=N−C=S)). On the basis of the obtained results it was possible to make general conclusions about the change of the absorption band positions of NCS group of thiocarbonyl compounds in dependence on the bonding electrons of nitrogen atom of this group. The u.v. and n.m.r. spectra gave complete evidence of the structure of the synthesized products.

In the course of our previous works on synthesis, properties, and biological activity of 3,5-disubstituted tetrahydro-1,3,5-thiadiazine-2-thiones [1—5], we attempted to prepare further types of thiadiazines.

The studied thiadiazines were prepared by cyclization of thiocarbamoyl isothiocyanates with substituted aldimines. The thiocarbamoyl isothiocyanates were for the first time described by *Diveley* and *Davidson* [6, 7] and later by *Goerdeler* and *Lüdke* [8]. The appropriate secondary amine was treated with thiophosgene giving chlorides of thiocarbamide acids [9]. These were treated with potassium thiocyanate in a proper solvent to afford thiocarbamoyl isothiocyanates (Scheme 1).



Scheme 1

Simultaneously with the study of this problem, in 1970 *Goerdeler* and *Lüdke* [10] published their work dealing also with cyclization of thiocarbamoyl isothiocyanates with some aldimines. However, there have been no data till the present time in the literature on the complex study of spectral properties of the mentioned compounds, especially from the point of NCS group which is typical for them.

In the present work we turned attention to the preparation of 2,5,6-trisubstituted 5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones to bring more light to the physicochemical properties of thiocarbonyl heterocyclic compounds containing $=N-\underset{|}{C}=S$ group.

Experimental

N-Benzylidenemethylamine (*I*) (b.p. 67°C/11 torr), *N*-benzylideneethylamine (*II*) (b.p. 64°C/11 torr), *N*-(4-methoxybenzylidene)methylamine (*III*) (b.p. 130°C/18 torr), and *N*-(4-nitrobenzylidene)methylamine (*IV*) (m.p. 106°C) were prepared by condensation of the appropriate aldehydes with amines according to *Campbell* and *Sommers* [11].

Dimethylthiocarbamoyl chloride (*V*) (m.p. 43°C, b.p. 45°C/1 torr), diethylthiocarbamoyl chloride (*VI*) (m.p. 49°C, b.p. 43°C/1 torr), (3-oxapentamethylene)thiocarbamoyl chloride (*VII*) (m.p. 60°C), and pentamethylenethiocarbamoyl chloride (*VIII*) (m.p. 14°C, b.p. 33°C/1 torr) have been already described in the literature [9, 10].

Infrared spectra were taken with a double-beam UR-20 (Zeiss, Jena) spectrophotometer (calibrated with polystyrene foil) in the range of 800—3600 cm^{-1}. The spectra were measured in NaCl cells of 0.26 mm thickness, concentration in chloroform was 0.02 mol l^{-1}.

Ultraviolet spectra were taken on a Perkin—Elmer 402 recording spectrophotometer at 20 ± 2°C (concentration 4×10^{-5}—5×10^{-5} mol l^{-1}; 10-mm cells).

Nuclear magnetic resonance spectra were taken on a Tesla BS 487 A spectrometer in $CDCl_3$ at 80 MHz using hexamethyldisiloxane (HMDS) as internal standard.

The characterization and spectral data of the compounds *IX*—*XIX* and *V*—*VIII* are in Tables 1 and 2, respectively; n.m.r. data of the starting aldimines are in Table 3.

2,5,6-Trisubstituted 5,6-dihydro-4H-1,3,5-thiadiazine-4-thiones (IX—XIX)

The appropriate thiocarbamoyl chloride (*V*—*VIII*) (0.05 mole) was dissolved in the thoroughly dried acetone (50 ml). A suspension of dried (at 120°C) fine powdery potassium thiocyanate (4.9 g; 0.05 mole) in acetone (100 ml) was added to the cooled solution under stirring and excluding the air moisture. The temperature was allowed to rise moderately by heating on a water bath and kept at 40—45°C for 3 hours (in the case of derivatives *XIV*—*XVI* for 12 hours). In the course of reaction the content of the test-tube changed its colour from yellow to red while potassium chloride was formed. When the reaction was finished the solvent was distilled off and dry benzene (100 ml) was added to the residue.

Potassium chloride was filtered off and the appropriate aldimine (*I*—*IV*) (0.05 mole) dissolved in dry benzene (50 ml) was successively added to the solution of thiocarbamoyl isothiocyanate under stirring. The reaction proceeded under cooling (derivatives *XI*, *XIII*, *XV*, *XVI*, and *XIX*) or at room temperature (derivatives *IX*, *X*, *XII*, *XIV*, *XVII*, and *XVIII*). The reaction mixture was allowed to stay till crystallization of the product, which was filtered off and crystallized from the proper solvent.

