CROATICA CHEMICA ACTA CCACAA 47 (2) 127—133 (1975)

CCA-863

YU ISSN 0011-1643
547.821
Original Scientific Paper

Syntheses of New Pyrazolo-, and Tetrazolopyridines

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Received May 28, 1974

By the reaction of cyanoacetamide and acetylacetone we prepared some new pyrazolo(3,4-b) pyridines (*8, 8a, 9*) and tetrazolo(1,5-a) pyridines (*6, 12, 16*) over several reaction steps. Azido--tetrazolo isomerisation of tetrazolo (1,5-a) pyridines (*6, 12, 16*) has been investigated on the basis of their i. r. and n. m. r. spectra in three solvents (dimethyl sulfokside, chloroform and trifluoroacetic acid). Compound *8* can be detected as a tetrazolo tautomer in the solid state as well as in solutions. Compound *16* in the solid state exists only in the tetrazolo form, while in solutions it exists in both forms. Compound *12* in the solid state exists only in the azido form, while in solutions it exists in both forms.

INTRODUCTION

Syntheses of several title compounds have been reported by a number of authors: pyrazolo(3,4-b)pyridine-type compounds, *e. g.*, have been prepared by condensing either aminopyrazoles with acetonylacetone[1], or halogenopyridines with hydrazine[2], while tetrazolo(1,5-a)pyridines were synthesized from 2-hydrazinopyridines and nitrous acid[3], or from halogenopyridines and sodium azide[4–6].

In this work we describe the syntheses some new members of these series as objects for the investigations of their chemical properties.

