N-Substituted pyridinethiocarboxamides and related compounds as potential antituberculotics

[a]J. MOLLIN, [a]K. POLÁŠKOVÁ, and [b]Ž. ODLEROVÁ

[a]*Department of Inorganic and Physical Chemistry, Faculty of Natural Sciences, Palacký University, CS-771 46 Olomouc*

[b]*Research Institute of Preventive Medicine, CS-833 01 Bratislava*

Received 14 July 1987

Pyridine- and pyrazinethiocarboxamides have been acylated with acid anhydrides and added to isocyanates and isothiocyanates. Antimycobacterial activity of the reaction products has been followed. The influence of substituents on antimycobacterial activity of the compounds tested herein has been compared to the analogous dependence obtained with thiobenzamide derivatives.

С помощью ангидридов карбоновых кислот проведено ацилирование пиридин- и пиразинтиокарбоксамидов, и полученные продукты смешаны с изоцианатами и изотиоцианатами. Исследована антимикобактериальная активность продуктов этой реакции. Влияние заместителей на антимикобактериальную активность в изучаемых соединениях сопоставляется с влиянием заместителей, наблюдаемым в ряду производных тиобензамида.

Substitution on nitrogen of the functional group of thiocarboxamides influences their antimycobacterial activity. The substituent effect is reflected in change of electron density on the functional group and in change of lipophility of the whole molecule. Those substituents which increase the electron density of the functional group and practically do not change lipophility bring about a decrease in antimycobacterial activity. The substituents withdrawing electrons from the functional group at practically constant lipophility, increase the antimycobacterial activity [1, 2]. The substituent may affect the antimycobacterial activity of thiocarboxamides also by changing their lyophility and lipophility [2]. These conclusions were derived from experiments where acylation and nucleophilic addition of thiocarboxamides to isothiocyanates increased their antimycobacterial activity and addition to isocyanates had ambiguous effect [2]. Significant raise in antimycobacterial activity of thiobenzamides, brought about by substitution, prompted us to widen the experiments to pyridine- and pyrazinethiocarboxamides, since some of them have also practical use.

Table 1

Analyses of the prepared compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				M.p./°C	Solvent[a]
			C	H	Cl	N		
V	$C_{13}H_{10}N_2S$	226.28	69.00	4.45	—	12.38	78—79	Ethanol
			68.72	4.55	—	12.64		
VI	$C_9H_{10}N_2OS$	194.22	55.65	5.18	—	14.42	157—158	Ethanol
			55.07	4.87	—	14.70		
VII	$C_8H_9N_3S_2$	211.26	45.48	4.29	—	19.88	150—152	DMSO, $CHCl_3$
			45.34	4.24	—	20.50		
VIII	$C_{13}H_{11}N_3S_2$	257.27	60.68	4.31	—	16.32	245	DMSO, $CHCl_3$
			60.77	3.80	—	16.21		
IX	$C_{13}H_{10}ClN_3OS$	291.67	53.71	3.12	12.19	14.45	195—197	DMSO, $CHCl_3$
			53.62	3.28	12.20	14.58		
X	$C_{13}H_{10}ClN_3OS$	291.67	53.71	3.12	12.19	14.45	194—196	DMSO, $CHCl_3$
			53.95	3.28	12.12	14.76		
XI	$C_{15}H_{14}ClN_3OS$	319.76	56.34	4.41	11.09	13.13	129—131	DMSO
			56.27	4.20	11.30	13.33		

Table 1 (Continued)

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				M.p./°C	Solvent[a]
			C	H	Cl	N		
XII	$C_{15}H_{14}ClN_3OS$	319.76	56.34	4.41	11.09	13.13	148–151	DMSO
			56.39	4.24	11.26	13.06		
XIII	$C_8H_9N_3S_2$	211.26	45.48	4.29	—	19.88	146–147	DMSO, $CHCl_3$
			44.61	4.00		20.55		
XIV	$C_{13}H_{10}ClN_3OS$	291.67	53.71	3.12	12.19	14.45	193–194	DMSO, $CHCl_3$
			53.85	3.32	12.13	14.39		
XV	$C_{13}H_{10}ClN_3OS$	291.67	53.71	3.12	12.19	14.45	240–241	DMSO, $CHCl_3$
			54.37	3.19	12.14	14.47		
XVI	$C_7H_8N_4S_2$	212.25	39.61	3.80		26.38	137–139	Ethanol
			39.99	3.53		26.10		
XVII	$C_{12}H_9ClN_4OS$	292.69	49.24	3.09	12.11	19.13	178–179	Ethanol
			49.69	2.87	11.68	19.32		
XVIII	$C_{12}H_9ClN_4OS$	292.69	49.24	3.09	12.11	19.13	207–209	$CHCl_3$
			49.21	3.01	11.40	19.17		

a) In recrystallization of some compounds it was advantageous to alternate the solvents dimethyl sulfoxide with chloroform.

