SYNTHESIS OF PYRIDO[1,2-*a*]-1,3,5-TRIAZINES. REACTIONS OF 2-PYRIDYL ISOTHIOCYANATE WITH COMPOUNDS CONTAINING A C=N BOND

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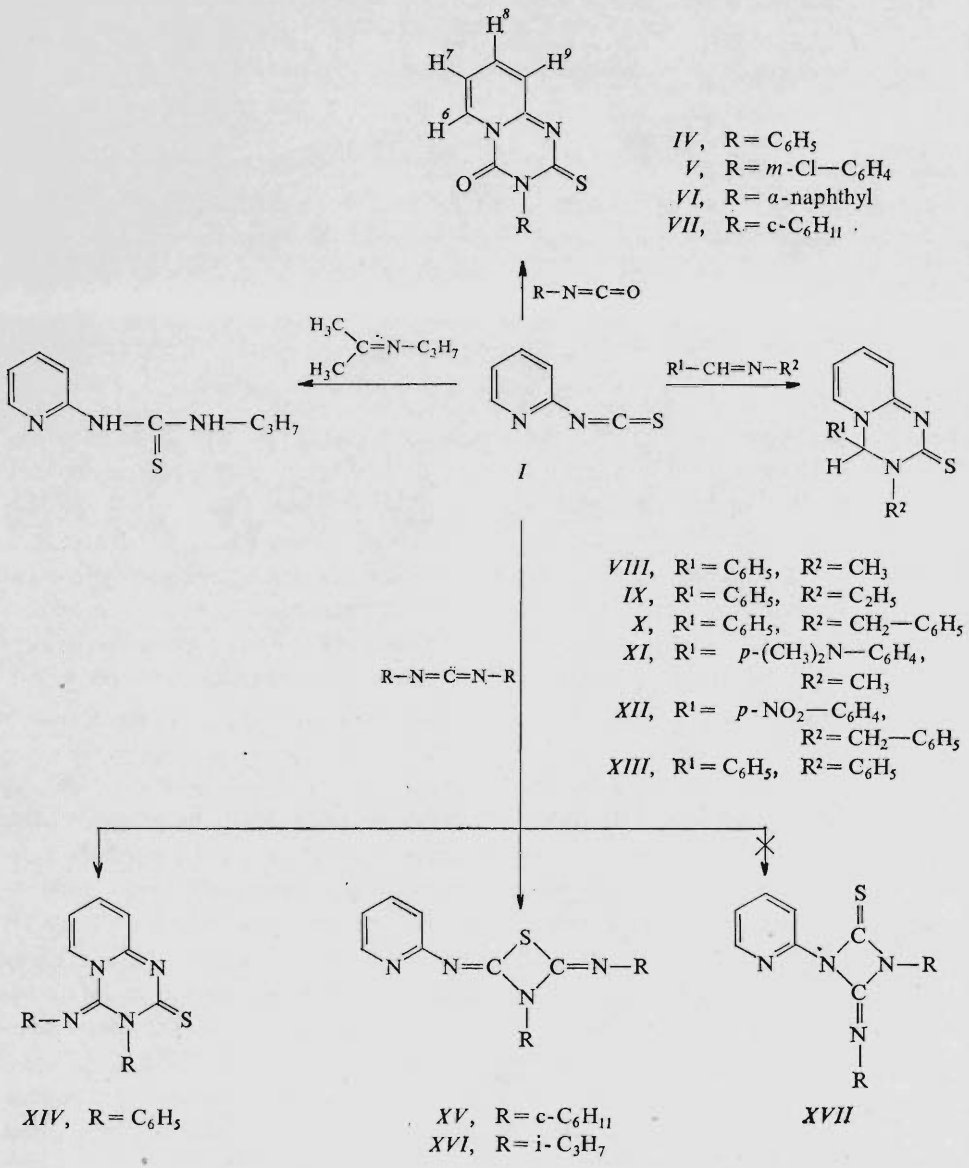
New pyrido[1,2-*a*]-1,3,5-triazine derivatives were prepared by the [4+2]cycloaddition reaction of 2-pyridyl isothiocyanates with isocyanate, aldimines, and N,N'-diphenylcarbodiimide. On the other hand, reaction of 2-pyridyl isothiocyanate with aliphatic carbodiimides afforded [2+2]cycloaddition products, 1,3-thiazetidines.