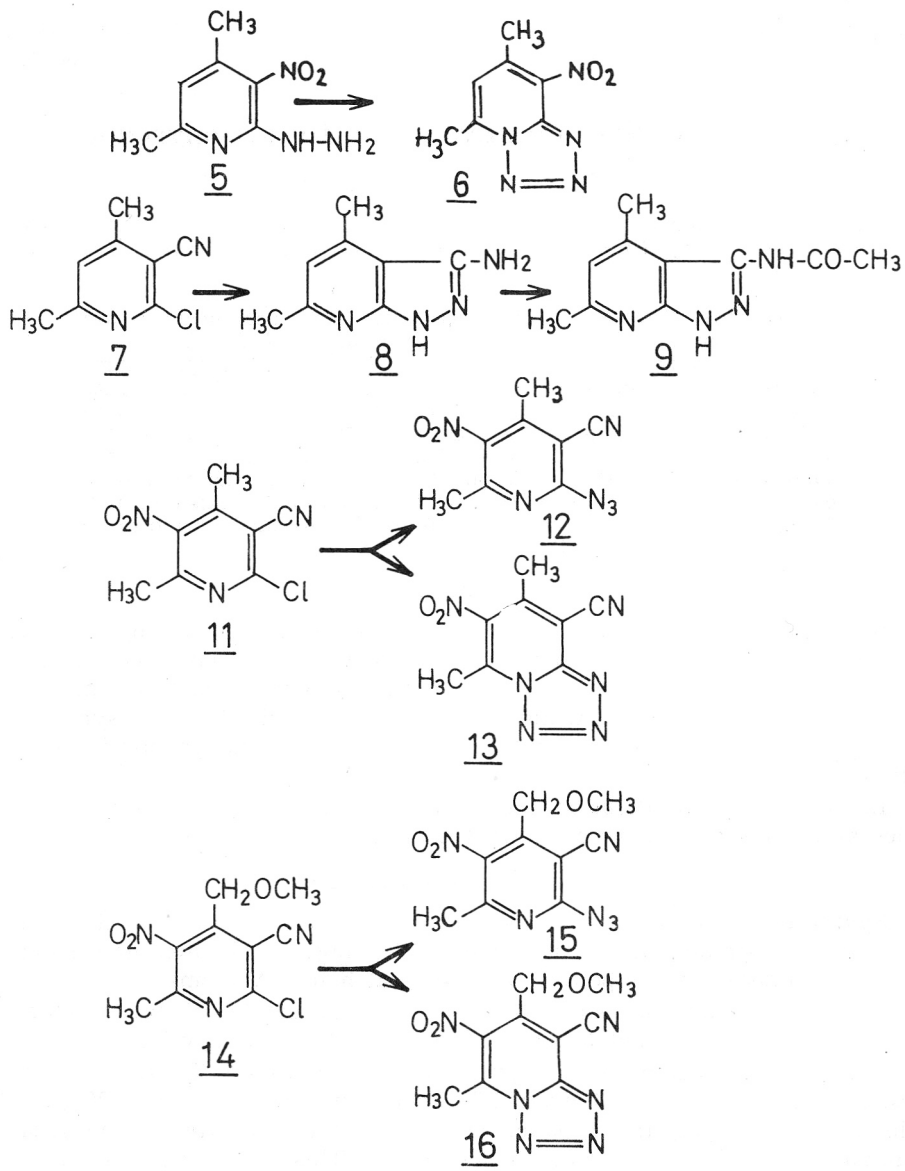
RESULTS AND DISCUSSION

Syntheses. — Conventional preparative methods were applied, starting from cyanoacetamide and acetylacetone and leading, over known intermediates, to new condesed-ring compounds with several hetero-*N* atoms.

The pyridine nucleus was generated by condensation[7] of cyanoacetamide and acetylacetone to yield 3-cyano-4,6-dimethyl-2-hydroxypyridine *(1)*.

The pathway leading to the pyrazolo(3,4-b)derivative *(8)*, starts by conversion of *(1)* to 2-chloro-3-cyano-4,6-dimethylpyridine *(7)*[8] with $PCl_5/POCl_3$ followed by reacting the product with hydrazine hydrate to the desired 3-amino-4,6-dimethylpyrazolo(3,4-b)pyridine *(8)*. This stage probably involved nucleophilic substitution at the 2-position of the pyridine ring with subsequent intramolecular addition of the hydrazino-group to the cyano triple bond. The resulting condensed-ring compound is obviously capable of undergoing imino-enamino tautomerism[9], but a large predominance of the enamino isomer is strongly suggested by i. r. data (absorption bands at wavenumbers corresponding to an NH_2-grouping, *viz.* 3390 and 3380 cm^{-1}, respectively).

SCHEME 1.



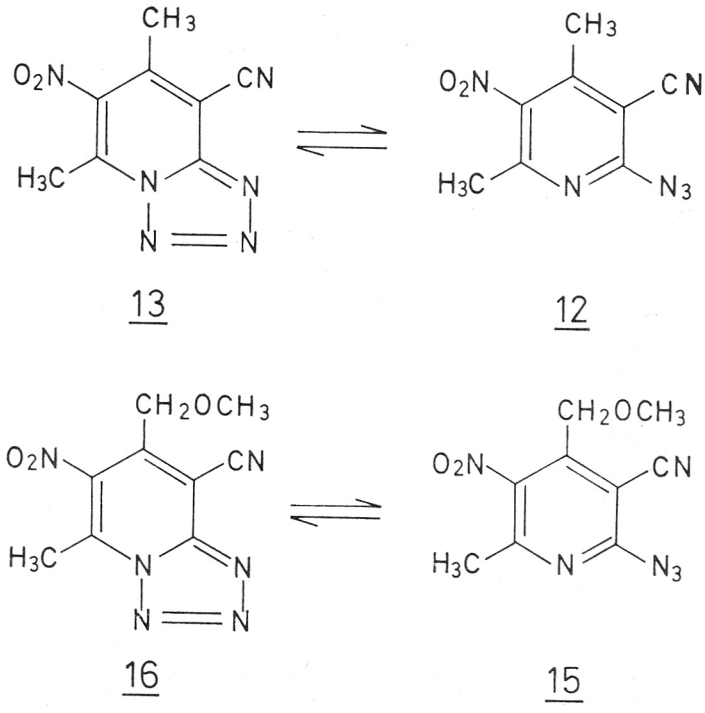
Compd. *(8)* readily reacted with acetyl chloride to give the acetamido-derivative *(9)*, and formed a promptly crystallizing picrate with picric acid.

A pathway directed toward the tetrazolopyridine derivative *(6)* started from *(1)*, which, on refluxing for 8 hrs. in 75% sulfuric acid, decarboxylated to 4,6-dimethyl-2-hydroxypyridine *(2)*[10,11]. Nitration of the latter gave 4,6-di-

methyl-3-nitro-2-hydroxypyridine *(3)*[12]. As the next step following the nitration, the hydroxy-group of compound *(3)* was substituted by a chlorine atom using PCl_5, to give 2-chloro-4,6-dimethyl-3-nitropyridine *(4)*[13]. The reaction with hydrazine converted the chloro derivative to 4,6-dimethyl-2--hydrazino-3-nitropyridine *(5)*[13], which gave a characteristic benzylidene derivative with benzaldehyde. Cyclization of *(5)* to 5,7-dimethyl-8-nitrotetrazolo (1,5-a)pyridine *(6)* in the final stage of this patway was achieved with $NaNO_2$ in aqueous hydrochloric acid solution. Although, we have expected a mixture of azido and tetrazolo isomers, the n. m. r. and i. r. spectra of compound *(6)* recorded in three solutions (DMSO-d_6, $CDCl_3$ and TFA), show only the presence of the tetrazolo form.

