A STUDY OF THE REACTION OF 2-PYRIDYL ISOTHIOCYANATE WITH AZOIMIDE

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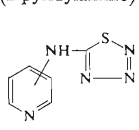
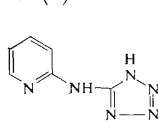
From the reaction mixture of 2-pyridyl isothiocyanate with azoimide in dioxane 5-(2-pyridylamino)tetrazole, 2-pyridylthiourea and elemental sulfur were isolated instead of the expected 5-(2-pyridylamino)-1,2,3,4-thiatriazole. The mechanism of the reaction mentioned was studied on the basis of the synthesis of the assumed intermediates and the isolation of the intermediates by means of compounds with an activated acetylenic or ethylenic bond.

In the preceding paper[1] we investigated the reactions of pyridyl isothiocyanates with diazo compounds and azoimide. Azoimide reacted with 3- and 4-pyridyl isothiocyanates under formation of 5-(3-pyridylamino)-1,2,3,4-thiatriazole (*I*) and 5-(4-pyridylamino)-1,2,3,4-thiatriazole (*II*), while the products of the reaction of 2-pyridyl isothiocyanate with azoimide in dioxane were 5-(2-pyridylamino)tetrazole (*III*) and elemental sulfur. 2-Pyridylthiourea (*IV*) was detected by TLC of the reaction mixture and isolated from it in low yield by column chromatography.

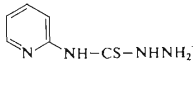
The different reaction course is probably due to the low thermal stability of the 5-(2-pyridylamino)-1,2,3,4-thiatriazole (*V*) formed. Thermal decomposition of 1,2,3,4-



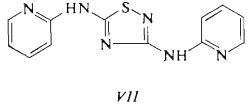
I, 3-substituted
II, 4-substituted



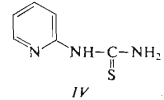
III



VIII



VII



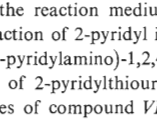
IV

SCHEME 1

-thiatriazoles to nitrogen, sulfur and an organic fragment belongs to their characteristic properties[2]. Especially 1,2,3,4-thiatriazoles with a bound electronegative atom in the position 5 decompose with ease, for example numerous 5-alkoxy and 5-aryloxy-1,2,3,4-thiatriazoles already decompose at room temperature[3,4]. Therefore it may be assumed that the electron-accepting effect of the 2-substituted pyridine ring causes decomposition of the initially formed thiatriazole *V* to intermediate *VI*, which reacts with the azoimide present in the reaction mixture to tetrazole *III*, Scheme 1.

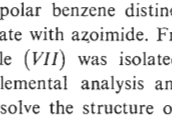
In order to check the truth of the mentioned explanation of the formation of tetrazole *III*, 2-pyridylthiourea[5] (*IV*) was prepared by independent synthesis. It was dehydrosulfurated with yellow mercuric oxide to 2-pyridylcyanamide (*VI*) in a 42·9% yield. The latter gives with azoimide corresponding tetrazole derivative *III* (Scheme 1) if the reaction conditions were such as in the case of 2-pyridylisothiocyanate.

A change of the reaction medium to non-polar benzene distinctly affected the course of the reaction of 2-pyridyl isothiocyanate with azoimide. From the reaction mixture 3,5-di(2-pyridylamino)-1,2,4-thiadiazole (*VII*) was isolated together with a small amount of 2-pyridylthiourea (*IV*). Elemental analysis and the observed spectral properties of compound *VII* did not solve the structure of the compound unambiguously. The main fragments of the molecular ion in its mass spectrum are *A* and *B*. The same fragments may also be expectred in the cleavage of the isomeric



A

m/z 151 (34 % rel. int.)

