SYNTHESIS OF SOME PYRIDYL SUBSTITUTED UREAS AND THIOUREAS

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Thirty five pyridyl-substituted ureas and thioureas were synthesized in order to study the relationship between chemical structure and biological activity. These compounds were obtained by the reaction of pyridylamines with isocyanates and isothiocyanates, as well as by the desulfurization of the corresponding thioureas. When tested, all these compounds exhibited weak physiological activity.

Very few pyridyl-substituted ureas and thioureas are described in the literature. In order to continue previously published investigations [1, 2], and to study the interrelations between chemical structure and physiological activity, a series of pyridyl-substituted ureas and thioureas were synthesized. In these compounds, the pyridine nucleus is either directly linked to the carbamide residue or is separated from it. Owing to the difficulty in obtaining some isocyanates, we first tried the possibility of preparing pyridylureas by desulfurizing the corresponding thioureas [2]. When salts and oxides of lead and mercury were employed for this purpose, it was difficult to isolate individual compounds from the reaction products. Good results were obtained by employing potassium iodate in alkaline medium as the desulfurizing agent, as described for the synthesis of arylureas [3]. The reaction proceeded smoothly in the N-phenyl-N'-(pyridyl-2) thioureas only. N-Phenyl-N'-(pyridyl-2) ethylthiourea did not react with potassium iodate. Products of unknown structure were obtained by the reaction of N-(m-tolyl)-N'-(pyridyl-3) thiourea and of N,N'-di(pyridyl-2) thiourea with potassium iodate. The first one yielded an oil, and the second one a crystalline substance melting at 235.5° C.

EXPERIMENTAL

The reaction of pyridylamines with isocyanates (isothiocyanates) was conducted according to the previously described method [1,2].

2 g of substituted thiourea, potassium iodate and KOH were heated by mixing with 30–35 ml of water until a negative reaction with an alkaline solution of potassium plumbite was obtained. The reaction mixture was cooled, the precipitate filtered off and was washed with water to a neutral reaction. The yield of unpurified product was 92–95%. After recrystallization from methanol, the yield decreased to 55–60%. An additional extraction of products from the mother liquor was not attempted.

Tables 1 and 2 summarize the characteristics of the compounds obtained.

REFERENCES

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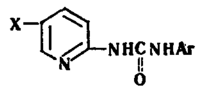
Table 1

Melting Points and Analytical Data of Pyridyl Substituted Ureas of the General Formula:



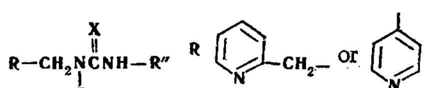
X	Ar	Mp., °C (ex EtOH)	Empirical formula	N, % found	N, % calculated
H	$o\text{-}CH_3C_6H_4$	209—211*	$C_{13}H_{13}N_3O$	18.17	18.49
Cl	$o\text{-}CH_3C_6H_4$	189—191*	$C_{13}H_{12}ClN_3O$	16.11	16.06
H	$m\text{-}CH_3C_6H_4$	158—160*	$C_{13}H_{13}N_3O$	18.49	18.49
Cl	$m\text{-}CH_3C_6H_4$	193—195*	$C_{13}H_{12}ClN_3O$	16.26	16.06
H	$p\text{-}CH_3C_6H_4$	172—173*	$C_{13}H_{12}N_3O$	18.78	18.49
Cl	$p\text{-}CH_3C_6H_4$	216—218*	$C_{13}H_{12}ClN_3O$	16.21	16.06
H	$o\text{-}CH_3OC_6H_4$	201—203*	$C_{13}H_{13}N_3O_2$	16.97	17.27
Cl	$o\text{-}CH_3OC_6H_4$	215—217*	$C_{13}H_{12}ClN_3O_2$	15.21	15.13
H	$p\text{-}CH_3OC_6H_4$	206—207	$C_{13}H_{13}N_3O_2$	17.42	17.27
Cl	$p\text{-}CH_3OC_6H_4$	196—197	$C_{13}H_{12}ClN_3O_2$	15.29	15.13
Cl	$p\text{-}CH_3OC_6H_4$	192—193**	$C_{13}H_{12}ClN_3OS$	14.44	14.30
H	$p\text{-}C_2H_5OC_6H_4$	178—180*	$C_{14}H_{15}N_3O_2$	16.12	16.33
Cl	$p\text{-}C_2H_5OC_6H_4$	173—175*	$C_{14}H_{14}ClN_3O_2$	14.68	14.40
H	$m\text{-}NO_2C_6H_4$	234—235	$C_{12}H_{10}N_4O_3$	21.72	21.71
Cl	$m\text{-}NO_2C_6H_4$	252—253	$C_{12}H_9ClN_4O_3$	19.01	19.14
H	$p\text{-}NO_2C_6H_4$	247—251***	$C_{12}H_{10}N_4O_3$	21.99	21.71
Cl	$p\text{-}NO_2C_6H_4$	267—270	$C_{12}H_9ClN_4O_3$	19.50	19.14
H	$\alpha\text{-}C_{10}H_7$	232—234	$C_{16}H_{13}N_3O$	16.00	15.96
Cl	$\alpha\text{-}C_{10}H_7$	236—237	$C_{16}H_{12}ClN_3O$	14.05	14.11
H	$\beta\text{-}C_{10}H_7$	240—242	$C_{16}H_{13}N_3O$	16.26	15.96
Cl	$\beta\text{-}C_{10}H_7$	243—246	$C_{16}H_{12}ClN_3O$	14.26	14.11

