Reactions of 2-chloronicotinoyl isothiocyanate and 2,6-dimethyl-4-chloronicotinoyl isothiocyanate with thiols and sodium hydrogen sulfide

D. KOŠČIK and P. KRISTIAN

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

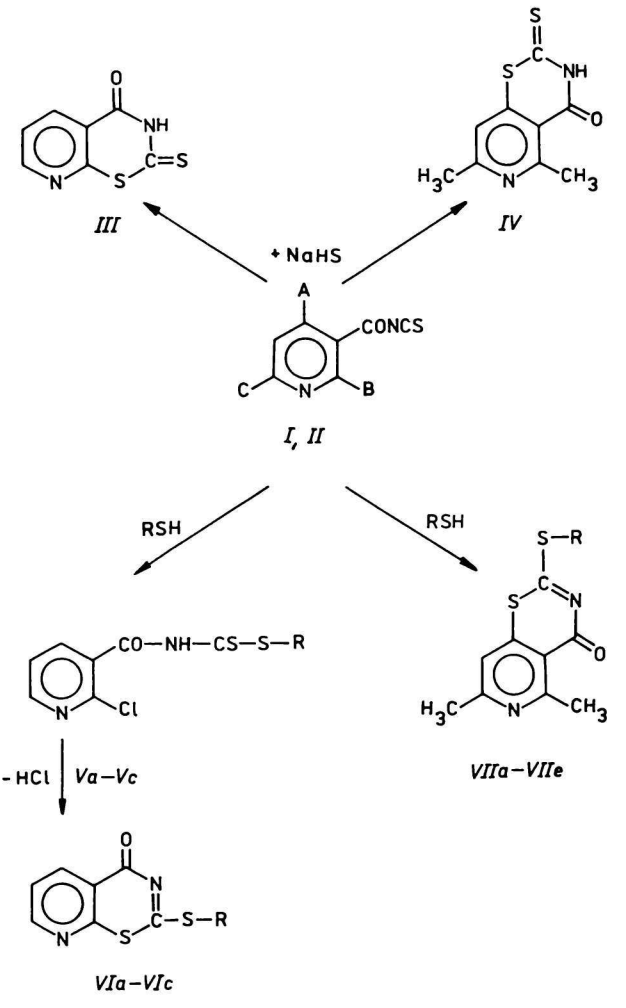
Received 4 November 1982

The reactions of 2-chloronicotinoyl and 2,6-dimethyl-4-chloronicotinoyl isothiocyanates with thiols affording the corresponding 2-alkyl(aryl)thio--4-oxopyridothiazines were studied. In the reaction of 2-chloronicotinoyl isothiocyanate it was possible to isolate also the corresponding dithiocarbamates as intermediates. Halonicotinoyl isothiocyanates reacted similarly with sodium hydrogen sulfide under the formation of 2-thio-4-oxopyridothiazines. The structures of the synthesized compounds were proved by their i.r., u.v., ^{1}H-n.m.r., ^{13}C-n.m.r., and mass spectra.

Изучены реакции 2-хлорникотиноил- и 2,6-диметил-4-хлорникотиноилизотиоцианатов с тиолами, приводящие к соответствующим 2-алкил(арил)тио-4-оксопиридотиазинам. При реакции 2-хлорникотиноилизотиоцианата было возможно выделить в качестве промежуточных соединений и соответствующие дитиоуретаны. Аналогично реагируют галогенникотиноилизотиоцианаты с кислым сульфидом натрия с образованием 2-тио-4-оксопиридотиазинов. Структура синтезированных соединений была подтверждена изучением их ИК, УФ, ^{1}H-ЯМР, ^{13}C-ЯМР и масс-спектров.

In our previous works [1, 2] we paid attention to synthesis of pyrido[3,2-*e*]-(1,3)thiazine and pyrido[3,4-*e*](1,3)thiazine skeletons by the reaction of the appropriate halonicotinoyl isothiocyanates with aliphatic and aromatic amines. Similar skeletons have been prepared by *Zawissa et al.* [3] and *Kuebel et al.* [4] by condensation of ethyl 2-chloronicotinate with different substituted thioureas. In the present work we have studied the reactions of 2-chloronicotinoyl isothiocyanate *I* and 2,6-dimethyl-4-chloronicotinoyl isothiocyanate *II* with sodium hydrogen sulfide as well as with alkane- and arenethiols.