Experimental

2-Ethylthioisonicotinamide (Léčiva, Prague), isonicotinonitrile (Merck), pyrazinecarboxamide (Merck), 3- and 4-chlorophenyl isocyanates (Merck), methyl (Fluka) and phenyl (Lachema, Brno) isothiocyanates were commercial preparations, pure grade.

N-Benzylnicotinamide [3], thioisonicotinamide (*I*) [4], and thionicotinamide (*II*) [5] were prepared according to the respective literature. Pyrazinethiocarboxamide (*III*), *N*-benzylthiobenzamide (*IV*), and *N*-benzylthionicotinamide (*V*) were prepared by general method [6]. *N*-Propionylthionicotinamide (*VI*) was prepared by propionylation of (*II*) [7]. By addition of thiocarboxamides to isocyanates and isothiocyanates, respectively, [2, 8] the following compounds were prepared: *N*-(*N*-methylthiocarbamoyl)thioisonicotinamide (*VII*), *N*-(*N*-phenylthiocarbamoyl)thioisonicotinamide (*VIII*), *N*-[*N*-(3-chlorophenyl)carbamoyl]thioisonicotinamide (*IX*), *N*-[*N*-(4-chlorophenyl)carbamoyl]thioisonicotinamide (*X*), *N*-[*N*-(3-chlorophenyl)carbamoyl]-2-ethylthioisonicotinamide (*XI*), *N*-[*N*-(4-chlorophenyl)carbamoyl]-2-ethylthioisonicotinamide (*XII*), *N*-(*N*-methylthiocarbamoyl)thionicotinamide (*XIII*), *N*-[*N*-(3-chlorophenyl)carbamoyl]-thionicotinamide (*XIV*), *N*-[*N*-(4-chlorophenyl)carbamoyl]thionicotinamide (*XV*), *N*-(*N*-methylthiocarbamoyl)pyrazinethiocarboxamide (*XVI*), *N*-[*N*-(3-chlorophenyl)-carbamoyl]pyrazinethiocarboxamide (*XVII*), and *N*-[*N*-(4-chlorophenyl)carbamoyl]pyrazinethiocarboxamide (*XVIII*).

IR spectra were measured on a Specord IR-75 spectrometer in dichloromethane in KBr cells of 0.63 mm thickness. All compounds prepared were tested on selected mycobacterial strains by the method described earlier [9, 10].

Results and discussion

The results of analyses and melting points of compounds *I* to *IV* were consistent with the literature data [4, 5, 11, 12], those of the compounds prepared herein are presented in Table 1. Though the literature [2, 13] brings general descriptions of syntheses and properties of *N*-acylthiocarboxamides, we succeeded only in preparation of compound *VI* in pure state. The other crude products, formed on acetylation, propionylation, and butyrylation of primary thiocarboxamides, on recrystallization from aqueous alcohol changed colour from red, characteristic of *N*-acylthiocarboxamides, to yellow, characteristic of primary thiocarboxamides. Recrystallization of the crude product obtained on acylation yielded in most cases the original thiocarboxamide, as indicated by the results of analyses and melting points. It appears, therefore, that *N*-acylpyridinethiocarboxamides and *N*-acylpyrazinethiocarboxamides hydrolyze rapidly and consequently, they are unsuitable for prospective pharmacological use. Additions of thiocarboxamides to isocyanates and isothiocyanates were carried out similarly as in the case of thiobenzamides [2] and led to compounds of the following type

$$R—C(S)—NH—C(X)—NH—R', \text{ where } X = O, S$$

In their purification it was advantageous to alternate solvents, namely dimethyl sulfoxide with chloroform.

The antimycobacterial activities of compounds, expressed by minimal inhibition concentration (MIC), are presented in Table 2. Comparison of the values for *II* and *V* shows that substitution on nitrogen of the functional group with benzyl brought about a drop of MIC. This effect was observed earlier [1] and the validity of this recognition appears to be general. The addition products of thiocarboxamides to methyl isothiocyanate have MIC also lower than the primary thiocarboxamide, as follows from comparison of *I* with *VII*, *II* with *XIII*, and *III* with *XVI*. The same conclusions were arrived at with thiobenzamides [2]. The MIC values of addition products of thiocarboxamides and isocyanates did not change unambiguously when compared to that of the basic thiocarboxamide. Similar result was found also in the previous communication [2], where addition of thioacetamide, well soluble in water, to phenyl isocyanate increased the antimycobacterial activity of the reaction product in comparison with that of thioacetamide. Addition of the less water-soluble thiobenzamide to phenyl isocyanate brought about a decrease in antimycobacterial activity of the reaction product against the activity of thiobenzamide. Experimental data for quantitative interpretation of this phenomenon are still missing.