*Obtained by desulfurizing the corresponding thioureas.

**N-(p-methoxyphenyl)-N'-(5-chloropyridyl-2)thiourea. Found, %: 10.66. Calculated, %: S 10.91.

***According to literature data [4]: mp 242°-247° C.

Table 2



I II

X	R	R′	R″	Mp., °C (ex EtOH)	Empirical formula	N, % found	N, % calculated
O	I	H	$o\text{-}ClC_6H_4$	110 —111	$C_{14}H_{13}ClN_3O$	15.59	15.24
O	I	H	$p\text{-}CH_3OC_6H_4$	136 —137	$C_{15}H_{17}N_3O_2$	15.39	15.49
O	I	H	$m\text{-}NO_2C_6H_4$	142 —143	$C_{14}H_{14}N_4O_3$	19.25	19.57
O	I	H	$p\text{-}NO_2C_6H_4$	169 —172	$C_{14}H_{14}N_4O_3$	19.51	19.57
O	I	H	$\alpha\text{-}C_{10}H_7$	189.5—191	$C_{18}H_{17}N_3O$	14.49	14.42
O	I	H	C_2H_5	201 —202*	$C_{20}H_{23}N_7O_6$	21.81	21.44
S	I	H	$m\text{-}CH_3C_6H_4$	105 —106	$C_{15}H_{17}N_3$	15.54	15.48
S	I	H	$p\text{-}CH_3C_6H_4$	116 —117	$C_{15}H_{17}N_3$	15.53	15.48
S	I	H	$p\text{-}CH_3OC_6H_4$	122 —123	$C_{15}H_{17}N_3OS$	14.78	14.62
S	I	H	$\alpha\text{-}C_{10}H_7$	119 —120	$C_{18}H_{17}N_3S$	13.66	13.67
O	I	C_6H_5	C_2H_5	57 — 58	$C_{16}H_{19}N_3O$	15.51	15.60
O	I	$\beta\text{-}C_{10}H_7$	C_2H_5	163 —164*	$C_{30}H_{29}N_7O_6$	16.64	16.80
S	I	$\alpha\text{-}C_{10}H_7$	$\alpha\text{-}C_{10}H_7$	130 —131	$C_{28}H_{23}N_3S$	9.63	9.69
O	II	C_2H_5	C_2H_5	203 —204*	$C_{21}H_{25}N_7O_6$	20.70	20.63
S	II	C_2H_5	C_3H_5	177 —178.5*	$C_{22}H_{25}N_7O_5S$	19.71	19.63
S	II	C_2H_5	$\beta\text{-}C_{10}H_7$	127 —128.5	$C_{18}H_{17}N_3S$	12.71	13.07

*As picrolonate.