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Syntheses of Some *N*-Substituted Thiocarbamylpiperidines and Thiocarbamylmorpholines

M. Tišler

Institute of Organic Chemistry, University of Ljubljana, Slovenia, Yugoslavia

Received May 16, 1957

Syntheses of some *N*-substituted thiocarbamylpiperidines (I—VIII) and thiocarbamylmorpholines (IX—XVIII) from piperidine or morpholine and the corresponding isothiocyanates are described. The substances were tested for their tuberculostatic activity.

Pursuing our work on synthetic tuberculostatics and related compounds[19, 20, 21] we have synthesized some *N*-substituted thiocarbamylpiperidines and thiocarbamylmorpholines, which were tested for their tuberculostatic activity.

It is known that thiourea exhibits a week tuberculostatic activity and there are known many substituted thioreas with tuberculostatic activity of different degree. Some of them were also active when tested against human leprosy[2] and influenza-virus infections in mice[3]. Thiourea is incorporated also in thiosemicarbazones and this fact prompted extensive research of many related compounds.

Investigations of Mantegazza and coworkers[15] who synthesized and tested many *N*-arylthioureas, and of other authors disclosed that *N,N'*-disubstituted thioureas do not give satisfactory results in the treatment of experimental tuberculosis[4, 6, 7, 12, 14, 16]. Subsequently some thiourea derivatives of sulphanilamides and aromatic amino acids were synthesized and tested[11].

On the other side, Barry and Twomey[1] have established that some piperidine derivatives of long chain fatty acids exhibited good tuberculostatic activity *in vitro*. These findings incited the preparation of new piperidine and morpholine derivatives with incorporation of thiourea group. Some of the above mentioned compounds are already known in the literature and we have prepared some new compounds from piperidine and morpholine and the corresponding isothiocyanates in ethereal solution. The advantage of this method is that the formed derivatives are of low solubility in ether.

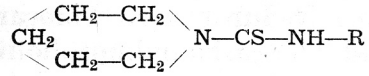
Substances, which are presented in Tables I and II exhibit no appreciable tuberculostatic activity, which was measured *in vitro* on the liquid culture medium Sula[18] with the strain of *Mycobacterium tuberculosis* H 37Rv. Only *N*-(4'-dimethylaminophenyl)-thiocarbamylpiperidine (VII) showed complete inhibition at the concentration of 5 γ/ml.

Using the above described procedure, some *N*-substituted thiocarbamylpiperidines, which are already described in the literature were synthesized.

These substances are presented in Table III and none of them showed an inhibition effect at the concentration of 1 and 5 γ/ml.

TABLE I.

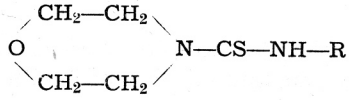
N-Substituted Thiocarbamylpiperidines



Compound No.	R	M. p. °C	Formula	Analyses, %N calc'd	found	Recryst. EtOH:H_2O
I	2′,3′-dimethylphenyl-	138	$C_{14}H_{20}N_2S$	11,28	11,02	3:1
II	2′,4′-dimethylphenyl-	119	$C_{14}H_{20}N_2S$	11,28	11,24	1:1
III	2′,5′-dimethylphenyl-	118	$C_{14}H_{20}N_2S$	11,28	11,33	2:1
IV	2′-methoxyphenyl-	61	$C_{13}H_{18}ON_2S$	11,19	11,38	2:1
V	4′-methoxyphenyl-	146	$C_{13}H_{18}ON_2S$	11,19	11,16	3:1
VI	3′-chlorophenyl-	135	$C_{12}H_{15}N_2SCl$	11,00	11,03	1:0
VII	4′-dimethylaminophenyl-	129	$C_{14}H_{21}N_3S$	15,95	15,83	1:1
VIII	Cyclohexyl-	133	$C_{12}H_{22}N_2S$	12,38	12,30	3:1

TABLE II.

N-substituted Thiocarbamylmorpholines



Compound No.	R	M. p. °C	Formula	Analyses, %N calc'd	found	Recryst. EtOH:H_2O
IX	Phenyl-	134	$C_{11}H_{14}ON_2S$	12,60	12,68	1:0
X	2′-methylphenyl-	144	$C_{12}H_{16}ON_2S$	11,85	12,02	1:0
XI	2′-methoxyphenyl-	91	$C_{12}H_{16}O_2N_2S$	11,10	11,16	1:1
XII	2′,3′-dimethylphenyl-	147	$C_{13}H_{18}ON_2S$	11,19	11,07	1:0
XIII	2′,4′-dimethylphenyl-	148	$C_{13}H_{18}ON_2S$	11,19	11,30	1:0
XIV	2′,5′-dimethylphenyl-	156	$C_{13}H_{18}ON_2S$	11,19	11,33	1:0
XV	3′-chlorophenyl-	162	$C_{11}H_{13}ON_2SCl$	10,91	11,08	1:0
XVI	4′-dimethylaminophenyl	170	$C_{13}H_{19}ON_3S$	15,84	15,98	1:0
XVII	Benzyl-	100	$C_{12}H_{16}ON_2S$	11,85	12,00	3:1
XVIII	Cyclohexyl-	136	$C_{11}H_{20}ON_2S$	12,27	12,33	2:1

TABLE III.

N-substituted Thiocarbamylpiperidines

R	M. p. observed °C	M. p. reported in literature, °C
Phenyl-	99	96[9], 98[10], 99[13], 103-4[17]
2′-methylphenyl-	98	98[10]
3′-methylphenyl-	102	95[5]
4′-methylphenyl-	134	132[10]
4′-chlorophenyl-	153	147[5]
4′-bromophenyl-	166	159[5]
Benzyl-	88	87-8[8]
1′-naphtyl-	125	120[5]
Methyl-	131	125[10], 129[13]

EXPERIMENTAL

All melting-points were determined with Kofler's heating microscope.

General procedure for the preparation of N-substituted thiocarbamylpiperidines and thiocarbamylmorpholines.

0.02 mole of piperidine or morpholine was dissolved in ether (10 ml.) and the solution was cooled with ice. Separately, 0.02 mole of the corresponding isothiocyanate was dissolved in ether (10 ml.; in the case of some sparingly soluble isothiocyanates some more ether was required) and added, in one portion, to the cooled ethereal solution of piperidine or morpholine. The formed derivative soon precipitates and after standing on ice for further 15 min. it was filtered and recrystallised from alcohol or alcohol-water mixture, as indicated in Table I and II. Yields were 82—90%.

Acknowledgements. Grateful acknowledgement is made to Professor M. Perpar for her interest and to Dr. S. Banič of the Microbiological Institute of the Faculty of Medicine in Ljubljana for testing the compounds.

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IZVOD

Sinteze nekih *N*-supstituiranih tiokarbamilpiperidina i tiokarbamilmorfolina

M. Tišler

Pripravljeni su *N*-supstituirani tiokarbamilpiperidini (I—VIII) i tiokarbamilmorfolini (IX—XVIII) iz piperidina ili morfolina i odgovarajućih izotiocianata. Kod sintetiziranih spojeva ispitivana je njihova tuberkulostatična aktivnost.

INSTITUT ZA ORGANSKU KEMIJU
UNIVERZE U LJUBLJANI
SLOVENIJA

Primljeno 16. svibnja 1957.