ADDITION-CYCLIZATION REACTIONS OF 2-PYRIDYL ISOTHIOCYANATE

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Addition-cyclization reactions of 2-pyridyl isothiocyanate with enamines and C-acids afforded derivatives containing pyrido[1,2-*a*]pyrimidine skeleton. Cyclization with a series of phenylhydrazones gave substituted triazolidines. The IR, UV, ^{1}H-NMR and ^{13}C-NMR spectra of the synthesized compounds are discussed.

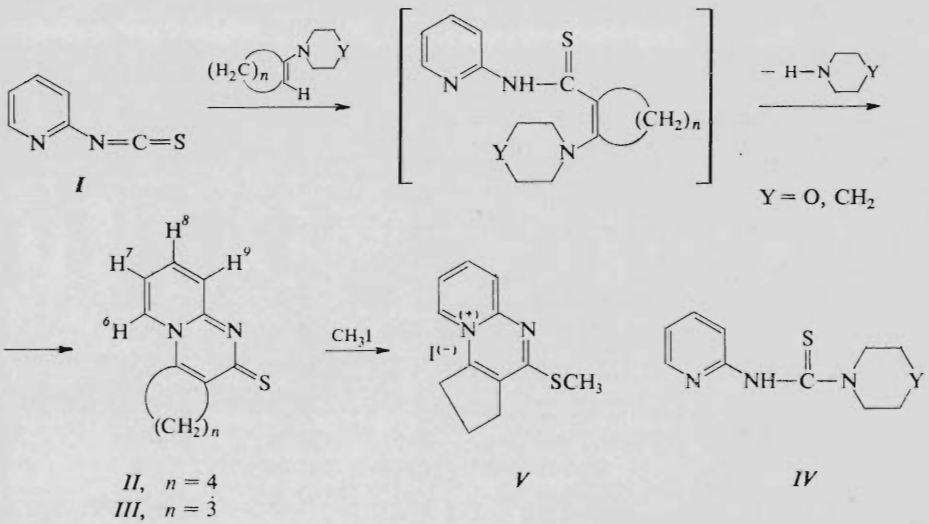
In our preceding communication[1] we studied the use of the 1,3-diazadiene system of 2-pyridyl isothiocyanate in the synthesis of pyrido[1,2-*a*]-1,3,5-triazine derivatives *via* [4+2]cycloaddition reactions with C=N bond-containing compounds. Our present paper concerns the application of addition-cyclization reactions of 2-pyridyl isothiocyanate in the preparation of other N-bridgehead heterocycles.

In order to synthesize derivatives of the pyrido[1,2-*a*]pyrimidine type[2-5] we used cyclic enamines as the cyclization components. The reaction of 2-pyridyl isothiocyanate (*I*) with morpholinocyclohexene and piperidinocyclopentene afforded 3,4-tetramethylenepyrido[1,2-*a*]pyrimidine-2-thione (*II*) and 3,4-trimethylenepyrido-[1,2-*a*]pyrimidine-2-thione (*III*), respectively (Table I, Scheme 1). In this reaction, the enamines afford secondary amines which can react competitively with the present 2-pyridyl isothiocyanate. The corresponding thiourea *IV* was isolated from the reaction mixture only in the case of morpholine. The vicinal ^{1}H-NMR coupling constants, $^3J_{H^6,H^7}$ (7·1 Hz and 6·9 Hz for the respective fused heterocycles *II* and *III*), prove the dearomatization of the pyridine nucleus[1]. Peaks due to molecular ions were observed in the mass spectra of both compounds. Electronic spectra of the compounds *II* and *III* display characteristic absorption bands at 353 nm (log ε 4·42) and 346 nm (log ε 4·49), respectively. Chemical proof of the suggested structure consisted in the reaction of compound *III* with methyl iodide which gave the heteroaromatic system V (Table I, Scheme 1). The presence of the pyridinium nitrogen shifts markedly downfield (about 0·6 ppm) the pyridine proton signals in the ^{1}H-NMR spectrum. In the ^{13}C-NMR spectrum, the CH_3S signal is located at 12·46 ppm.

