SYNTHESIS AND PROPERTIES OF 3-THIONO DERIVATIVES OF PYRIDO[2,3-e]-ASYM-TRIAZINE

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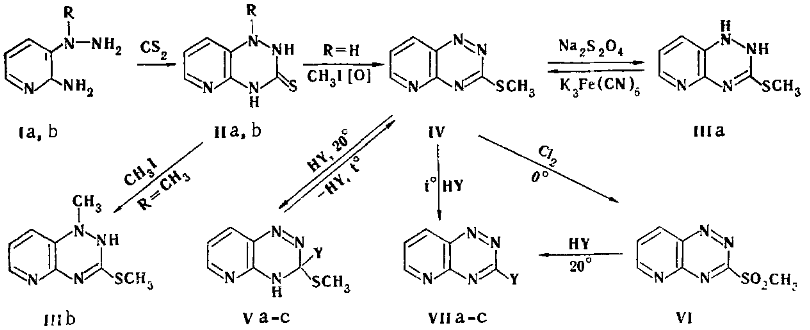
2-Amino-3-hydrazinopyridine reacts with carbon disulfide to give 1,2,3,4-tetrahydropyrido[2,3-e]-asym-triazine-3-thione. The methylthio derivative obtained from it is oxidized to the sulfone, which undergoes exchange of the methylsulfonyl group for an amine residue in the cold. The methylthio derivative undergoes this sort of reaction only on heating, whereas in the cold it reacts with amines to give adducts that are unstable in solution and on heating.

The interest in the chemistry of pyrido-asym-triazines has recently grown in connection with the detection of the biological activity of these compounds [1, 2]. However, insufficient study has been devoted to the chemistry of these compounds because of the inaccessibility of pyrido-asym-triazines.

Compounds with a pyridotriazine system are obtained by cyclization of o-nitroguanidinopyridines in alkaline media [3] and of o-aminohydrazinopyridines with ethyl orthoformate in acidic media, and also by cyclodehydration of o-aminoacylhydrazinopyridines [4].

We have obtained the previously unknown 1,2,3,4-tetrahydropyrido[2,3-e]-asym-triazine-3-thione (IIa) and 1-methyl-1,2,3,4-tetrahydropyrido[2,3-e]-asym-triazine-3-thione (IIb) by cyclization of 2-amino-3-hydrazinopyridine (Ia) and 2-amino-3-α-methylhydrazinopyridine (Ib).



I,IIa R=H; b R=CH_3; Va Y=morpholinyl b Y=N_2H_3; c Y=butylamino;VIIa Y=morpholinyl;
b Y=pyrrolidinyl

The thione structure of these compounds follows from the absence of the characteristic absorption band of the SH group in the IR spectra.

Compounds IIa, b are crystalline substances that are quite soluble in alkalis and concentrated acids and only slightly soluble in most organic solvents.

The methylthio derivatives were obtained by methylation of IIa, b with methyl iodide in alkaline media. Thus 3-methylthiopyrido[2,3-e]-asym-triazine (IV) is obtained as yellow needles from IIa, and colorless 1-methyl-3-methylthio-1,2-dihydropyrido[2,3-e]-asym-triazine (IIIb) is obtained from IIb. It is interesting that methylation of triazinethione IIa gives directly methylthio compound IV, i.e., oxidative aromatization of dihydro derivative of IIIa occurs under the methylation conditions. Compound IV reacts with sodium hydrosulfite in an aqueous suspension to give again colorless 1,2-dihydro-3-methylthiopyrido[2,3-e]-asym-triazine (IIIa); reconversion is accomplished by the action of a solution of $K_3Fe(CN)_6$ and also by storage in air of an alcohol

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TABLE 1. Pyrido[2,3-e]-asym-triazines

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IIa	225—227	$C_6H_6N_4S$	43.2	3,4	33,4	43,4	3,6	33,7	55
IIb	205—206	$C_7H_8N_4S$	46,5	4,4	30,8	46,7	4,5	31,1	45
IIIa	215—217	$C_7H_8N_4S$	46,5	4,4	30,8	46,7	4,5	31,1	80
IIIb	195—196	$C_8H_{10}N_4S$	50,1	5,4	28,4	49,5	5,2	28,9	70
IV	160—161	$C_7H_6N_4S$	47,2	3,5	31,5	47,2	3,4	31,5	50
VI	105—110 (dec.)	$C_7H_8N_4SO_2 \cdot \cdot 2HCl$	30,6	3,2	20,1	30,1	2,8	19,8	80
VI	175—176	$C_7H_6N_4SO_2$	40,0	3,1	26,5	40,0	2,9	26,7	60
VIIa	137—138	$C_{10}H_{11}N_5O$	54,9	5,2	31,9	55,3	5,1	32,2	50
VIIb	105—106	$C_{10}H_{11}N_5$	59,4	6,0	34,2	59,7	5,5	34,8	30