Table 1

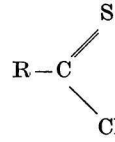
Characterization of the trisubstituted 2-R¹-5-R²-6-R³-5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones

Compound	R¹, R², R³	Formula	*M*	Calculated/found % N	Calculated/found % S	Yield [%]	M.p. [°C] chloroform–ether	$\tilde{\nu}$(C=N)	$\tilde{\nu}$ N–C=S	$\tilde{\nu}$ of the substituent	λ_{max} log ε	Chemical shift τ_{R3}	τ_{CH}	τ_{R2}	τ_{R1}
	Dimethylamino					55									
IX	Methyl	$C_{12}H_{11}N_4S_2O_2$	307.37	18.22	20.82	yellowish-	174–176	1565	1295	1570 (NO₂)	299	2.27	3.70	6.95	7.01
	4-Nitrophenyl			18.28	20.32	-red crystals				1350 (NO₂)	4.18				
	Diethylamino					97									
X	Methyl	$C_{15}H_{21}N_3S_2O$	323.45	12.91	19.72	white	132–134	1545	1302	1260 (O–CH₃)	304	3.11	4.30	6.47	6.68
	4-Methoxyphenyl			12.73	19.64	crystals					4.22	6.29			9.02
	Diethylamino					88									
XI	Ethyl	$C_{15}H_{21}N_3S_2$	307.46	13.63	20.80	white	155–156	1550	1310		307	2.80	4.25	6.24	6.72
	Phenyl			13.27	20.62	crystals					4.20			8.72	9.05
	Diethylamino					92									
XII	Methyl	$C_{14}H_{18}N_4S_2O_2$	338.42	16.54	18.91	light-yellow	154–156	1555	1295	1570 (NO₂)	300	2.20	4.03	6.31	6.43
	4-Nitrophenyl			16.69	18.93	crystals				1355 (NO₂)	4.31				8.43
	Diethylamino					93									
XIII[a]	Methyl	$C_{14}H_{19}N_3S_2$	293.43	14.31	21.81	white	159–160	1550	1300		306	2.73	4.22	6.28	6.64
	Phenyl			14.15	21.38	needles					4.22				9.09
	Morpholino					88				1530 (NO₂)					
XIV	Methyl	$C_{15}H_{16}N_4S_2O_3$	364.41	15.31	17.67	light-yellow	187–189	1535	1295	1350	300	2.38	3.71	6.35	6.40
	4-Nitrophenyl			15.42	17.70	crystals				1120 (C–O–C)	4.30				
	Morpholino					92									
XV	Methyl	$C_{15}H_{19}N_3S_2O_2$	351.45	15.94	18.21	white	156–158	1540	1300	1120 (C–O–C)	304	2.93	4.17	6.47	6.45
	4-Methoxyphenyl			15.92	18.26	crystals				1257 (O–CH₃)	4.28	6.22			
	Morpholino					69									
XVI	Methyl	$C_{14}H_{17}N_3S_2$	291.45	14.41	20.91	white	162–165	1540	1295	1112 (C–O–C)	306	2.72	4.14	6.38	6.52
	Phenyl			14.42	20.86	crystals					4.21				
	Piperidino					88									
XVII	Methyl	$C_{15}H_{18}N_4S_2O_2$	350.43	15.98	18.26	yellow	172–174	1540	1300	1535 (NO₂)	304	2.13	4.32	6.32	6.55
	4-Nitrophenyl			16.06	18.21	crystals				1360	4.33				8.48
	Piperidino					83									
XVIII	Methyl	$C_{16}H_{21}N_3S_2O$	335.49	12.54	19.03	white	146–148	1540	1300	1260 (O–CH₃)	300	3.02	4.22	6.41	7.20
	4-Methoxyphenyl			12.41	18.79	crystals					4.34	6.22			8.50
	Piperidino					71									
XIX	Methyl	$C_{15}H_{19}N_3S_2$	305.45	13.74	20.91	white	164–166	1545	1300		306	2.72	4.19	6.38	6.45
	Phenyl			13.65	20.47	crystals					4.26				8.53

a) The preparation is described in [10].