In our previous work[1] we investigated 1,3-dipolar cycloadditions of 2-, 3- and 4-pyridyl isothiocyanates. Of the three position isomeric pyridyl isothiocyanates, the 2-pyridyl derivative *I* is the most interesting being an N-heteroaromate with an N=C double bond in the α-position, *i.e.* a 1,3-diazadiene. This system is capable of [4+2]cycloadditions with suitable dienophiles. This tendency[2,3] manifests itself also by dimerization of *I* at room temperature, leading to 3-(2-pyridyl)pyrido-[1,2-*a*]-1,3,5-triazine-2,4-dithione (*II*). This communication concerns utilization of the 1,3-diazadiene grouping of 2-pyridyl isothiocyanate in the preparation of new pyrido[1,2-*a*]-1,3,5-triazine derivatives[4-6], containing a C=S group in the position 2.

In solution, the dimer *II* was transformed at 70°C into the monomer *I* which on cooling to room temperature reacted spontaneously with isocyanates as the more reactive partners to give 3-substituted pyrido[1,2-*a*]-1,3,5-triazin-4-one-2-thiones *IV*–*VII* (Table I, Scheme 1). In order to identify unambiguously the prepared compounds, we compared their spectral properties with those of 3*H*-pyrido[1,2-*a*]--1,3,5-triazin-4-one-2-thione (*III*), prepared by an independent route[4] from 2-amino-pyridine and ethoxycarbonyl isothiocyanate. The identical UV spectrum (Table II) and chemical shifts of signals due to protons of the dearomatized pyridine nucleus in the ^{1}H-NMR spectrum (Table II) confirmed the presence of the pyrido[1,2-*a*]--1,3,5-triazine skeleton in the synthesized derivatives. Another proof of the dearomatization was the value of the vicinal coupling constant $^3J_{H^6,H^7}$ (7·0–7·5 Hz as compared with 4·5–6 Hz for an aromatic nucleus[7]). The mass spectra of compounds *IV*–*VI* did not exhibit any molecular ions but only products of the retro-Diels–Alder splitting. Molecular ions were not observed even at ionizing energy 15 eV. The colour of compounds *IV*–*VII* is typical. The extended conjugation of π-bonds across two

heterocyclic nuclei manifests itself in the electronic spectrum by an absorption band at 378–389 nm (log ε 3·00–3·88). The IR spectra display strong absorption bands due to C=C, C=N ring stretching vibrations at 1530–1550 cm^{-1} and 1 634 to 1 647 cm^{-1}, respectively, and C=O stretching vibration bands at 1 727–1 748 cm^{-1}.



SCHEME 1

The reactivity of the 1,3-diazadiene grouping of 2-pyridyl isothiocyanate toward the C=N bond was further utilized in cycloaddition reactions with aldimines (Scheme 1). The reaction afforded 3,4-disubstituted 4*H*-pyrido[1,2-*a*]-1,3,5-triazine-2-thiones *VIII*–*XII* (Table I) in yields ranging from 27·7% to 85·9%. Compound *XIII* was obtained in a yield of only 6·3%, together with benzaldehyde and 1-phenyl-3-(2-pyridyl)thiourea. Reaction with N-isopropylidenepropylamine (*i.e.* ketimine) gave solely 1-propyl-3-(2-pyridyl)thiourea (Scheme 1). The formation of thioureas is probably related to the facile hydrolysis of the primarily arising [4+2]cycload-