Isothiocyanates *I* and *II*, obtainable only in a crude state [1, 2], gave with sodium hydrogen sulfide unstable dithiocarbamates readily cyclizing to the corresponding

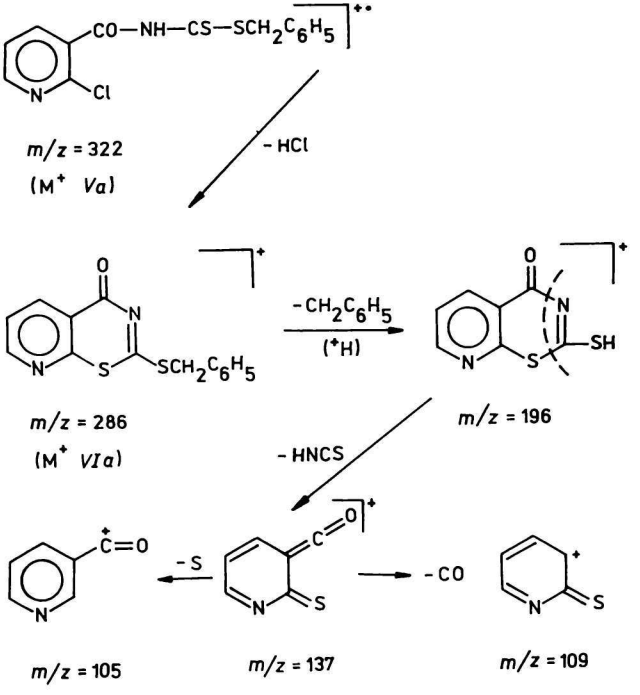


Scheme 1

R	*a* $C_6H_5CH_2$	*b* C_6H_5	*c* p-ClC_6H_4	*d* C_3H_7	*e* i-C_3H_7
		A	B	C	
	I	H	Cl	H	
	II	Cl	CH_3	CH_3	

2-thio-4-oxopyridothiazines *III* and *IV* (Scheme 1). 2-Chloronicotinoyl isothiocyanate reacted with phenylmethanethiol,thiophenol, and 4-chlorothiophenol under the formation of oily dithiocarbamates *Va—Vc* which after staying for several days became solid and could be crystallized. Dithiocarbamates *V* under reflux in alcohol or toluene in the presence of triethylamine or pyridine afforded the corresponding cyclic 2-substituted 4-oxopyrido[3,2-*e*](1,3)thiazines *VIa—VIc*. Under similar conditions from isothiocyanate *II* 2-substituted 5,7-dimethyl-4--oxopyrido[3,4-*e*](1,3)thiazines *VIIa—VIIe* were formed directly. The synthesized coloured compounds (Table 1) are well soluble in polar solvents.

Infrared spectra of dithiocarbamates *Va—Vc* revealed strong absorption bands $\tilde{\nu}$(C=O) in the region of 1685—1688 cm^{-1} and $\tilde{\nu}$(NH—C=S) at 1456—1463 cm^{-1}. In the cyclization products *VIa—VIc* and *VIIa—VIIe* a moderate shift of the band $\tilde{\nu}$(C=O) to lower wavenumbers 1660—1670 cm^{-1} was observed as expected and a new band belonging to exocyclic C=N bond appeared at $\tilde{\nu}$ = 1570 cm^{-1} (Table 1). In the ^{1}H-n.m.r. spectra of the prepared dithiocarbamates *V* and their cyclic products resonance signals of hydrogens of the pyridine ring as well as of the protons of substituents of alkane- and arenethiol groups (Table 1) were observed. The u.v. spectra of the synthesized pyridothiazines *VI*