Another synthesis of the pyrido[1,2-*a*]pyrimidine skeleton started from 2-pyridyl isothiocyanate (*I*) and C-acids, of which we used diethyl malonate, ethyl cyanoacetate and ethyl acetoacetate. The C-acid anion, generated by sodium hydride, added

primarily to 2-pyridyl isothiocyanate to afford sodium salt of thioacetamide which on acidification with dilute hydrochloric acid was transformed into the thioacetamide derivatives *VI* – *VIII* (Table I, Scheme 2). The IR spectrum of N-(2-pyridyl)-α,α-bis-(ethoxycarbonyl)thioacetamide (*VI*) displays a C=O absorption band at 1749 cm^{-1} and an N—H band at 3 280 cm^{-1}; its ^{1}H-NMR spectrum exhibits a methine proton signal at 5·08 ppm, the coupling constant of the pyridine H – 5 and H – 6 protons, $^3J_{H^5,H^6}$, is 4·5 Hz.

Cyclization of the thioacetamide *VI* with sodium ethoxide in ethanol afforded 3-ethoxycarbonyl-2-mercaptopyrido[1,2-*a*]pyrimidin-4-one (*IX*) (Table I, Scheme 2). Its IR spectrum exhibits a triplet at 1 634, 1 680 and 1 723 cm^{-1} due to stretching vibrations of the respective endocyclic C=N, pyrimidine C=O, and ester C=O bonds. The dearomatization of the pyridine nucleus is indicated by the value of the



SCHEME 1

coupling constant $^3J_{H^6,H^7}$ (6·8 Hz) in the ^{1}H-NMR spectrum. Since no methine proton signal was observed in its ^{1}H-NMR spectrum, the synthesized compound could be assigned the thiol form *IX* rather than the thione structure *XIX*. Another structural proof is the absence of the C=S carbon atom signal and of the sp^3 hybridized pyrimidine carbon atom in the ^{13}C-NMR spectrum. Fragmentation of the molecular ion of *IX* is shown in Scheme 3. The thiol form was confirmed chemically by reaction with ethyl bromide, affording the derivative *XII* (Table I, Scheme 2).

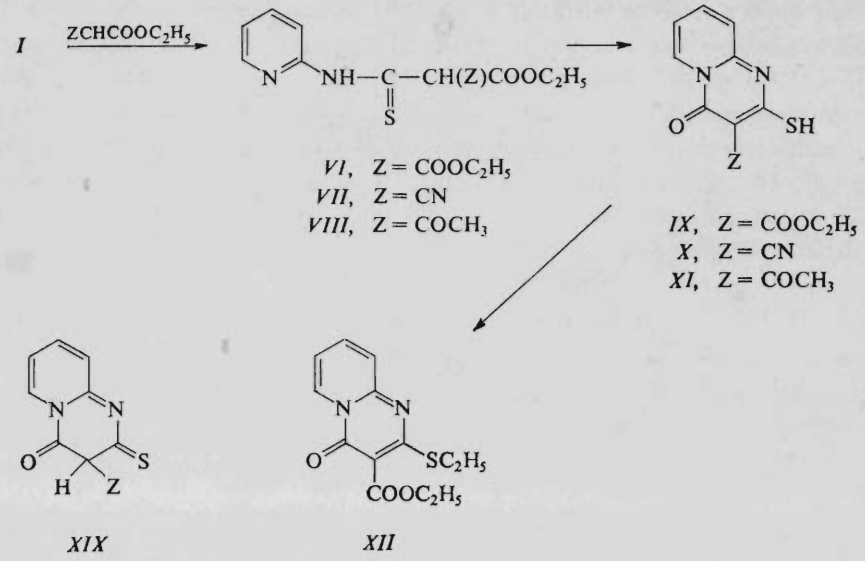
N-(2-Pyridyl)-α-cyano-α-ethoxycarbonylthioacetamide (*VII*), formed from ethyl cyanoacetate and 2-pyridyl isothiocyanate (*I*), was directly thermally cyclized to give

3-cyano-2-mercaptopyrido[1,2-*a*]pyrimidin-4-one (*X*) (Table I, Scheme 2). Its IR spectrum displays the absorption bands ν(C=N) at 1 638 cm^{-1}, ν(C=O) at 1 708 cm^{-1}, and ν(C≡N) at 2 223 cm^{-1}. Its structure agrees with the fragmentation of the $M^{+\cdot}$ ion. Because of the low solubility of the compound *X* it was not possible to measure its NMR spectra, Cyclization of N-(2-pyridyl)-α-acetyl-α-ethoxycarbonyl-thioacetamide (*VIII*) with sodium ethoxide in ethanol afforded 3-acetyl-2-mercapto-pyrido[1,2-*a*]pyrimidin-4-one (*XI*) in 11% yield. The same compound was prepared by Kato[6] from 2-pyridyl isothiocyanate and diketene.