Table 2

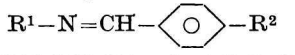
Characterization and spectral data of the substituted thiocarbamoyl chlorides



Compound	R	Yield [%]	M.p. [°C]	$\tilde{\nu}(\rangle\dot{N}-C=S)$ |	$\tilde{\nu}(C-Cl)$	λ_{max} [nm] log ε
V	Dimethylamino	70	43	1525	810	247 4.14
VI	Diethylamino	67	49	1510	830	250 4.17
VII	Morpholino	91	60	1500	830	253 4.01
VIII	Piperidino	80	14	1480	820	252 4.00

Table 3

Nuclear magnetic resonance spectral data of the synthesized aldimines



Compound	R^1	R^2	τ_{R^1}	τ_{CH}	τ_{R^2}
I	Methyl	H	6.54	1.8	
II	Ethyl	H	8.72 6.24	1.87	
III	Methyl	4-Methoxy	6.56	1.91	6.31
IV	Methyl	4-Nitro	6.45	1.78	

Results and discussion

The preparation of thiocarbamoyl isothiocyanates from thiocarbamoyl chlorides using silver or lead thiocyanate in a nonpolar organic solvent was not successful. The best yields were obtained in the reaction of thiocarbamoyl chloride with potassium thiocyanate in a polar solvent (acetone, acetonitrile). The reaction time was dependent on the polarity of solvent as well as on the structure of the carbon residue. Thiocarbamoyl chlorides of the cyclic secondary amines required longer reaction times than their dialkylamino analogs. So for instance the reaction time of the morpholino derivative (*VII*) was 12 hours, while that of the dimethyl- (*V*) and diethylamino derivative (*VI*), respectively was 2 hours.

The isolation of thiocarbamoyl isothiocyanates as pure compounds is very difficult and results in low yields [10]. Consequently, the mentioned compounds were not isolated but their benzene solutions (pure enough) were used for further cyclization. When preparing thiadiazinethiones with aldimines, it is advantageous to perform the reaction under cooling because at higher temperatures dimer might form, and consequently, lower yields are obtained. This dimer separates from the reaction medium as a brownish-red or dark brown oil. The possibility of dimerization of thiocarbamoyl isothiocyanates was observed by *Spurlock* and *Newallis* [12] (Scheme 1).

Thiadiazinethiones (*IX*—*XIX*) showed two significant bands in i.r. spectra typical for their skeleton. It was an intensive absorption band of the stretching vibrations ($\tilde{\nu}$(C=N)) in the range of 1550 cm^{-1} and an absorption band of medium intensity at 1300 cm^{-1} which belonged to the mixed copulation vibrations of atomic group ($\tilde{\nu}$(=N—C=S)) [13].

In contrast to thiadiazinethiones, the appropriate thiocarbamoyl chlorides (*V*—*VIII*) showed the respective absorption band at 1480—1525 cm^{-1} (Table 2). This band was significantly influenced by the character of the *N*-substituent.

The obtained results point to the possibility of generalizing the knowledge on spectral properties of thiocarbonyl compounds with the NCS group. Such types of compounds where the nitrogen atom was in sp^2 hybridization state (=N—C=S) showed an absorption band in the region of 1300 cm^{-1} (*e.g.* 2-thioxo-4-oxo-3,4-dihydro-2*H*-1,3-benzoxazines [14], 2,5,6-trisubstituted 5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thiones). Compounds with the nitrogen atom in the sp^3 hybridization state (=N—C=S, and —NH—C=S, respectively) could be identified by an intensive absorption band in the range of 1480—1530 cm^{-1} (*e.g.* monothiourethanes [14, 15], thiocarbamoyl chlorides).

The u.v. spectra of the studied compounds measured in the range of 220—400 nm were characterized by an intensive absorption band $\lambda \sim 300$ nm. Regarding the high intensity of the absorption maxima ($\log \varepsilon$ 4.3), it was possible to presume that an absorption combined with the $\pi \rightarrow \pi^*$ transition state of the chromophoric system present in the thiadiazine skeleton was involved (Scheme 1, Fig. 1).

Because the substituents on the secondary amino group practically did not differ in their polar properties, the shifts of absorption maxima in the u.v. region were not significant. If extreme electron acceptor substituents were in the 6 position (for example

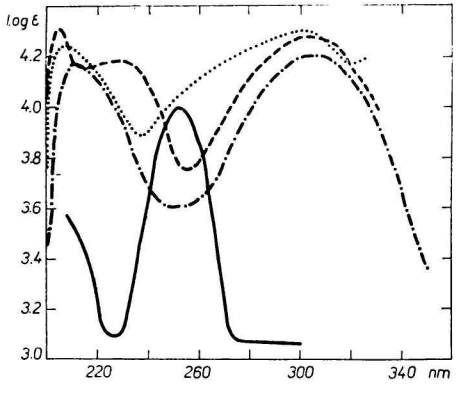


Fig. 1. Ultraviolet absorption spectra.
——— 2-morpholino-5-methyl-6-phenyl-5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thione (*XVI*);
– – – – 2-morpholino-5-methyl-6-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thione (*XV*);
2-morpholino-5-methyl-6-(4-nitrophenyl)-5,6-dihydro-4*H*-1,3,5-thiadiazine-4-thione (*XIV*);
–.–.–.– (3-oxapentamethylene)thiocarbamoyl chloride (*VII*).