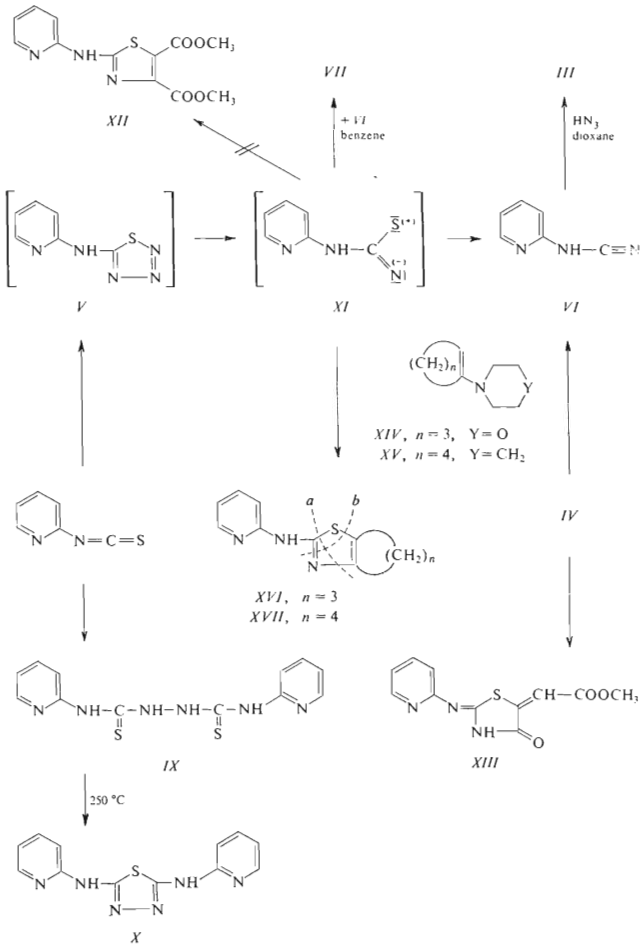


B

m/z 120 (57 %)

2,5-di(2-pyridylamino)-1,3,4-thiadiazole (*X*). Therefore we prepared 1,6-di(2-pyridyl)-hydrazodithiocarbonamide (*IX*) on synthesis from 2-pyridyl isothiocyanate and 2-pyridylthiosemicarbazide[6] (*VIII*). It was thermally cyclized to 2,5-di(2-pyridylamino)-1,3,4-thiadiazole (*X*), Scheme 1. The distinctly different UV spectra of compounds *VII* and *X* represent a clear proof of the difference of their structures. The determined values of the main absorption maxima, λ_{max} 257 or 302 nm are in good correlation with the UV spectra of similar 1,2,4-thiadiazoles[7] or 1,3,4-thiadiazoles[8], respectively.

On the basis of the data obtained we proposed a reaction mechanism for the reaction of 2-pyridyl isothiocyanate with azoimide according to Scheme 2. The primarily formed thermally labile 1,2,3,4-thiatriazole *V* decomposes under elimination of nitrogen and the formation of the intermediate *XI*, from which sulfur is eliminated under formation of 2-pyridylcyanamide *VI*. This gives 1,2,4-thiadiazole derivative *VII* by 1,3-dipolar cycloaddition reaction with the intermediate *XI* present, the


XII
VII
+ VI
benzene
III
HN3
dioxane
V
XI
VI
XIV, n = 3, Y = O
XV, n = 4, Y = CH2
IV
XVI, n = 3
XVII, n = 4
IX
XIII
250 °C
X

SCHEME 2

existence time of which in benzene is probably longer than in dioxane. The assumption of dipole *XI* is substantiated on the basis of data from literature. Neidlein and Salzmann[9] studied thermal decomposition of 1,2,3,4-thiatriazolidines, and they used the dipole formed after splitting off of nitrogen in 1,3-dipolar cycloadditions, for example with carbodiimides. With the aim of proving the existence of the dipolar derivative *XI* we therefore carried out the reaction of 2-pyridyl isothiocyanate with azoimide in the presence of dimethyl butinedioate. Instead of the expected 2-(2-pyridylamino)-4,5-bis(methoxycarbonyl)thiazole (*XII*), Scheme 1, we isolated from the reaction mixture 2-(2-pyridylimino)-5-methoxycarbonylmethylidenethiazolidin-4-one (*XIII*). Its formation can be explained by the reaction of 2-pyridylthiourea with dimethyl butinedioate, which was also confirmed by independent synthesis under conditions used in the reaction studied. The reaction of thioureas with dimethyl butinedioate has been described in literature[10,11].

After the failure to isolate the intermediary *XI* with a reagent containing an electron-deficient triple bond we used a substance with an electron-rich double bond as trapping agent, *i.e.* morpholinocyclopentene (*XIV*) and piperidinocyclohexene (*XV*), Scheme 1. From the reaction mixture we could isolate only 2-(2-pyridylamino)--4,5-(tri or tetramethylene)thiazole (*XVI* or *XVII*, resp.), which was formed by the splitting off of the base from the primarily formed cycloadduct. The fragmentation of prepared heterocycle in mass spectrum (paths *a*,*b*) represents a proof of the structure given.

EXPERIMENTAL

The melting points were determined on a Kofler block, the IR spectra were measured on a UR 20 (Zeiss, Jena) and the UV spectra on a Specord UV VIS (Zeiss, Jena) spectrophotometer, the mass spectra on a MS 902 S (AEI Manchester) spectrometer and the ^{1}H NMR spectra on a Tesla BS 487 C Instrument (80 MHz).