Scheme 2

Table 1

Physicochemical and spectral properties of the prepared compounds *III*—*VII*

Compound	Formula M_r	M.p./°C Solvent	Yield %	w_i (calc.)/w_i (found) % C	% H	% N	IR $\tilde{\nu}$(CO)/cm^{-1} $\tilde{\nu}$(CN)/cm^{-1}	^{1}H-NMR[a] (δ_i/ppm)[d] H_α—H_γ H_β	 $CH_3\alpha$ $CH_3\alpha'$	R	UV[c] λ_{max} nm^{-1} log {ε}
III	$C_7H_4N_2OS_2$	250—251	47	42.84	2.05	14.27	1710	8.73—8.50	—	—	217/4.19
	196.3	acetone—water		42.75	2.07	14.11	—	7.47			
IV	$C_9H_8N_2OS_2$	228	40	48.19	3.59	12.49	1698	—	2.55	—	230/4.16
	224.3	acetone—water		48.11	3.60	12.23	—	7.26	2.96		
Va[b]	$C_{14}H_{11}ClN_2OS_2$	141	38	52.09	3.43	8.68	1687	8.66—7.99	—	4.6 (CH_2)	238/4.31
	322.8	acetone—water		52.10	3.51	8.77	—	7.55		7.7—7.5 (arom)	
Vb	$C_{13}H_9ClN_2OS_2$	132	43	50.56	2.94	9.07	1688	8.5—8.1	—	7.8—7.6 (arom)	258/4.17
	308.8	acetone—water		50.66	2.99	9.04	—	7.46			
Vc	$C_{13}H_8Cl_2N_2OS_2$	161	46	45.50	2.35	8.16	1685	8.6—7.9	—	7.6—7.5 (arom)	244/4.21
	343.3	acetone—water		45.61	2.41	8.20	—	7.37			
VIa[c]	$C_{14}H_{10}N_2OS_2$	164	42	58.72	3.52	9.78	1650	8.5—8.0	—	4.57 (CH_2)	280/4.23
	286.4	methanol—water		58.61	3.51	9.62	1575	7.60		7.6—7.5 (arom)	
VIb	$C_{13}H_8N_2OS_2$	170	46	57.33	2.96	10.28	1660	8.5—8.1	—	7.7—7.5 (arom)	226/4.16
	272.4	methanol—water		57.11	2.99	10.46	1577	7.65			
VIc	$C_{13}H_7ClN_2OS_2$	201	48	50.90	2.29	9.13	1660	8.6—8.1	—	7.5—7.4 (arom)	220/4.11
	306.8	methanol—water		50.72	2.40	9.21	1570	7.46			
VIIa	$C_{16}H_{14}N_2OS_2$	145	53	61.12	4.49	8.91	1670	—	2.56	4.56 (CH_2)	247/4.13
	314.4	$CHCl_3$—petroleum ether		61.08	4.56	9.00	1570	6.94	2.95	7.9—7.7 (arom)	
VIIb	$C_{15}H_{12}N_2OS_2$	152	47	59.98	4.03	9.33	1666	—	2.50	7.7—7.5 (arom)	222/4.08
	300.4	$CHCl_3$—petroleum ether		59.86	4.03	9.48	1570	6.84	2.92		
VIIc	$C_{15}H_{11}ClN_2OS_2$	216	51	53.80	3.31	8.37	1680	—	2.50	7.7—7.6 (arom)	225/4.14
	334.9	$CHCl_3$—petroleum ether		53.91	3.29	8.39	1570	6.99	2.90		

Compound	Formula M_r	M.p./°C Solvent	Yield %	w_i (calc.)/w_i (found) % C	% H	% N	IR $\tilde{\nu}$ (CO)/cm^{-1} $\tilde{\nu}$ (CN)/cm^{-1}	^{1}H-NMR[a] (δ_r/ppm)[d] H_α—H_γ H_β	$CH_3\alpha$ $CH_3\alpha'$	R	UV[e] λ_{max} nm^{-1} log {ε}
VIId	$C_{12}H_{14}N_2OS_2$	212—213	56	54.13	5.25	10.51	1663	—	2.57	1.06 (CH_3)	230/4.11
	266.2	$CHCl_3$—petroleum ether		54.18	5.28	10.58	1570	7.12	3.02	2.0—1.7	
VIIe	$C_{12}H_{14}N_2OS_2$	203—205	49	54.11	5.29	10.51	1663	—	2.57	3.5—3.3 (CH_2)$_2$ 1.47 (CH_3)$_2$	229/5.13
	266.4	$CHCl_3$—petroleum ether		54.20	5.31	10.43	1570	7.10	3.00	1.56 (CH)	

a) Solvent $CDCl_3$ + DMSO-d_6; *b*) mass spectrum (*m/z* (% rel. int.)): 322 (26); 286 (100); 196 (90); 137 (64); 109 (51); 105 (43); 91 (24); 77 (48); *c*) mass spectrum (*m/z* (% rel. int.)): 286 (100); 196 (93); 137 (71); 109 (51); 105 (47); *d*) relative chemical shifts of hydrogen protons of the substituent; *e*) [ε] = dm^3 mol^{-1} cm^{-1}.

and *VII* revealed the characteristic absorption bands at $\lambda = 220$—230 nm. The only exceptions were the benzyl derivatives (*VIa*, *VIIa*) which absorbed at higher values. With the product *III* also the ^{13}C-n.m.r. spectrum was measured and the resonance signals were assigned to the appropriate carbon atoms by the "off resonance" method. The structure of the dithiocarbamate *Va* as well as the cyclic product *VIa* was proved also by mass spectra which were in agreement with general knowledge on fragmentation of pyridothiazine skeletons obtained thus far [1, 5]. While in the spectrum of pyridothiazine *VIa* the molecular ion M^+ ($m/z = 286$) was most intensive, with the corresponding dithiocarbamate *Va* the intensity of the molecular peak M^+ ($m/z = 322$) was very low. During measurement this compound cyclized to the corresponding heterocycle *VIa* on splitting off hydrogen chloride and the fragmentation ion M^+-HCl represented the base peak in the spectrum (Scheme 2).