4-nitrophenyl), a slight hypsochromic shift to lower wavenumbers was observable. This might be due to low basicity of the nitrogen atom in the azomethine group which interfered with the mesomeric conjugation of the chromophoric system by a $-I$ effect (Fig. 1, Table 1). For comparison, there is in Fig. 1 the u.v. spectrum of thiocarbamoyl chloride where the chlorine atom influenced the chromophoric system by a strong $-I$ as well as $+M$ effect tended against the original conjugation. Consequently, the thiocarbamoyl chlorides absorbed at much lower wavenumbers than their cyclic derivatives ($\lambda_{max} \sim 250$ nm, $\log \varepsilon \sim 4$; Table 2).

The cyclization reactions of thiocarbamoyl isothiocyanates with aldimines could be demonstratively followed by n.m.r. spectra. *N*-Alkylaldimines due to spin-spin interaction through π electrons of double bond were characterized by the secondary splitting of the resonance signal of the tertiary hydrogen as well as of the alkyl groups (so-called long-range coupling). In the case of benzylidenemethylamine and its substituted aryl derivatives, a doublet of methyl group in the region of τ 6.5 and a quartet of the tertiary hydrogen at τ 1.8—1.9 appeared in the spectra. The adduct formed after cyclization due to the interrupted conjugation between the nitrogen atom and the tertiary CH group did not show the splitting of the mentioned resonance signals on the n.m.r. spectrum. The tertiary protons of CH of the cyclization products in the thiadiazine skeleton were shifted to higher values due to the lowered deshielding ability of the nitrogen atom bound to CH group by a single bond (Table 3).

The n.m.r. spectra of 2-diethylamino derivatives (*X*—*XIII*) showed a triplet and a quartet proving the presence of C_2H_5 group. The piperidine compounds (*XVII*—*XIX*) showed a broad resonance band of the methylene groups at τ 8.5. At cyclization products with the morpholino residue (*XIV*—*XVI*), this resonance band of the methylene groups was shifted to lower τ values because of the $-I$ effect of the oxygen atom.

Acknowledgements. The elemental analyses were accomplished at the Department of Organic Chemistry, Faculty of Natural Sciences, Komenský University, Bratislava. We thank Mrs V Hain, Mr A. Dorčák, and Mr A. Burger for taking the u.v., and n.m.r. spectra.

References

1. Bernát, J. and Kristian, P., *Collect. Czech. Chem. Commun.* ***33***, 4283 (1968).
2. Bernát, J., Uher, M., and Kristian, P., *Chem. Zvesti* ***23***, 365 (1969).
3. Kristian, P. and Bernát, J., *Collect. Czech. Chem. Commun.* ***34***, 2952 (1969).
4. Kristian, P., Antoš, K., Drobnica, Ľ., Nemec, P., and Bernát, J., *Czechoslov. Patent* 138 082 (1970).
   Kristian, P., Antoš, K., Drobnica, Ľ., Nemec, P., and Bernát, J., *Czechoslov. Patent* 138 083 (1970).
6. Diveley, W. R., *US Patent* 3 166 564 (1965); *Chem. Abstr.* ***62***, 9145*f* (1965).
7. Davidson, J. S., *J. Chem. Soc.* (London) ***1966***, 2069.
8. Goerdeler, J. and Lüdke, H., *Tetrahedron Lett.* ***20***, 2455 (1968).
9. von Braun, J. and Stechele, F., *Ber.* ***36***, 2274 (1903).
10. Goerdeler, J. and Lüdke, H., *Chem. Ber.* ***103***, 3393 (1970).
11. Campbell, B. K., Campbell, K. W., and Sommers, A. H., *J. Amer. Chem. Soc.* ***66***, 82 (1944).
12. Spurlock, L. A. and Newallis, P. E., *J. Org. Chem.* ***33***, 2073 (1968).
13. Rao, C. N. R. and Venkataraghavan, R., *Spectrochim. Acta* ***18***, 541 (1962).
14. Novotná, M., Kristian, P., and Bernát, J., *Chem. Zvesti* ***26***, 543 (1972).
15. Brutovská, A. and Kristian, P., *Chem. Zvesti* ***23***, 736 (1969).

Translated by A. Kardošová