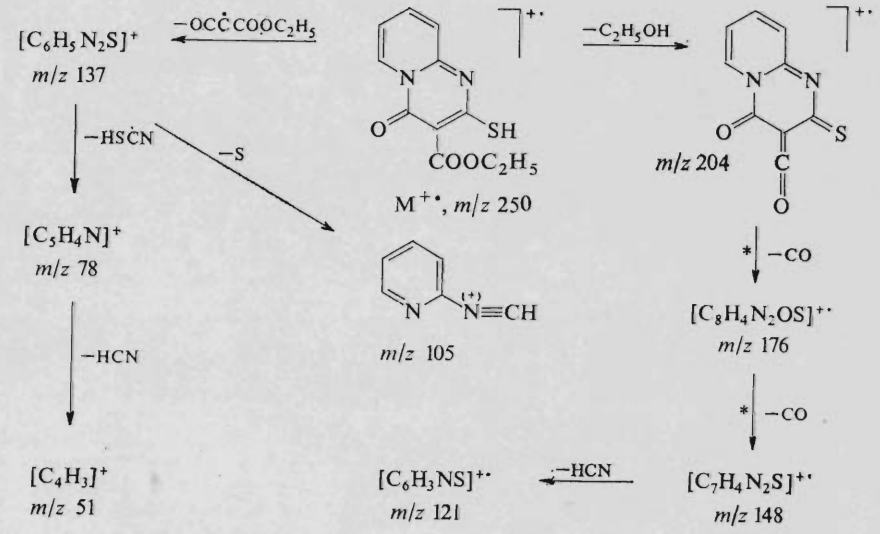
TABLE I

Physical constants and analyses of the synthesized compounds

Compound	Formula (mol.w.)	Calculated/Found		M.p., °C (Yield, %)
		% N	% S	
II	$C_{12}H_{12}N_2S$	12·95	14·82	259–261
	(216·3)	12·62	14·66	(69·4)
III	$C_{11}H_{10}N_2S$	13·85	15·85	276–279
	(202·3)	14·05	15·88	(79·2)
V	$C_{12}H_{13}IN_2S$	8·14	9·32	283–287
	(344·2)	8·32	9·16	(87·8)
VI	$C_{13}H_{16}N_2O_4S$	9·46	10·82	oil
	(296·3)	9·65	10·93	(82·8)
VIII	$C_{12}H_{14}N_2O_3S$	10·52	12·04	81–83
	(266·3)	10·76	12·06	(76·9)
IX	$C_{11}H_{10}N_2O_3S$	11·19	12·81	221–223
	(250·3)	11·36	12·71	(50·5)
X	$C_9H_5N_3OS$	20·68	15·78	305–307
	(203·2)	20·81	15·74	(59·1)
XII	$C_{13}H_{14}N_2O_3S$	10·07	11·52	72–74
	(278·3)	10·31	11·29	(75·5)
XIV	$C_{15}H_{16}N_4S$	19·70	11·27	135–137
	(284·4)	19·93	11·46	(47·5)
XV	$C_{17}H_{18}N_4S$	18·05	10·33	142–144
	(310·4)	18·16	10·57	(16·1)
XVI	$C_{18}H_{20}N_4S$	17·27	9·88	164–166
	(324·4)	17·28	9·87	(58·6)