TABLE I

Pyrido[1,2-*a*]-1,3,5-triazine-2-thione derivatives

Compound	Formula (mol.w.)	Calculated/Found		M.p., °C (yield, %)
		% N	% S	
IV	$C_{13}H_9N_3OS$ (255·3)	16·46 16·62	12·56 12·36	199–201 (71·8)
V	$C_{13}H_8N_3ClOS$ (289·7)	14·50 14·74	11·07 11·32	192–194 (83·0)
VI	$C_{17}H_{11}N_3OS$ (305·4)	13·76 13·44	10·50 10·31	196–198 (91·8)
VII	$C_{13}H_{15}N_3OS$ (261·3)	16·08 16·34	12·27 12·02	204–206 (24·5)
VIII	$C_{14}H_{13}N_3S$ (255·3)	16·46 16·68	12·56 12·78	213–215 (65·0)
IX	$C_{15}H_{15}N_3S$ (269·4)	15·60 15·38	11·90 11·68	225–228 (85·9)
X	$C_{20}H_{17}N_3S$ (331·4)	12·67 12·83	9·67 9·76	192–193 (85·8)
XI	$C_{16}H_{18}N_4S$ (298·4)	18·78 18·99	10·75 10·73	224–226 (80·5)
XII	$C_{20}H_{16}N_4O_2S$ (376·4)	14·88 15·01	8·52 8·51	183–185 (27·7)
XIII	$C_{19}H_{15}N_3S$ (317·4)	13·24 13·42	10·10 10·17	149–150 (6·3)
XIV	$C_{19}H_{14}N_4S$ (330·4)	16·96 16·85	9·70 9·58	259–261 (24·8)

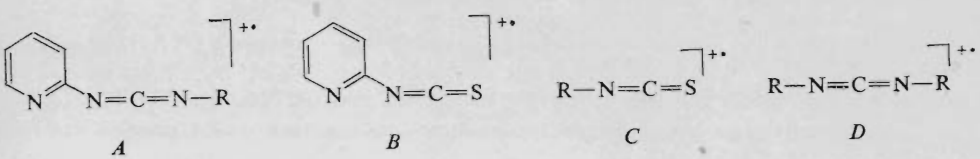
ducts[8], since the aldimines (as well as the ketimine) remain unchanged even after 3 hours'reflux in benzene. Both the IR and UV spectra (λ_{max} 378–388 nm; log ε 4·06–4·21) of compounds *VIII*–*XIII* agree with the suggested structures. Their mass spectra again exhibit only fragments of the retro-Diels–Alder cleavage. Owing to insolubility of the compounds, it was not possible to measure their ^{1}H-NMR spectra.

We used also symmetrical carbodiimides as the reactive C=N components in the reaction with 2-pyridyl isothiocyanate. The nature of the carbodiimide grouping affects substantially the reaction course. Whereas the reaction with N,N'-diphenylcarbodiimide led to 3-phenyl-4-phenyliminopyrido[1,2-*a*]-1,3,5-triazine-2-thione (*XIV*), *i.e.* to a [4+2]cycloadduct (Scheme 1, Table I), N,N'-dicyclohexylcarbodiimide and N,N'-diisopropylcarbodiimide reacted under the same conditions (benzene, reflux for 1 h) in a [2+2]cycloaddition in periselective mode across the C=S linkage to give 3-cyclohexyl-4-cyclohexylimino-2-(2-pyridylimino)-1,3-thiazetidine (*XV*) and 3-isopropyl-4-isopropylimino-2-(2-pyridylimino)-1,3-thiazetidine (*XVI*), respectively (Scheme 1). Structure of the cycloadducts was proved by IR, UV, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The UV spectrum of the thermally more stable, orange-coloured pyrido[1,2-*a*]-1,3,5-triazine derivative *XIV* exhibits an absorption band at 393 nm (log ε 3·99); its IR spectrum displays bands at 1 692 cm^{-1} and 1 637 cm^{-1} due to the respective exocyclic and endocyclic C=N bonds. In the mass spectrum only products of the retro-Diels–Alder cleavage were observed. The presence of free C=S group is indicated by the positive Feigl test[9]. In addition, the magnitude of the coupling constant $^3J_{H^6,H^7}$ (7·1 Hz) in the ^{1}H-NMR spectrum proves a dearomatization of the pyridine nucleus. On the contrary, the derivatives *XV* and *XVI* are colourless, low-melting (<80°C), compounds. Their respective UV absorption maxima are located at 309 nm (log ε 4·26) and 308 nm (log ε 4·33). Both the compounds *XV* and *XVI* exhibit a strong band at 1 643 cm^{-1} and 1 642