A pathway, starting once more with compd. *(1)*, leads to the tetrazolopyridine derivative *(13)*: nitration of *(1)* gave 3-cyano-4,6-dimethyl-2-hydroxy--5-nitropyridine *(10)*[7] which, in the next stage, was converted with $PCl_5/POCl_3$ to 2-chloro-3-cyano-4,6-dimethyl-5-nitropyridine *(11)*[7]. By a reaction of the latter with sodium azide, in the presence of lithium chloride, a solid product was obtained, representing a mixture of azido and tetrazolo isomers *(12)* and *(13)*, respectively. This heterogenity was recognized from i. r.-absorption data for the above solid product, and was rationalized as a consequence of azido-

SCHEME 2.



-tetrazolo interconversion. Bands characteristic for a tetrazolo ring[14] appear at 1100, 995, and 735 cm^{-1} in the KBr-pellet i. r.-spectrum, in addition to a markedly stronger band at 2140 cm^{-1} characteristic of an azido group[15]. The azido form thus seems to be predominantly represented in the mixture of isomers. Interestingly, the opposite result was obtained, when the reaction with sodium azide and lithium chloride was repeated with a methoxymethyl analogue *(14*)*. In the i. r.-spectrum of the resulting solid product the bands characteristic for the tetrazolo ring (appearing at 1085, 995.5, and 735 cm^{-1}) were much stronger than the band due to the azido-group, indicating that this product consisted almost entirely of the tetrazoloform *(16)*.

Azido—tetrazolo isomerization of pairs *(12)/(13)* and *(15)/(16)*. — Papers on azido-tetrazolo isomerization have formely appeared in the literature[16]. With tetrazolopyridines the equilibrium concentrations of isomers in solution were influenced both by substituents on the pyridine ring[17,18] and by the nature of the solvent[18,19]. In this Laboratory, the azido-tetrazolo isomerizations were studied both in the solid mixtures and in solvents, such as $CHCl_3$ and DMSO, by i. r.-spectroscopy, and in other solvents, TFA, $CDCl_3$ and DMSO-d_6 by n. m. r. spectroscopy. Spectral data derived from this studies are shown on Tables I and II.

TABLE I

I. r. spectra of Tetrazolo and Azido Isomers

$\tilde{\nu}$ / cm^{-1}	Compounds 13 ⇌ 12	Compounds 16 ⇌ 15
$\nu^{KBr}_{N_3}$	2140 (s)*	2140 (w)
$\nu^{KBr}_{C=N}$	1100; 995; 735 (w)*	1085; 995.5; 735 (s)
$\nu^{CHCl_3}_{N_3}$	2140 (s)	2140 (s)
$\nu^{CHCl_3}_{C=N}$	—	—
$\nu^{DMSO}_{N_3}$	2140 (m)*	2140 (m)
$\nu^{DMSO}_{C=N}$	735 (m)	1100; 735 (m)

* s = strong, w = weak, m= middle

* This compound is an intermediate of industrial vitamin B_6 synthesis. A sample was generously donated by PLIVA Chemical and Pharmaceutical Works, Zagreb.

TABLE II

N. m. r.-spectra of Tetrazolo and Azido Isomers

Compound	Solvent	Tetrazolo tautomer				Azido tautomer				Ratio azido/tetrazolo
		5-CH_3	7-CH_3	-OCH_3	-CH_2-	6-CH_3	4-CH_3	-OCH_3	-CH_2-	
13 ⇌ 12	TFA	3.13	2.82			2.61	2.52			10 : 8.6
	$CDCl_3$	3.10	2.78			2.58	2.49			10 : 0.023
	DMSO-d_6	3.01	2.70			3.21	2.52			6.8 : 10
16 ⇌ 15	TFA	3.20		3.60	5.11	2.62		3.53	4.83	10 : 5.5
	$CDCl_3$	3.11		3.41	4.91	2.53		3.33	4.61	10 : 0.54
	DMSO-d_6	3.00		3.24	4.83	2.51		3.23	4.60	1.5 : 10

Concentration relationships of isomers in solid equilibrium mixtures, as indicated by i. r. data, were already mentioned above.

