SYNTHESES OF BISHETEROCYCLES FROM 2-HYDRAZINO-3-AMINOPYRIDINE

G. A. Mokrushina, I. Ya. Postovskii,
and S. K. Kotovskaya

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2-Hydrazino-3-aminopyridine reacts with carbon disulfide in an alkaline medium to give 1H-3-aminoimidazo[4,5-b]pyridine-2-thione and in a neutral medium to give 8-amino-3-thio-sym-triazolino[4,3-a]pyridine. The reaction of 2-α-methylhydrazino-3-aminopyridine with carbon disulfide leads to anhydro-1-methyl-3-mercapto-8-amino-sym-triazolo[4,3-a]pyridinium betaine.

1,2,3,4-Tetrahydropyrido[2,3-e]asym-triazine-3-thione is formed in the reaction of 2-amino-3-hydrazinopyridine with carbon disulfide [1]. In the present research we investigated the reaction of an isomeric compound – 2-hydrazino-3-aminopyridine (Ia) [2] – with carbon disulfide, in which one might have expected the formation of three cyclization products: 1,2,3,4-tetrahydropyrido[2,3-e]-asym-triazine-2-thione (II), 1H-3-aminoimidazo[4,5-b]pyridine-2-thione (III), and 8-amino-3-thio-sym-triazolino]4,3-a]pyridine (IVa). Each of these compounds could be of interest as a potentially physiologically active compound.

In the case of cyclization in a weakly alkaline medium we isolated product III. Its structure was proved by deamination to imidazo[4,5-b]pyridine-2-thione (V), which was identical to the product obtained from 2,3-diaminopyridine [3]. The corresponding methylthio derivative VI is formed by methylation of III with methyl iodide in an alkaline medium. Its structure was confirmed by deamination to 2-methylthioimidazo[4,5-b]pyridine (VII).

8-Amino-3-thio-sym-triazolino[4,3-a]pyridine (IVa) was obtained as a result of the reaction of 2-hydrazino-3-aminopyridine (Ia) with carbon disulfide in a neutral medium. Its IR spectrum contains bands of stretching vibrations of an amino group (3417 and 3341 cm^{-1}). The UV spectra (Fig. 1) of IVa and 8-chloro-3-thio-sym-triazolino[4,3-a]pyridine (IVb), which was specially obtained from comparison, are of the same type, and this indicates that they have similar electronic structures. The chemical shifts in the PMR spectra for the 1-H, 2-H, and 3-H protons in IVb with respect to the signal of dimethyl sulfoxide (DMSO) are 8.13, 6.85, and 7.54 ppm, whereas they are 7.52, 6.73, and 6.27 ppm in the spectrum of IVa. The certain shift to stronger field for the signals of the pyridine protons of IVa as compared with IVb is due to the electron-donor character of the amino group. The spin–spin coupling constants of the protons of IVa,b are equal and have the following numerical values: J_{12} = 8.0, J_{13} = 2.0, and J_{23} = 8.0 Hz.

As in the case of the cyclization of 2-α-methylhydrazinopyridine with thiophosgene [4], betaine VIII was isolated from the reaction of 2-α-methylhydrazino-3-aminopyridine [2] with carbon disulfide. The presence of a free amino group is confirmed by the formation of azomethine X and by the absorption of its stretching vibrations in the IR spectrum. 1-Methyl-3-methylthio-8-amino-sym-triazolo[4,3-a]pyridinium iodide (IX) is formed by methylation of VIII with methyl iodide.

Thus, in contrast to the reaction of 2-amino-3-hydrazinopyridine with carbon disulfide [1], closing to an imidazole or triazole ring rather than the formation of a triazine ring occurs in the reaction with the isomeric 2-hydrazino-3-aminopyridine.

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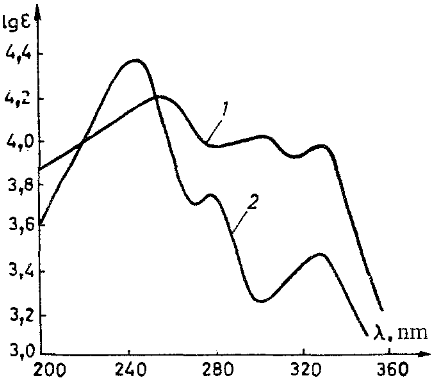
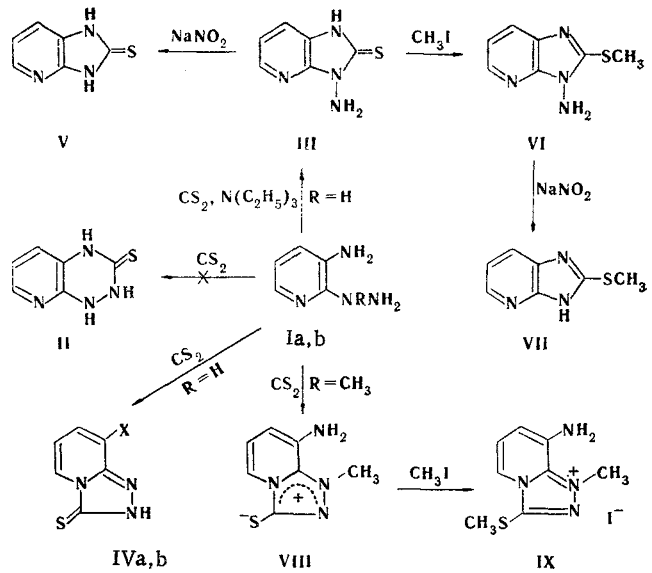


Fig. 1. UV spectra of IVa,b in 0.1 M NaOH.