Experimental

2-Chloronicotinoyl isothiocyanate (*I*) and 2,6-dimethyl-4-chloronicotinoyl isothiocyanate (*II*) were prepared from the corresponding chlorides and ammonium isothiocyanate in acetone [1, 2].

The i.r. spectra were measured in chloroform on a Specord 75 IR (Zeiss, Jena) apparatus in the range of $\tilde{\nu} = 400$—4000 cm^{-1}. The u.v. spectra of compounds ($c = 10^{-4}$—10^{-5} mol dm^{-3} in methanol) were taken on a Perkin—Elmer 402 spectrophotometer in 1 cm cells. The ^{1}H-n.m.r. spectra were measured on a Tesla BS 497 spectrometer at 80 MHz and the ^{13}C-n.m.r. spectra on a Tesla BS 567 A spectrometer at 100 MHz in the mixture of chloroform—dimethyl sulfoxide-d_6 (internal standard TMS). Mass spectra were taken on an MS-902 (AEI, Manchester) apparatus at 70 eV and 120 °C of the ionization chamber.

2-Thio-4-oxopyrido[3,2-e](1,3)thiazine III and 2-thio-5,7-dimethyl-4-oxopyrido[3,4-e](1,3)thiazine IV

Sodium hydrogen sulfide, prepared by introducing hydrogen sulfide (13.5 mmol) into the solution of sodium hydroxide (13.5 mmol) in methanol (25 cm^3), was added to the acetone solution of isothiocyanate *I* and *II*, respectively, prepared from the corresponding chloride (10 mmol). The formed oily compound became gradually solid. The crude product was filtered off, washed with water, dried, purified by charcoal, and recrystallized from a suitable solvent (Table 1). ^{13}C-N.m.r. spectrum of *III*: $\delta_r(C=O) = 161.1$ ppm; $\delta_r(C=S) = 193.3$ ppm.

S-Aryl-2-chloronicotinoyldithiocarbamates Va—Vc

Isothiocyanate *I*, prepared from the corresponding chloride (10 mmol), was dissolved in acetone (10 cm^3) and added into the solution of arenethiol (10 mmol) in acetone (10 cm^3). The mixture was allowed to stay at room temperature for 2 days. The precipitated dithiocarbamate was filtered off and the supernatant was slowly poured into cold water (150 cm^3) under stirring giving another portion of dithiocarbamate. The combined products were dissolved in acetone, purified by charcoal, and crystallized from a suitable solvent (Table 1).

2-Arylthio-4-oxopyrido[3,2-e](1,3)thiazines VIa—VIc

Dithiocarbamate *Va—Vc* (5 mmol) was refluxed in toluene (30 cm^3) and triethylamine (1 cm^3) for 5 h. After cooling the precipitate was filtered off, washed with water, and crystallized from a suitable solvent (Table 1).

2-Alkyl(aryl)thio-5,7-dimethyl-4-oxopyrido[3,4-e](1,3)thiazines VIIa—VIIe

Alkane(arene)thiol (8 mmol) was dissolved in dry acetone (15 cm^3) and poured with stirring into the solution of isothiocyanate *II*, prepared from chloride (10 mmol). Then triethylamine (1 cm^3) was added and stirring was continued for 6 h. The reaction mixture was poured into cold water and the formed precipitate was filtered off and crystallized from a suitable solvent (Table 1).

Acknowledgements. We thank Ing. J. Leško, CSc. (Laboratory of Mass Spectrometry, Slovak Technical University, Bratislava) for measuring the mass spectra.

References

1. Koščik, D., Kristian, P., Gonda, J., and Dandárová, M., *Collect. Czech. Chem. Commun.*, in press.
2. Koščik, D., Kristian, P., and Forgáč, O., *Collect. Czech. Chem. Commun. 48*, 3426 (1983).
3. Zawissa, T., Malinka, W., and Jakobiec, T., *Pol. J. Chem. 54*, 1875 (1980).
4. Kuebel, B. and Rehling, H., *Justus Liebigs Ann. Chem. 9*, 1402 (1980).
5. Schroth, W., Herrman, S., Feustel, C., Schmidt, S., and Jamil, K., *Pharmazie 32*, H. 8/9 (1977).

Translated by A. Kardošová