THE REACTION OF 3- AND 4-AMINOPYRIDINES WITH ISOCYANATES AND ISOTHIOCYANATES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 2, pp. 281–283, 1968

UDC 541.69 : 547.822.7'495

The reaction of 3- and 4-aminopyridines with some isocyanates and isothiocyanates has been studied, and it has been shown that in the majority of cases aryl isothiocyanates form symmetrical diaryl- and dipyridylthioureas. The hypothesis has been put forward on the possible occurrence of the reaction of the isothiocyanates with 3- and 4-aminopyridines.

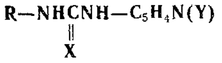
As compared with 2-aminopyridine [1] and pyridylethylated amines [2], the reaction of 3- and 4-aminopyridines (**I**) and (**II**) with isocyanates and, particularly, isothiocyanates takes place in a considerably more complex manner. The reaction of primary amines with isocyanates generally takes place in the following way:

$$RNH_2+OCNR' \rightarrow RNHCONHR'$$

Isothiocyanates react analogously. However, when **I** and **II** reacted with p-tolyl isothiocyanate, in each case only N,N'-di(p-tolyl)thiourea was isolated. With o-tolylisothiocyanate, **I** gave N,N'-di(o-tolyl)thiourea and **II** a resinous product from which it was impossible to isolate individual substances. With phenyl isothiocyanate, **I** in benzene gave N-phenyl-N'-3-pyridylthiourea, which it was impossible to purify by recrystallization. The pure product was obtained by fusing the reactants. In both analogous cases, **II** gave only N,N'-diphenylthiourea. From the products of the reaction of **I** with m-tolyl isothiocyanate in benzene we isolated N-m-tolyl-N'-3-pyridylthiourea and N,N'-di(m-tolyl)thiourea. However, when the same reactants were fused, pure N-m-tolyl-N'-3-pyridylthiourea was obtained. Attempts to obtain N-m-tolyl-N'-4-pyridylthiourea by an analogous method and also a change in the order of mixing of the components or a decrease in the reaction time did not lead to the desired result. In the latter case, and also in the analogous experiment with phenyl isothiocyanate, the initial **II** was recovered. In the other cases it was possible to isolate only N,N'-di(m-tolyl)thiourea.

From the products of the reaction of **II** with α- and β-naphthyl isothiocyanates the corresponding symmetrical dinaphthylthioureas were obtained. The dinaphthylthiourea was also obtained by the reaction of **I** with β-naphthyl isothiocyanate. However, α-naphthyl isothiocyanate and **I** gave N-α-naphthyl-N'-3-pyridylthiourea. Among the products of the reaction of o-methoxyphenyl isothiocyanate with **II**, 26% of N,N'-di(o-methoxyphenyl)thiourea was found. The latter was also obtained by fusing **I** with o-methoxyphenyl isothiocyanate. After reaction in benzene, on the other hand, N,N'-di(3-pyridyl)thiourea was isolated.

There is information in the literature on the thermal instability of unsymmetrical ureas and thioureas. Davis [3] has shown that thioureas and N-alkyl-N'-arylureas are converted at the melting point and above into the symmetrical compounds. In Kurzer's opinion [4], amines and isocyanates are intermediates in this conversion. A similar point of view has been maintained by Capps [5], who observed a marked lowering of the melting points of aryl thioureas in repeated determinations in one and the same capillary. Our results are in harmony with the Davis-Kurzer scheme.



$$R{-}NH\underset{\overset{\|}{X}}{C}NH{-}C_5H_4N(Y)$$

X	Y	R	Mp, °C (from ethanol)	Empirical formula	N, % found	N, % calculated	Yield, %
O	3	C_6H_5	186	$C_{12}H_{11}N_3O$	19.72	19.71	100
O	3	o-ClC_6H_4	197 —198	$C_{12}H_{10}ClN_3O$	17.01	16.97	100
O	4	o-ClC_6H_4	163 —164.5	$C_{12}H_{10}ClN_3O$	16.73	16.97	90
O	3	m-ClC_6H_4	184 —185	$C_{12}H_{10}ClN_3O$	16.60	16.97	100
O	4	m-ClC_6H_4	222 —223	$C_{12}H_{10}ClN_3O$	16.70	16.97	93
O	3	p-$CH_3OC_6H_4$	155 —156	$C_{13}H_{13}N_3O_2$	17.41	17.27	100
O	4	p-$CH_3OC_6H_4$	166.5—168	$C_{13}H_{13}N_3O_2$	17.25	17.27	88
O	3	m-$NO_2C_6H_4$	215 —217	$C_{12}H_{10}N_4O_2$	21.72	21.71	80
O	4	m-$NO_2C_6H_4$	230 —232	$C_{12}H_{10}N_4O_2$	21.82	21.71	55
O	3	p-$NO_2C_6H_4$	222 —223	$C_{12}H_{10}N_4O_2$	21.44	21.71	67
O	3	α-$C_{10}H_7$	234.5—236.5	$C_{16}H_{13}N_3O$	15.94	15.96	96
O	3	β-$C_{10}H_7$	237 —241	$C_{16}H_{13}N_3O$	16.09	15.96	95
O	3	C_2H_5	123 —124	$C_8H_{11}N_3O$	25.33	25.14	90
O	4	C_2H_5	252 —253[1*]	$C_{18}H_{19}N_7O_6$	22.72	22.83	—
S	3	m-$CH_3C_6H_4$	152	$C_{13}H_{13}N_3S$	17.06[2*]	17.27	100
S	3	α-$C_{10}H_7$	197.5—198.5	$C_{16}H_{14}N_3S$	14.80[3*]	15.04	70
S	3	C_3H_5	195 —196[1*]	$C_{19}H_{19}N_7O_5S$	21.46[4*]	21.43	90

[1*] In the form of the picrolonate.

[2*] Found, %: S 13.07%. Calculated: S 13.18%.

[3*] Found, %: S 11.49%. Calculated: S 11.48%.

[4*] Found, %: S 7.16%. Calculated: S 7.00%.

As noted above, when **I** reacts with aryl isothiocyanates, both unsymmetrical arylpyridylthioureas and symmetrical diaryl- and dipyridylthioureas are formed. The presence of these products in the reaction mixture gives grounds for assuming that in the reactions of **I** and **II** with isothiocyanates arylpyridylthioureas are first formed which then undergo conversions analogous to those found previously for arylureas. The driving force of such a conversion is the different basicities of the aminopyridine and the arylamine, on the one hand, and the different reactivities of the pyridyl isothiocyanate and aryl isothiocyanate formed, on the other. It is worth noting that in the cases that we studied, the conversion took place at the boiling point of the benzene solutions, or on heating in a water bath.

In the reaction of aryl and alkyl isocyanates with **I**, in all the cases studied aryl- and alkyl-3-pyridylureas were isolated. Some complications were observed in the reactions with **II**. Thus, in the products of the reaction with phenyl isocyanate only N,N'-diphenylurea was isolated. In addition, the purification of N-ethyl-N'-4-pyridyl-urea proved to be difficult, and it was characterized in the form of the picrolonate.

EXPERIMENTAL

The reaction of 3- and 4-aminopyridines with isocyanates (isothiocyanates) was carried out a) by boiling a mixture of equimolecular amounts (0.02 mole each) in 20 ml of benzene for 3–8 hr, b) without a solvent with heating in the water bath for 2–3 hr. The characteristics of the compounds obtained are given in the table.

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6 April 1966

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