In solution, however, conditions may be quite different, depending on the solvent. I. r. spectra recorded with liquid films (Table I) show that the azido--form is predominant in $CHCl_3$-solution, regardless of the substituent occupying the 4-position, while in DMSO solution both the azido- and tetrazolo--forms occur in comparable concentrations regardless, again, of the substituent in the 4-position. N. m. r. spectra (*cf.* data in Table II) recorded in TFA show a shift of equilibrium favoring the azido-form, for either CH_3- or CH_3OCH_2--substituted derivatives; however, an opposite relationship holds in DMSO-d_6 solution. All these results agree with previously reported data by other authors[18–21]. N. m. r. data obtained with $CDCl_3$-solutions show the presence of almost exclusively the azido-form in this solvent, which is consistent with results for $CHCl_3$-solutions indicated by i. r. data.

EXPERIMENTAL*

Compounds (*1*)[7], (*2*)[10], (*3*)[12], (*4*)[13], (*5*)[13], (*7*)[8], (*10*)[7], and (*11*)[7] were synthetised by the procedure described in the literature.

3-Amino-4,6-dimethylpyrazolo(3,4-b)pyridine (8)

A solution of 1 g (6.0 mmol) (*7*) in 50 ml abs. ethanol is heated and kept under reflux for 10 min. before adding 2 ml of 80% hydrazine hydrate. With continuous refluxing, crystals began to separate after 8 hrs. Refluxing is discontinued after an additional hour, and the suspension filtered while hot. The solid product was purified by recrystallization from methanol, giving 0.69 g (71.4%) of (*8*), m. p. 239—240 °C. I. r. (KBr-pellet) absorption bands (cm^{-1}): 3390 and 3380 (ν_{NH_2}), 3170 (ν_{NH}), 1600 ($\nu_{C=N}$), 1308 (ν_{C-N}). N. m. r. spectrum (CD_3COOD), singlets (δ): 2.52 (4-CH_3), 2.61 (6-CH_3), 3.42 (3-NH_2), 6.71 (H_5). Mass spectrum, m/e M^+ (rel. abundance): 162 (100%), 133 (19.7%), 107 (31.4%).

* All m. p.'s uncorrected. Spectrometers used to record i. r., n. m. r., and mass spectra were: a Perkin-Elmer Infracord Model 137 infrared spectrophotometer, a Varian A-60 NMR-spectrometer, and a Varian CH7 mass spectrometer.

Anal. $C_8H_{10}N_4$ (162.19) calc'd.: C 59.24, H 6.21, N 34.55%
found: C 59.53, H 6.45, N 34.39%

Picrate: 0.5 g (3.08 mol) (*8*) in 10 ml abs. ethanol was mixed with 1 ml saturated ethanolic picric acid, and the mixture was heated for 5 min. The yellow crystals separated thereupon were collected and recrystallized from aqueous ethanol to give 1.05 g (87%) purified picrate, m. p. 250—252 °C.

Anal. $C_8H_{10}N_4 \cdot C_6H_3N_3O_7$ (391.29) calc'd.: C 42.29, H 3.34, N 25.05%
found: C 42.67, H 3.50, N 25.37%

3-Acetamido-4,6-dimethylpyrazolo(3,4-b)pyridine (9)

1 ml Acetyl chloride was added to a solution of 0.5 g (3.08 mmol) (8) in 40 ml of nitrobenzene, and mixture was refluxed for 2 hrs. The solid obtained by removal of solvent under reduced pressure was crystallized twice from aqueous methanol under decoloration with active carbon. 0.22 g (36%) of (9), m. p. 275—276 °C, was obtained. Mass spectrum, *m/e* M^+ (rel. abundance): 204 (21.1%), 162 (100%).

Anal. $C_{10}H_{12}N_4O$ (204.23) calc'd.: C 58.81, H 5.92, N 27.44%
found: C 58.81, H 6.19, N 27.36%

5,7-Dimethyl-8-nitrotetrazolo(1,5-a)pyridine (6)