TABLE II
UV and ^{1}H-NMR spectra of compounds *III* and *IV*

Compound	R	λ_{max}, nm (log ε)				δ, ppm				$^3J_{H^6,H^7}$, Hz
						H–6	H–8	H–7	H–9	
III	H	208 (4·15)	243 (4·02)	306 (4·32)	384 (3·88)	8·50	8·00	7·01–7·28		7·0
IV	C_6H_5	208 (4·33)	245 (3·93)	309 (4·16)	378 (3·75)	8·49	8·03	7·03–7·51		7·0

cm^{-1}, respectively, and a medium band at 1 731 cm^{-1} and 1 745 cm^{-1}, respectively, due to two non-equivalent exocyclic C=N bonds[10]. The respective values 4·7 Hz and 4·8 Hz of the coupling constants $^3J_{H^5,H^6}$ in the ^{1}H-NMR spectra show an aromatic character of the pyridine nucleus. The absence of a C=S carbon atom signal in the ^{13}C-NMR spectrum, together with the negative Feigl test show that the studied derivatives *XV* and *XVI* have the 1,3-thiazetidine skeleton and not the alternative structure *XVII*. Besides the $M^{+\bullet}$ ions, mass spectra of the compounds *XV* and *XVI* contain the fragments A, B, C and D, arising by degradation of the four-membered heterocycle.



A *B* *C* *D*

Our present results agree with the literature data. Ulrich and collaborators[11–13], who performed a series of reactions of alkyl and aryl isothiocyanates with carbodiimides, ascribed the 1,3-diazetidine structure to the resulting cycloadducts, by analogy with isocyanates, reacting exclusively at the C=N bond[14]. It has been shown by thermolysis of cycloadducts[15], stereochemical studies[16,17] and Feigl test that the $\pi_s^2 + \pi_a^2$ cycloaddition proceeds periselectively at the C=S bond of the NCS group, giving rise to 1,3-thiazetidine derivatives[18]. The discussed thermal [2+2] cycloaddition is generally reversible and, under provision of suitable structure of reactants, [4+2]cycloaddition products are obtained at elevated temperature of after prolonged reaction time[5,19]. 2-Pyridyl isothiocyanate was treated with dicyclohexylcarbodiimide also in toluene but even after reflux for 5 hours no [4+2]cycloaddition product was isolated.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were measured in KBr on a UR-20 (Zeiss, Jena) spectrophotometer, UV spectra in methanol on a UV-VIS Specord (Zeiss, Jena) spectrophotometer. ^{1}H-NMR spectra were taken on a Tesla BS-487C (Tesla, Brno) 80 MHz instrument in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. ^{13}C-NMR spectrum of compound *XV* was measured on a Jeol FX-100 FT spectrometer (25·05 MHz). Mass spectra were determined on an MS 902S (AEI Manchester) spectrometer.

The starting 2-pyridyl isothiocyanate dimer was prepared by decomposition of triethylammonium 2-pyridyldithiocarbamate with phosgene[3]. Phenyl, *m*-chlorophenyl, α-naphthyl, and cyclohexyl isothiocyanates were commercially available samples. N-Benzylideneaniline, N-*p*-nitrobenzylidenebenzylamine, N-*p*-dimethylaminobenzylideneethylamine, N-benzylidenemethylamine, N-benzylidenebenzylamine, N-benzylideneethylamine and N-isopropylidenepropylamine were prepared according to ref.[20,21]; diphenylcarbodiimide, dicyclohexylcarbodiimide and diisopropylcarbodiimide were synthesized according to ref.[22–24].

Reaction of 2-Pyridyl Isothiocyanate with Isocyanates

A solution of 2-pyridyl isothiocyanate dimer (1·36 g; 0·005 mol) in benzene (50 ml) was refluxed for 5 min. After cooling, a solution of the appropriate isocyanate (0·01 mol) in benzene (10 ml) was added and the mixture was set aside at room temperature for 24 h. The separated crystals were filtered, washed with benzene and crystallized from chloroform–acetone. This procedure was used in the preparation of compounds *IV*—*VI*.

In the reaction with cyclohexyl isocyanate the solvent was distilled off under diminished pressure and the residue was chromatographed on a silica gel column in a chloroform–acetone (4 : 1) mixture. Crystallization of the second fraction from acetone afforded the product *VII*.