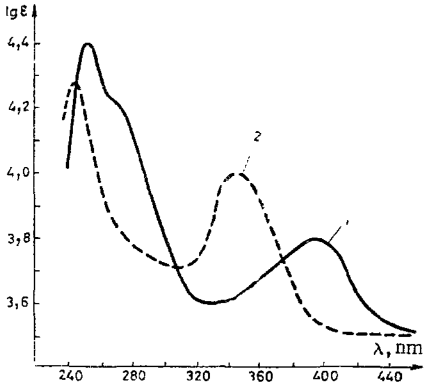


Fig. 1. UV spectrum: 1) 3-methylthiopyrido-[2,3-e]-asym-triazine (IV) in alcohol; 2) 3-methylthiopyrido[2,3-e]-asym-triazine (IV) in 20% solution of morpholine in alcohol.

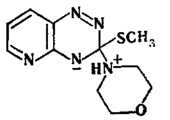
solution of IIIa (this conversion can be followed spectrometrically). The structures of IIa, b and IV were confirmed by their IR spectra – stretching vibrations of the NH group are observed in the spectra of IIIa, b at 3150-3250 cm^{-1}, whereas the vibrations of an NH group are absent in the spectrum of IV.

Oxidation of an aqueous suspension of methylthio derivative IV with chlorine gave 3-methylsulfonyl-pyrido[2,3-e]-asym-triazine (VI), which was isolated in the dihydrochloride form. This confirms that methylation of thione IIa occurs at the thione group rather than at the nitrogen atom. The moist dihydrochloride of VI is extremely unstable in air, but it can be stored for several days unchanged over P_2O_5. The isolation of sulfone VI in free form is difficult because of its exceptionally high reactivity. Thus it reacts with a 1.5-2-fold excess of amine at room temperature in a few minutes to give nucleophilic substitution products VII. The proposed method for the preparation of 3-substituted pyrido[2,3-e]-asym-triazine derivatives is simpler than the multistep method described in [3].

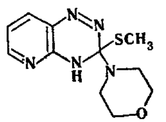
During a study of the nucleophilic substitution of the methylthio group in IV we made an interesting observation. Whereas the expected replacement of the methylthio group by a morpholine residue occurs when it is heated with excess morpholine, a compound with a composition corresponding to the product of addition of a molecule of the amine to methylthio compound IV is formed at room temperature. We also observed the formation of this sort of adduct in the reaction of methylthio compound IV with morpholine, hydrazine, and butylamine. In the first two cases the adducts were isolated in crystalline form, and in the last case the adduct was detected spectrophotometrically.

Compounds V are extremely unstable – they gradually split out amines (particularly readily when they are heated) in air to give starting methylthio compound IV. Splitting out of morpholine at 95-100° was observed during a study of adduct Va (in which the amine is morpholine) by thermogravimetry, and melting of starting IV was recorded at 155-160°. Decomposition of adducts V to the starting components also occurs when they are dissolved in various solvents (alcohol, benzene, and ether).

During a study of the reaction of methylthio compound IV with amines in solution we observed that its electronic spectrum changes when amine is added: the intensity of the maximum at 390 nm decreases, and a new maximum appears at 350 nm. A gradual decrease in the maximum at 390 nm (until it vanishes completely) is observed as the amine concentration increases, and there is a corresponding increase in the maximum at 350 nm (Fig. 1). The presence of a hypsochromic shift makes it possible to assume that V is not a charge-transfer complex (CTC), especially since the methylthio compound does not form an adduct with more basic tertiary amines (for example, with triethylamine). When deuterohydrazine is added to the methylthio compound, one observes a shift of the signal of the methyl group in the PMR spectrum from δ 2.55 ppm to stronger field to δ 2.40 ppm, whereas the protons of the pyridine fragments are not shifted. It can be concluded from these data that adduct formation occurs at the carbon atom in the 3 position, where the electron density is reduced. Considering all of the above, two possible structures A and B can be assumed for adducts V.



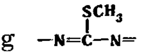
A



B

Structure A is excluded on the basis of the fact that the IR spectrum of adduct Va (in which the amine is morpholine) does not contain any absorption at 2300-2700 cm^{-1} characteristic for the NH group. At the same time the spectrum contains two absorption bands at 3180 and 3100 cm^{-1}, which can be assigned to the vibrations of the NH group of adduct V. These bands are absent in the spectrum of starting methylthio compound IV.