0.5 g (2.2 mmol) of (5) was dissolved in 10 ml of a mixture of equal volumen of conc. hydrochloric acid, and cooled to 0 °C. To this solution, ice-cold saturated aqueous sodium nitrite was gradually added with stirring and keeping temperature below 2 °C, until no further release of brown vapors was apparent. The reaction mixture was then poured into ice, and solid separating thereupon filtered with suction. After thoroughly washing with cold water, the product was dried and crystallized from absolute ethanol. 0.45 g (84.6%) of purified (6), m. p. 183—184 °C was obtained. I. r. absorption bands (cm^{-1}); (KBr-pellet): 1645 ($\nu_{C=N}$), 1550 ($\nu_{N=N}$), 1510 (ν_{C-NO_2}), 1030 ($\nu_{\text{tetrazolo ring}}$); ($CHCl_3$): 1045 ($\nu_{\text{tetrazolo ring}}$); (DMSO): 1025 ($\nu_{\text{tetrazolo ring}}$). N. m. r. spectrum ($\delta$); DMSO-$d_6$: 2.65 (singlet, 7-$CH_3$), 2.89 (doublet, 5-$CH_3$), 7.46 (singlet, H_6) $J = 1.00$ Hz (5-CH_3, H_6); TFA: 3.07 (singlet, 7-CH_3), 3.18 (doublet, 5-CH_3), 7.62 (singlet, H_6), $J = 0.9$ Hz (5-CH_3, H_6); $CDCl_3$: 2.7 (singlet, 7-CH_3), 2.99 (doublet, 5-CH_3), 7.00 (singlet, H_6), $J = 1.1$ Hz (5-CH_3, H_6). Mass spectrum, *m/e* M^+ (rel. abdundance): 193 (47.6%), 92 (100%), 67 (97.4%).

Anal. $C_7H_7N_5O_2$ (193.17) calc'd.: C 43.52, H 3.65, N 36.26%
found: C 43.26, H 3.90, N 36.16%

2-Azido-3-cyano-4,6-dimethyl-5-nitropyridine (12)

A solution containing 0.5 g (2.9 mmol) (*11*), 0.2 g (3.1 mmol) sodium azide, and 0.18 g (4.2 mmol) lithium chloride in 15 ml dimethylformamide was stirred 3 min. at 5 °C in a moisture-protected vessel. The reaction mixture was poured into 30 g of ice, whereupon the crude product separated and was filtered with suction. After recrystallization from 96% ethanol 0.31 g (61.6%) (*12*), m. p. 106—107 °C, was obtained. I. r. (KBr-pellet) absorption bands (cm^{-1}): 2250 (ν_{CN}), 2140 (ν_{N_3}); data from liquid films, see Table I. N. m. r. spectrum: see Table II. Mass spectrum, *m/e* M^+ (rel. abdundance): 218 (100%), 192 (5.6%), 117 (61.1%), 90 (70.4%), 65 (96.3%).

Anal. $C_8H_6N_6O_2$ (218.18) calc'd.: C 44.04, H 2.77, N 38.52%
found: C 44.34, H 2.91, N 38.42%

8-Cyano-7-methoxymethyl-5-methyl-6-nitrotetrazolo(1,5-a)pyridine (16)

The procedure described for preparation of (*12*) was followed starting with 5 g (0.025 mol) of 2-chloro-3-cyano-4-methoxymethyl-6-methyl-5-nitropyridine*, except

* See footnote on page 5.

that stirring was carried on for 2 hrs. at room temperature. Pouring the reaction mixture on 150 g of ice resulted in separation of a product which was filtered with suction, and recrystallized from 96% ethanol to give 4.0 g (77.8%) of purified product, m. p. 88—89 °C. I. r. (KBr-pellet) absorption bands (cm^{-1}): 1660, 1085, 995, and 735 ($\nu_{C=N}$); liquid-film data are shown in Table I. N. m. r. spectra: see Table II. Mass spectrum, *m/e* M^+ (rel. abundance): 248 (12.1%), 51 (27.3%), 45 (100%).

Anal. $C_9H_8N_6O_3$ (248.20) calc'd.: C 43.55, H 3.25, N 33.86%
found: C 43.84, H 3.61, N 33.58%

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SAŽETAK

Sinteze novih pirazolo- i tetrazolopiridina

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Kondenzacijom cijanoacetamida i acetilacetona preko niza reakcija sintetizirani su neki novi pirazolo[3,4-b]piridini *(8, 8a* i *9)* i tetrazolo[1,5-a] piridini *(6, 12* i *16).* Azidotetrazolo izomerizacija tetrazolo[1,5-a]piridina *(6, 12* i *16)* je izučavana na osnovu i. r. i n. m. r. spektara snimljenih u tri otapala (dimetilsulfoksid, kloroform i trifluoroctena kiselina). U krutom stanju kao i u otapalima spoj *8* se nalazi isključivo u tetrazolo formi. Spoj *16* u krutom stanju egzistira kao tetrazolo oblik, dok se u otapalima javlja u oba oblika. Spoj *12* u krutom stanju postoji kao azido-oblik, a u otapalima se konstatiraju i azido-oblik i tetrazolo-oblik.

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Prispjelo 28. svibnja 1974.