Reaction of 2-Pyridyl Isothiocyanate with Aldimines and Ketimine

A solution of 2-pyridyl isothiocyanate dimer (1·36 g; 0·005 mol) in benzene (50 ml) was refluxed for 5 min. To the hot solution, the appropriate aldimine or ketimine (0·01 mol) in benzene (10 ml) was added. The mixture was refluxed for 1 h, the crystals were collected on filter, washed with ether and crystallized from a dimethylformamide–methanol mixture. This procedure was used in the preparation of compounds *VIII*—*XII*. After reaction with N-benzylideneaniline, the solvent was removed by distillation under diminished pressure and the residue was chromatographed on a silica gel column with chloroform as eluant. Distillation of the first fraction afforded benzaldehyde (0·65 g), the second fraction on crystallization from ethanol gave 1·71 g 1-phenyl-3-(2-pyridyl)thiourea, m.p. 167—169°C (reported[25] m.p. 168°C). Elution with methanol yielded compound *XIII* which was purified by crystallization from methanol. Also the product of reaction with N-isopropylidenepropylamine was isolated by chromatography on a column of silica gel; 0·96 g of 1-propyl-3-(2-pyridyl)thiourea, m.p. 83—85°C (reported[26] m.p. 87·5°C).

Reaction of 2-Pyridyl Isothiocyanate with Carbodiimides

A solution of the corresponding carbodiimide (0·01 mol) in benzene (10 ml) was added to a hot solution of 2-pyridyl isothiocyanate dimer (1·36 g; 0·005 mol) in benzene (50 ml) which had been refluxed for 5 min. The mixture was refluxed for 1 h, set aside at room temperature for 24 h and the solvent was distilled off under diminished pressure.

In the reaction with diphenylcarbodiimide, the residue was dissolved in acetone (10 ml) and light petroleum was added until the mixture became turbid. After standing for 24 h the separated crystals were filtered, washed with ether and crystallized from acetone, affording the compound *XIV*.

In the case of dicyclohexylcarbodiimide and diisopropylcarbodiimide, the residue was chromatographed on a column of silica gel (eluant chloroform). Crystallization of the first fraction from acetone–light petroleum afforded the compounds *XV* and *XVI*. 3-Cyclohexyl-4-cyclohexylimino-2-(2-pyridylimino)-1,3-thiazetidine (*XV*), m.p. 76—78°C; yield 1·74 g (50·3%). For $C_{19}H_{26}N_4S$ (342·5) calculated: 16·36% N, 9·36% S; found: 16·52% N, 9·56% S. UV spectrum in methanol, λ_{max}, nm (log ε): 206 (4·37), 253 (4·28), 266 (4·13), 309 (4·26). ^{1}H-NMR spectrum ($CDCl_3$), ppm: 1·15—2·32 (m, 20 H, 2 × C_6H_{11}), 3·00 (m, 1 H, H-cyclohexyl), 3·98 (m, 1 H, H-cyclohexyl), 6·91—7·16 (m, 2H, H—3 and H—5 of pyridine), 7·64 (m, 1 H, H—4 of pyridine), 8·35 (m, 1 H, H—6 of pyridine), $^3J_{H^5,H^6}$ 4·7 Hz. ^{13}C-NMR spectrum ($CDCl_3$), ppm: 157·6, 150·5, 147·5, 146·1, 138·1, 120·2, 119·8, 63·4, 54·9, 34·4, 30·3, 25·8, 25·2, 24·7. 3-Isopropyl-4-isopropylimino-2-(2-pyridylimino)-1,3-thiazetidine (*XVI*), yield 0·66 g (32·8%), m.p. 34—36°C. For $C_{13}H_{18}N_4S$ (262·4) calculated: 21·35% N, 12·22% S; found: 21·54% N, 12·21% S. UV spectrum in methanol, λ_{max}, nm (log ε): 204 (4·48), 253 (4·29), 262 (4·22), 308 (4·33). ^{1}H-NMR spectrum

($CDCl_3$), ppm: 1·24—1·53 (m, 12 H, 4 × CH_3-isopropyl), 3·33 (m, 1 H, H-isopropyl), 4·36 (m, 1 H, H-isopropyl), 6·93—7·17 (m, 2 H, H—3 and H—5 of pyridine), 7·66 (m, 1 H, H—4 of pyridine), 8·36 (m, 1 H, H—6 of pyridine), $^3J_{H5,H6}$ 4·8 Hz.

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