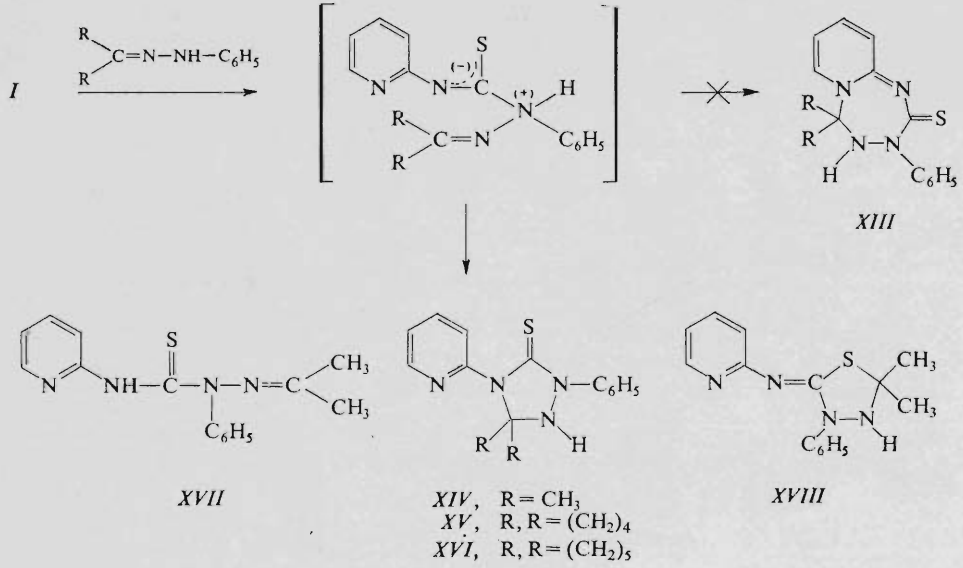
SCHEME 2



SCHEME 3

We intended to utilize the 1,3-diazadiene grouping also for the synthesis of the tetraazepine derivative *XIII* by reaction with hydrazones (Scheme 4), however, the arising betaine was cyclized to give the triazolidine derivatives *XIV*–*XVI* (Table I,

Scheme 4). The presence of signals due to the C=S and ring carbon atoms (at 175·95 and 80·69 ppm, respectively) in the ^{13}C-NMR spectrum proves that the compound *XIV* is 5,5-dimethyl-2-phenyl-4-(2-pyridyl)-1,2,4-triazolidine-3-thione and not the thiosemicarbazone *XVII* or the thiadiazolidine *XVIII*. The mass spectrum exhibits, in addition to the $M^{+\cdot}$ ion, the $(M)^{+\cdot}$—$(CH_3)_2C{=}NH$ and $(C_6H_5{-}N{=}NH)^{+\cdot}$ fragments (*m/z* 227 and 106, respectively). The absence of exocyclic C=N vibration bands in the IR spectrum, the small coupling constant $^3J_{H^5,H^6}$ (5·1 Hz) and the singlet at 1·70 ppm (6 H, 2 × CH_3) in the ^{1}H-NMR spectrum correspond also well with the suggested structure. Reaction of 2-pyridyl isothiocyanate with phenylhydrazones of alicyclic ketones afforded also triazolidine derivatives, as evidenced by spectral properties of the products, analogous to those described for the compound *XIV*. We thus obtained 2-phenyl-4-(2-pyridyl)-1,2,4-triazaspiro[4,4]nonane-3-thione (*XV*) and 2-phenyl-4-(2-pyridyl)-1,2,4-triazaspiro[4,5]-decane-3-thione (*XVI*) (Table I, Scheme 4).



SCHEME 4

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were taken on a UR 20 (Zeiss, Jena) spectrophotometer, UV spectra on a UV VIS Specord (Zeiss, Jena) instrument. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Jeol FX-100 spectrometer. Morpholinocyclohexene and piperidinocyclopentene were prepared according to ref.[10], diethyl malonate, ethyl cyanoacetate and ethyl acetoacetate were commercially available. Acetone phenylhydrazone,

cyclopentanone phenylhydrazone and cyclohexanone phenylhydrazone were prepared by condensation of phenylhydrazine with the corresponding ketones[9].

Reaction of 2-Pyridyl Isothiocyanate (*I*) with Enamines

A solution of the enamine (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 and taken down under diminished pressure. In the case of morpholinocyclohexene, the residue was mixed with acetone (20 ml), the crystalline material collected on filter, washed with acetone and crystallized from ethanol, affording the compound *II*. The acetone filtrate was taken down under diminished pressure and ethanol (10 ml) was added to the residue. The separated crystals were collected and crystallized from ethanol, yielding 0·8 g of the thiourea *IV*, 80–82°C. For $C_{10}H_{13}N_3SO$ (223·3) calculated: 18·82% N, 14·36% S; found: 18·73% N, 14·23% S. UV spectrum (methanol): λ_{max} 208 nm (log ε 4·03), 267 (4·19); IR spectrum (KBr), cm^{-1}: 1 532 (C=C_{arom}), 1 596 (C=N), 3 200 (NH). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·56–3·94 (m, 8 H, C_4H_8-morpholine), 6·94–7·14 (m, 1 H, pyridine H–5), 7·52–7·81 (m, 2 H, pyridine H–3 and H–4), 8·26 (m, 1 H, pyridine H–6). In the case of piperidinocyclopentene, the concentrated reaction mixture was chromatographed on a column of silica gel, using a chloroform–acetone (4 : 1) mixture as eluant. Crystallization of the last fraction from ethanol afforded the derivative *III*.