TABLE 1. Characteristics of the Synthesized Compounds (III-X)

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
III	285—287[a]	42,9	3,6	33,7	$C_6H_6N_4S$	43,3	3,6	33,7	70
IVa	220—222[b]	43,7	4,0	33,7	$C_6H_6N_4S$	43,3	3,7	33,7	82
IVb	300—302[a]	39,0	2,2	22,7	$C_6H_4N_3SCl$	38,9	2,3	22,5	90
VI	205—208[c]	46,2	4,8	31,2	$C_7H_8N_4S$	46,5	4,5	31,1	66
VII	210—212[b]	50,8	4,5	25,5	$C_7H_7N_3S$	50,9	4,3	25,4	70
VIII	273—277[b]	46,7	4,6	31,2	$C_7H_8N_4S$	46,7	4,6	31,1	75
IX	290—295[c]	30,0	3,7	17,4	$C_8H_{11}N_4SI$	29,8	3,5	17,4	56
X	310—315[d]	53,7	3,8	22,5	$C_{14}H_{12}N_5O_2S$	53,5	3,9	22,3	65

[a] By reprecipitation from alkali by the addition of acid. [b] From water. [c] From ethanol. [d] From DMF.



Ia R = H, b R = CH_3; IVa X = NH_2, b X = Cl

EXPERIMENTAL

The electronic spectra were recorded with a Specord UV-vis recording spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of DMSO solutions were recorded with a Perkin—Elmer R-12-B spectrometer (60 MHz). The physical constants and yields of the compounds are presented in Table 1.

1H-3-Aminoimidazo[4,5-b]pyridine-2-thione (III). A 4.4-g (36 mmole) sample of 2-hydrazino-3-aminopyridine (Ia) [2] was dissolved in ethanol, 8 ml (130 mmole) of carbon disulfide and 2 ml of triethylamine were added, and the mixture was refluxed for 1 h. The precipitate was removed by filtration. The product was quite soluble in alkali but insoluble in most organic solvents. It was purified by reprecipitation from 2 M NaOH by the addition of HCl.

Anhydro-1-methyl-3-mercapto-8-amino-sym-triazolo[4,3-a]pyridinium Betaine (VIII). A 1.6-g (12 mmole) sample of 2-α-methylhydrazino-3-aminopyridine was dissolved in ethanol, 5 ml (80 mmole) of carbon disulfide and 2 ml of triethylamine were added, and the mixture was refluxed for 5 h. A portion of the solvent was removed by distillation, the residual solution was cooled, and the resulting colorless crystalline precipitate was removed by filtration.

8-Amino-3-thio-sym-triazolino[4,3-a]pyridine (IVa). A 7.2-g (58 mmole) sample of 2-hydrazino-3-aminopyridine was dissolved in ethanol, 12 ml (200 mmole) of carbon disulfide was added, and the mixture was refluxed for 4-5 h. A portion of the solvent was removed by distillation, the residual mixture was cooled, and the resulting crystalline precipitate was removed by filtration. The product was soluble in water and ethanol but insoluble in benzene.

8-Chloro-3-thio-sym-triazolino[4,3-a]pyridine (IVb). This compound was obtained from 2-hydrazino-3-chloropyridine [5] by the method used to prepare IVa.

Imidazo[4,5-b]pyridine-2-thione (V). A solution of 0.13 g (1.8 mmole) of $NaNO_2$ in 3 ml of water was added dropwise to a suspension of 0.2 g 1.2 mmole) of III in 1 ml of concentrated HCl at no higher than 10°, after which the solution was allowed to stand at room temperature for 2 h. The precipitate was removed by filtration. The product (50% yield) was completely identical to the product obtained from 2,3-diaminopyridine [3] with respect to its UV and IR spectra.

3-Amino-2-methylthioimidazo[4,5-b]pyridine (VI). A 0.3-ml (48 mmole) sample of methyl iodide was added to 0.25 g (1.6 mmole) of III in 15 ml of water containing 0.63 g (16 mmole) of NaOH, and the mixture was allowed to stand at room temperature for 2 h. The precipitate was removed by filtration. The product was soluble in water, ethanol, and benzene.

2-Methylthioimidazo[4,5-b]pyridine (VII). A solution of 0.11-g (1.6 mmole) of $NaNO_2$ in 3 ml of water was added dropwise at no higher than 10° to 0.19 g (1 mmole) of VI in 1 ml of concentrated HCl, and the resulting solution was allowed to stand at room temperature for 24 h, after which it was made alkaline to pH 7. The precipitate was removed by filtration. The product was soluble in water and ethanol but insoluble in benzene.

1-Methyl-3-methylthio-8-amino-sym-triazolo[4,3-a]pyridinium Iodide (IX). A 0.25-g (1.4 mmole) sample of VIII was suspended in 15 ml of methanol, 2.5 ml (40 mmole) of methyl iodide was added, and the mixture was refluxed on a water bath for 10 min. Compound IX was precipitated by the addition of ether. The product was soluble in water and ethanol but insoluble in benzene.

Anhydro-1-methyl-3-mercapto-8-(4-nitrophenyl)azomethine-sym-triazolo[4,3-a]pyridinium Betaine (X). A 0.2-g (1.1 mmole) sample of VIII was dissolved in water, a solution of 0.17 g (1.1 mmole) of p-nitrobenzaldehyde in ethanol was added, and the mixture was refluxed for 5 min. The red finely crystalline precipitate was removed by filtration. The product was insoluble in water, ethanol, and benzene.

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