2-Pyridylcyanamide (*VI*)

A mixture of 2-pyridylthiourea[5] (*IV*) (1·53 g, 0·01 mol), acetone (50 ml) and yellow mercuric oxide (8·6 g, 0·04 mol) was refluxed for 45 min, cooled at room temperature and the solid phase filtered off. The filtrate was concentrated under reduced pressure to one tenth of its volume (elimination of acetone) and left to stand. The substance which crystallized out was filtered off under suction and washed with ether. Yield of compound *VI* was 0·48 g (42·9%). m.p. 147—148°C (lit.[5] gives m.p. 163°C). For $C_6H_5N_3$ (119·1) calculated: 60·49% C, 4·23% H, 35·28% N; found: 60·36% C, 4·11% H, 34·98% N. IR spectrum, cm^{-1} (KBr): 2 240 (C≡N), 3 193 (NH). Mass spectrum: M^+ 119 m/z.

Reaction of *VI* with Azoimide

A solution of azoimide (0·047 g, 1·1 mmol) in benzene was added into a solution of *VI* (0·12 g, 1 mmol) in dioxane (10 ml) and the mixture was allowed to stand at room temperature for 24 h.

The solvents were evaporated under reduced pressure and the residue was crystallized from methanol. Yield 0·13 g (80%) of 5-(2-pyridylamino)tetrazole (*III*), m.p. 170—180°C (lit.[1] gives m.p. 171—180°C).

Reaction of 2-Pyridyl Isothiocyanate with Azoimide in Benzene

A solution of the dimer of 2-pyridyl isothiocyanate (1·36 g, 5 mmol) in benzene (50 ml) was refluxed for 5 min, cooled at room temperature and a solution of azoimide (0·473 g, 11 mmol) in benzene was added to it. A reaction set in immediately under evolution of nitrogen. The mixture was allowed to stand for 24 h at room temperature, the solid phase was filtered off and crystallized from dimethyl-formamide. Yield, 0·36 g of 3,5-bis(2-pyridylamino)-1,2,4-thiadiazole (*VII*), m.p. 323—325°C. For $C_{12}H_{10}N_6S$ (270·3) calculated: 31·09% N, 11·86% S; found: 30·90% N, 12·16% S. UV spectrum, nm (methanol, saturated solution): 257, 300, 358. IR spectrum, cm^{-1} (KBr): 1 554, 1 597, 1 635, 3 220, 3 240. ^1H NMR spectrum, ppm (CF_3COOH): 8·18—7·92 (m, 4 H, 2 H(2) and 2 H(4)-pyridine), 7·38—7·02 (m, 4 H, 2 H(3) and 2 H(5)-pyridine). Mass spectrum, *m/z*, (rel. intensity, %) 271 (20), M^+ (100), 177 (17), 151 (34), 120 (57), 105 (34), 93 (34), 78 (63), 51 (20).

From the filtrate benzene was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (eluent $CHCl_3$). Crystallization of the first fraction from ethanol gave 0·12 g of *IV*, m.p. 141—143°C (lit.[5], m.p. 147°C).

2,5-Bis(2-pyridylamino)-1,3,4-thiadiazole (*X*)

A solution of the dimer of 2-pyridyl isothiocyanate (1·36 g, 5 mmol) in dioxane (20 ml) was refluxed for 5 min and added under stirring into a boiling solution of 2-pyridylthiosemicarbazide[6] (*VIII*) (1·68 g, 0·01 mol) in dioxane (40 ml). The mixture was kept boiling for 30 min. The precipitated material was filtered off, washed with acetone and crystallized from dimethylformamide. Yield, 2·2 g (72·4%) of 1,6-di(2-pyridyl)hydrazodithiocarbonamide (*IX*), m.p. 228—236°C. For $C_{12}H_{12}N_6S_2$ (304·4) calculated: 27·61% N, 21·07% S; found: 27·71% N, 20·84% S. UV spectrum (methanol): λ_{max} 268 nm (log ε 3·60), 290 (3·68). IR spectrum, cm^{-1} (KBr): 1 539, 1 609, 3 181, 3 228. Compound *IX* (0·3 g, 1 mmol) was heated without solvent at 240—250°C for 1 h and the melt formed was crystallized from dimethylformamide. Yield, 0·18 g (66·7%) of *X*, m.p. 308—310°C. For $C_{12}H_{10}N_6S$ (270·3), M^+ 270 *m/z*; calculated: 31·09% N. 11·86% S; found: 30·87% N, 11·73% S. UV spectrum (methanol): λ_{max} 206 nm (log ε 4·40), 252 (4·42), 302 (4·67). IR spectrum, cm^{-1} (KBr): 1 569, 1 610, 1 621, 3 170, 3 249. Mass spectrum: M^+ 270*m/z*.