Reaction of 3,4-Trimethylenepyrido[1,2-*a*]pyrimidine-2-thione (*III*) with Methyl Iodide

Methyl iodide (0·14 g; 0·001 mol) was added to a solution of the derivative *III* (0·2 g; 0·001 mol) in nitromethane (20 ml) and the mixture was refluxed for 2 h. The solvent was distilled off under diminished pressure and the residue crystallized from methanol, yielding 0·34 g of the product *V*.

Reaction of 2-Pyridyl Isothiocyanate (*I*) with C-Acids

Sodium hydride (0·24 g; 0·01 mol) was added at 5°C to a stirred solution of the C-acid (0·01 mol) in benzene (20 ml). A solution of *I* (prepared by reflux of its dimer for 5 min; 1·36 g; 0·005 mol) in benzene (50 ml) was then added dropwise and the mixture was stirred at room temperature for 24 h. The separated sodium salt of the thioacetamide was filtered, dissolved in water (50 ml) and acidified with dilute (1 : 1) hydrochloric acid.

When ethyl cyanoacetate was used, the separated solid was filtered, washed with water and crystallized from dimethylformamide, affording the derivative *X*.

In the case of diethyl malonate, the separated oil was extracted with chloroform (3 × 20 ml), the combined extracts were dried over calcium chloride and taken down under diminished pressure, affording N-(2-pyridyl)-α,α-bis(ethoxycarbonyl)thioacetamide (*VI*) as an oil (2·4 g). A solution of the thioacetamide *VI* (2·2 g; 0·076 mol) in ethanol (20 ml) was refluxed for 1 h with a solution of sodium ethoxide (from 0·18 g of Na and 10 ml of ethanol). After removal of solvent under reduced pressure, water (50 ml) was added and the mixture was acidified with dilute (1 : 1) hydrochloric acid (pH 4). The separated product was collected on filter, washed with water and crystallized from methanol, affording the product *IX*.

When the reaction was performed with ethyl acetoacetate, the obtained solid was extracted with chloroform (3 × 20 ml), the combined extracts were dried over calcium chloride and taken down under reduced pressure. Ether (10 ml) was added to the residue and the precipitated compound was filtered, yielding 2·0 g of N-(2-pyridyl)-α-acetyl-α-ethoxycarbonylthioacetamide

(*VIII*). A solution of *VIII* (1·7 g; 0·065 mol) in ethanol (10 ml) was refluxed with a solution of sodium ethoxide (made from 0·16 g of sodium and 10 ml of ethanol) for 1 h. The solvent was evaporated under diminished pressure, water (50 ml) was added to the residue and the mixture was acidified with dilute (1 : 1) hydrochloric acid (pH 4). The separated product was filtered, washed with water and chloroform (3 × 10 ml) and crystallized from dimethylformamide–ether, giving the product *XI*, m.p. 233—235°C (reported[6] m.p. 222°C).

Reaction of 3-Ethoxycarbonyl-2-mercaptopyrido[1,2-*a*]-pyrimidin-4-one (*IX*) with Ethyl Bromide

Triethylamine (0·11 g; 1 mmol), followed by ethyl bromide (0·11 g; 1 mmol), was added to a solution of compound *IX* (0·24 g; 1 mmol) in dioxane (30 ml) and the mixture was stirred at room temperature for 3 days. The solvent was removed under diminished pressure and the residue was mixed with chloroform (10 ml). The solution was washed with water (2 × 5 ml), dried over sodium sulfate, filtered and taken down. Crystallization of the residue from acetone–ether afforded the compound *XII*.

Reaction of 2-Pyridyl Isothiocyanate (*I*) with Hydrazones

A solution of 2-pyridyl isothiocyanate dimer (1·36 g; 0·005 mol) in benzene (50 ml) was refluxed for 5 min. A solution of the hydrazone (0·01 mol) in benzene (10 ml) was then added, the mixture was refluxed for 1 h and the solvent distilled off under reduced pressure. In the case of acetone phenylhydrazone, the residue was chromatographed on a column of silica gel, using chloroform as eluant. On crystallization from ethanol, the third fraction afforded the compound *XIV*. In the case of cyclopentanone or cyclohexanone phenylhydrazones, the residue was mixed with ether (10 ml) and the precipitated crystals were collected on filter and crystallized from ethanol, yielding the respective compounds *XV* and *XVI*.

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