Comparison of the MIC values in Table 2 reveals that the compounds *XI* and *XII* are the most interesting ones of the whole series, since their antimycobac-

Table 2

Antimycobacterial efficacy of the compounds

Compound	MIC · 10^4/(mol dm^{-3}) Against *Mycobacterium*		Compound	MIC · 10^4/(mol dm^{-3}) Against *Mycobacterium*	
	tuberculosis $H_{37}R_v$	*Kansassii* PKG 8		*tuberculosis* $H_{37}R_v$	*Kansassii* PKG 8
I	3.3	3.3	*XI*	0.12	1.1
II	10	> 10	*XII*	0.12	1.1
III	> 10	> 10	*XIII*	0.37	3.3
IV	3.3	3.3	*XIV*	1.1	> 10
V	3.3	10	*XV*	1.1	> 10
VI	3.3	10	*XVI*	0.37	1.1
VII	0.37	1.1	*XVII*	0.37	10
VIII	1.1	3.3	*XVIII*	1.1	> 10
IX	1.1	3.3	EA[a]	0.12	1.1
X	1.1	3.3	INH[b]	0.04	3.3

a) Ethionamide; *b*) isonicotinohydrazide.

terial activity is equal to that of the clinically used Ethionamide (*i.e.* 2-ethylthioisonicotinamide). Therefore, it appeared useful to measure their IR spectra, together with those of other *N*-(chlorophenylcarbamoyl)thioamides.

The IR spectra of all compounds studied revealed in the region of $\tilde{\nu} = 3350\,\mathrm{cm}^{-1}$ wide bands attributed to stretching vibrations of the N—H group involved in hydrogen bondings. The stretching vibrations of carbonyl group with the compounds *IX—XI*, *XIV*, and *XV* were observed at $\tilde{\nu} = 1720\,\mathrm{cm}^{-1}$, with the compounds *XII*, *XVII*, and *XVIII* at $\tilde{\nu} = 1710\,\mathrm{cm}^{-1}$. The vibrations belonging to C=C bond of the aromatic ring were observed in the region of about $\tilde{\nu} = 1600\,\mathrm{cm}^{-1}$. It appears, therefore, that polarization of linkages is in all *N*-(chlorophenylcarbamoyl) derivatives practically the same and the differences in MIC in this group of compounds are probably due to their different lipophility.

The possible practical application, together with adaptability of mycobacteria, led to continuous search for new compounds with high biological activity (see *e.g.* [14, 15]). Of thiocarboxamides mostly the primary thiocarboxamides with different basic skeleton have been studied [16]. On the basis of the results obtained herein, consistent with those published previously [1, 2], it appears that substitution of thiocarboxamides on the functional group brings about quantitative changes of MIC and thus, opens up a way to syntheses of new compounds with high antimycobacterial activity.

References

1. Mollin, J., Paukertová, H., and Odlerová, Ž., *Chem. Zvesti 38*, 629 (1984).
2. Mollin, J., Polášková, K., Odlerová, Ž., and Bekárek, V., *Collect. Czechoslov. Chem. Commun. 52*, 2087 (1987).
3. Vejdělek, Z. J., Trčka, V., and Protiva, M., *Chem. Listy 46*, 423 (1952).
4. Gardner, T. S. and Lee, J., *J. Org. Chem. 19*, 753 (1954).
5. Fairfull, A. E. S., Lowe, J. L., and Peak, D. A., *J. Chem. Soc. 1952*, 742.
6. Pravdić, N. and Hahn, V., *Croat. Chem. Acta 37*, 55 (1965).
7. Goerdeler, J. and Horstmann, H., *Chem. Ber. 93*, 663 (1960).
8. Hartmann, A., Uhlemann, E., Walter, M., and Hoyer, E., *Z. Chem. 21*, 271 (1981).
9. Odlerová, Ž., Medvecký, R., and Hammelová, E., *Studia Pneumol. Phtiseol. Czechoslov. 36*, 507 (1976).
10. Mollin, J., Odlerová, Ž., and Waisser, K., *Pharmazie 41*, 497 (1986).
11. Kuschner, S. and Williams, J., *J. Am. Chem. Soc. 74*, 3617 (1952).
12. Levi, T., *Gazz. Chim. Ital. 59*, 549 (1929).
13. Walter, W. and Voss, J., in *The Chemistry of Amides*. (Zabicky, J., Editor.) P. 445. Interscience, London, 1970.
14. Bukowski, L., *Pol. J. Pharmacol. Pharm. 38*, 91 (1986).
15. Bukowski, L., *Pol. J. Pharmacol. Pharm. 36*, 683 (1984).
16. Milczarska, B., Wrzesniowska, K., and Janowiec, M., *Pol. J. Pharmacol. Pharm. 33*, 217 (1981).

Translated by A. Kardošová