Trapping Experiment with Dimethyl Butinedioate

A solution of dimeric 2-pyridyl isothiocyanate (1·36 g, 5 mmol) in benzene (50 ml) was refluxed for 5 min, cooled to room temperature and a solution of azoimide (0·473 g, 11 mmol) in benzene was added to it. At the onset of nitrogen escape a solution of dimethyl butinedioate (1·42 g, 10 mmol) in benzene (10 ml) was added and the mixture was allowed to stand at room temperature for 24 h. The solid phase was filtered off and crystallized from dimethylformamide. Yield, 0·41 g of 2-(2-pyridylimino)-5-methoxycarbonylmethylidenethiazolidin-4-one (*XIII*), m.p. 267—269°C. For $C_{11}H_9N_3O_3S$ (263·3) calculated: 15·96% N, 12·18% S; found: 16·14% N, 12·04% S. UV spectrum (methanol): λ_{max} 206 nm (log ε 4·31), 253 (3·94), 335 (4·20). IR spectrum, cm^{-1} (KBr): 1 568, 1 633, 1 699 (C=O ring), 1 714 (C=O) ester. ^1H NMR spectrum, ppm (hexadeuteriodimethyl sulfoxide, *t* 100°C): 8·45 (m, 1 H, H(6)-pyridine), 7·85 (m, 1 H, H(4)-pyridine), 7·12 to

7·35 (m, 2 H, H(5) and H(3)-pyridine), 6·68 (s, 1 H, H ethylenic), 3·79 (s, 3 H, CH_3O). Mass spectrum, m/z (rel. intensity), %: M^+ (50), 204 (13), 147 (18), 119 (100), 85 (14), 78 (43).

Reaction of 2-Pyridylthiourea with Dimethyl Butinedioate

A mixture of 2-pyridylthiourea (0·38 g, 2·5 mmol) and dimethyl butinedioate (0·35 g, 2·5 mmol) in benzene (40 ml) was stirred at room temperature for 2 h. The solvent was distilled off under reduced pressure and the residue crystallized from dimethylformamide. Yield, 0·48 g (73·0%) of 2-(2-pyridylimino)-5-methoxycarbonylmethylidenethiazolidin-4-one (*XIII*), m.p. 266–268°C.

Trapping Experiment with Cyclic Enamines

A solution of dimeric 2-pyridyl isothiocyanate (1·36 g, 5 mmol) in benzene (50 ml) was refluxed for 5 min, cooled at room temperature and a solution of azoimide (0·473 g, 11 mmol) in benzene was added to it. When evolution of nitrogen began, a solution of enamine (10 mmol) in benzene (10 ml) was added and the mixture was stirred at room temperature for 3 h and allowed to stand for 24 h. The solvent was then evaporated under reduced pressure. If morpholinocyclopentene was used, the concentrated mixture was chromatographed on a silica gel column with chloroform. Crystallization of the third fraction from dimethylformamide–methanol gave 0·23 g of 2-(2-pyridylamino)-4,5-trimethylenethiazole (*XVI*), m.p. 197–199°C. For $C_{11}H_{11}N_3S$ (217·3) calculated: 19·34% N, 14·76% S; found: 19·36% N, 14·80% S. UV spectrum (methanol): λ_{max} 215 nm (log ε 4·08), 292 (4·22), 322 (4·27). ^{1}H NMR spectrum ppm (hexadeuteriodimethyl sulfoxide, t 50°C): 8·23 (m, 1 H, H(6)-pyridine), 7·63 (m, 1 H, H(4)-pyridine), 7·14–6·77 (m, 2 H, H(3) and H(5)-pyridine), 2·88–2·22 (m, 6 H, CH_2-trimethylene). Mass spectrum, m/z (rel. intensity, %): M^+ (100), 137 (18), 120 (12), 105 (9), 81 (10), 78 (27), 57 (15).

If piperidinocyclohexene was used, acetone (20 ml) was added to the residue and the precipitated crystals were filtered off and washed with acetone. Crystallization from a mixture of dimethylformamide–methanol gave 0·52 g of 2-(2-pyridylamino)-4,5-tetramethylenethiazole (*XVII*), m.p. 229–231°C. For $C_{12}H_{13}N_3S$ (231·3) calculated: 18·17% N, 13·86% S; found: 18·39% N, 14·00% S. UV spectrum (methanol): λ_{max} 212 nm (log ε 4·04), 287 (4·19), 316 (4·04), 287 (4·19), 316 (4·18). ^{1}H NMR spectrum, ppm (hexadeuteriodimethyl sulfoxide): 8·22 (m, 1 H, H(6)-pyridine), 7·62 (m, 1 H, H(4)-pyridine), 7·11–6·75 (m, 2 H, H(3) and H(5)-pyridine), 1·76 (m, 8 H, CH_2-tetramethylene). Mass spectrum, m/z (rel. intensity, %): M^+ (100), 203 (32), 137 (16), 120 (13), 78 (29), 51 (13).

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