SYNTHESIS OF THIOUREA DERIVATIVES

VII. ARYLTHIOCARBAMYL-1,4-THIAZANES

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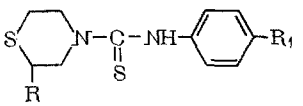
Previously [1, 2] we have described the synthesis and tuberculostatic activity of thiocarbamyl derivatives of piperazine. Continuing these studies it was of interest to synthetize the thiocarbamyl derivatives of 1,4-thiazane (1,4-thiomorpholine), since it is known that a number of 1,4-thiazane derivatives has a physiological action [3, 4] and several 1,3-thiazane derivatives and the thiourea derivatives of the morpholine series [6] have a definite antitubercular effect. Thiourea derivatives in the 1,4-thiazane series have not been described and their physiological properties have not been studied.

We have synthetized 1-arylthiocarbamyl-1,4-thiazanes of the formula



by bringing into reaction 2-methyl-1,4-thiazane and 1,4-thiazane with arylisothiocyanates under heating in anhydrous benzene. The arylisothiocyanates* required for the reaction were obtained by heating symmetrically disubstituted thiocarbanilides with acetic anhydride [7].

The synthesis of 1,4-thiazane and 2-methyl-1,4-thiazane was performed using the method described in [8, 9] by heating the hydrochloride of 2,2'-dichlorodiethylamine and N-2-chloroethyl-1-amino-2-chloropropane with sodium sulfide in 95% ethanol.

In Table 1 the 1,4-thiazane arylthiocarbamyl derivatives synthetized by us are indicated. The compounds are stable, easily crystallizing substances with clearly defined melting points, readily soluble in most organic solvents, more so in alcohol and insoluble in water and ether.

The compounds obtained have an insignificant tuberculostatic activity against the $H_{37}R_V$ and Academia* strains of Mycobacterium tuberculosis.

EXPERIMENTAL

All compounds indicated in Table 1 were obtained analogously.

2-(Methyl)-4-(n-tolylthiocarbamyl)-1,4-thiazane (VII). To a solution heated to boiling of 0.5 g 2-methylthiazane-1,4 in 10 ml anhydrous benzene 0.91 g butoxyphenylisothiocyanate dissolved in 5 ml anhydrous benzene is added gradually and the mixture is heated under stirring for 2 h. The solvent is distilled in vacuo and the residue is triturated with anhydrous ether. The crystalline precipitate is filtered off and washed with ether. The yield is 0.95 g (83% of the theoretical value) compound VII.

CONCLUSIONS

Substituted 1,4-thiazane thiocarbamyl derivatives were synthetized.

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TABLE 1. Properties of the 1-Arylthiocarbamyl-1,4-thiazanes I-XVIII

Compound	R	R_1	Melting point (deg), alcohol	Experimentally (%)				Gross molecular formula	Theoretically (%)			
				C	H	N	S		C	H	N	S
I	CH_3	OC_4H_9	118,5—20	59,30	7,44	8,69	19,25	$C_{16}H_{24}N_2OS_2$	59,25	7,41	8,64	19,75
II	CH_3	OC_4H_9-iso	129,5—130,5	59,27	7,28	8,86	19,91	$C_{16}H_{24}N_2OS_2$	59,25	7,41	8,64	19,75
III	CH_3	OC_5H_{11}-iso	121—121,5	60,22	7,65	8,27	18,96	$C_{17}H_{26}N_2OS_2$	60,35	7,69	8,28	18,93
IV	CH_3	OC_3H_7	95—97,5	58,20	6,93	9,48	20,71	$C_{15}H_{22}N_2OS_2$	58,06	7,10	9,03	20,64
V	CH_3	OCH_3	147—8	55,48	6,40	10,00	22,61	$C_{13}H_{18}N_2OS_2$	55,31	6,38	9,93	22,69
VI	CH_3	OC_2H_5	105—6	56,53	6,75	9,00	21,66	$C_{14}H_{20}N_2OS_2$	56,75	6,76	9,46	21,62
VII	CH_3	CH_3	124,5—126	58,65	6,75	10,41	23,63	$C_{13}H_{18}N_2S_2$	58,65	6,77	10,53	24,06
VIII	CH_3	Br	154—5	43,52	4,40	8,83	19,25	$C_{12}H_{15}BrN_2S_2$[1]	43,50	4,53	8,46	19,34
IX	CH_3	H	124—125,5	57,30	6,50	11,33	25,53	$C_{12}H_{16}N_2S_2$	57,14	6,35	11,11	25,40
X	H	H	170—2	55,72	6,02	11,60	26,07	$C_{11}H_{14}N_2S_2$	55,42	5,92	11,75	26,90
XI	H	CH_3	152—3	56,84	6,48	11,22	25,74	$C_{12}H_{16}N_2S_2$	57,09	6,38	11,09	25,40
XII	H	OCH_3	187—8	54,10	5,85	10,44	24,12	$C_{12}H_{16}OS_2$	53,69	6,00	10,43	23,89
XIII	H	OC_2H_5	151,5—153	55,16	6,50	9,78	22,47	$C_{13}H_{18}N_2OS_2$	55,28	6,42	9,91	22,70
XIV	H	OC_3H_7	156,5—157	56,93	7,20	9,49	21,93	$C_{14}H_{20}N_2OS_2$	56,71	6,80	9,45	21,63
XV	H	OC_4H_9	144—5	58,34	7,27	8,90	20,81	$C_{15}H_{22}N_2OS_2$	58,02	7,14	9,02	20,65
XVI	H	OC_4H_9-iso	166—167,5	58,55	7,27	9,10	20,84	$C_{15}H_{22}N_2OS_2$	58,02	7,14	9,02	20,65
XVII	H	OC_5H_{11}-iso	139—40	58,86	7,60	8,53	19,60	$C_{16}H_{24}N_2OS_2$	59,21	7,46	8,63	19,76
XVIII	H	Br	189,5—190,5	42,08	4,86	9,06	20,06	$C_{11}H_{13}BrN_2S_2$[2]	41,63	4,13	8,83	20,21

* Found, %: Br 24.19. Calc., %: Br 24.17.

† Found, %: Br 25.03. Calc., %: Br 25.18.

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