All of the data presented above make it possible to conclude that an adduct to which structure B can be assigned with a considerable degree of likelihood is formed in the cold in the reaction of amines with methylthio derivative IV.

The unusual addition of an amine to a heterocyclic compound at the ring  $-N{=}\overset{SCH_3}{\overset{|}{C}}-N{=}$ grouping is of interest for the study of the mechanism of nucleophilic substitution of a methylthio group by an amino group and is worthy of further study.

EXPERIMENTAL

The electronic spectra were obtained with a Specord UV-vis spectrophotometer. The IR spectra of KBr pellets of the compounds were measured with a UR-20 spectrometer. The PMR spectra were recorded with a Perkin–Elmer R 12B spectrometer with hexamethyldisiloxane as the internal standard. The decomposition temperatures of Va,b were determined with a Paulik–Paulik–Erdey derivatograph. The physical characteristics of II-VII are presented in Table 1.

2-Amino-3-hydrazinopyridine (Ia). This compound was obtained by reduction of 2-nitro-3-hydrazinopyridine [5] with tin in hydrochloric acid and was isolated in 75% yield as the dihydrochloride with mp 202-203° (dec., from 18% HCl). Found: C 30.3; H 5.2; N 28.4%. $C_5H_{10}Cl_2N_4$. Calculated: C 30.5; H 5.1; N 28.6%.

2-Amino-3-α-methylhydrazinopyridine (Ib). This compound was obtained by reduction of 2-nitro-3-α-methylhydrazinopyridine [5] by the method in [4]. The resulting solution was used for subsequent cyclization without isolation of Ib.

1,2,3,4-Tetrahydropyrido[2,3-e]-asym-triazine-3-thione (IIa). This compound was obtained by refluxing an alcohol solution of the dihydrochloride of Ia with a twofold molar excess of carbon disulfide at pH 7-8 for 5 h. Product IIa was removed by filtration and reprecipitated from alkaline solution by the addition of acid.

1-Methyl-1,2,3,4-tetrahydropyrido[2,3-e]-asym-triazine-3-thione (IIb). This compound was obtained from Ib by the method used to obtain IIa and was reprecipitated from alkaline solution by the addition of acid.

1-Methyl-3-methylthio-1,2-dihydropyrido[2,3-e]-asym-triazine (IIIb). A 0.1-g (0.51 mmole) sample of IIb was dissolved in a mixture of 10 ml of 50% aqueous alcohol and 0.15 ml of 30% aqueous NaOH, after which 0.3 g (2.10 mmole) of CH_3I was added, and the mixture was stirred for 5 min. The resulting shiny plates of IIIb were removed by filtration and crystallized from alcohol.

3-Methylthiopyrido[2,3-e]-asym-triazine (IV). A) A 0.2-g (1.12 mmole) sample of IIa was dissolved in 10 ml of water containing a 1.5-fold molar excess of alkali, after which 0.3 g (2.10 mmole) of CH_3I was added, and the mixture was allowed to stand at room temperature for 12 h. The resulting yellow needles of IV were removed by filtration and crystallized from water.

B) A 0.1-g (0.55 mmole) sample of IIIa was suspended in a solution of 0.1 ml of concentrated ammonium hydroxide, 0.5 g of $K_3Fe(CN)_6$ in 3 ml of water was added, and the mixture was stirred for 5 min. The mixture was then filtered to remove IV, which was washed with water.

1,2-Dihydro-3-methylthiopyrido[2,3-e]-asym-triazine (IIIa). A 0.2-g (1.12 mmole) sample of IV was stirred in a solution of 0.3 g of sodium hydrosulfite in 5 ml of water. The mixture was filtered to remove IIIa, which was washed with water.

3-Methylthio-3-morpholinyl-3,4-dihydropyrido[2,3-e]-asym-triazine (Va). A 0.2-g (1.12 mmole) sample of V was stirred in 5 ml of alcohol with 0.5 g (5.8 mmole) of morpholine for 5 min. The resulting precipitate was removed by filtration and washed with ether to give Va in 60% yield. Found: C 49.9; H 5.8; N 26.8%. $C_{11}H_{15}N_5O_5S$. Calculated: C 49.9; H 5.7; N 26.4%. Compound Va underwent decomposition to give starting methylthio compound IV during recrystallization from water and also when it was heated to 100°.

3-Methylthio-3-hydrazino-3,4-dihydropyrido[2,3-e]-asym-triazine (IVb). This compound was obtained in 60% yield by the method used to prepare Va. Found: C 40.1; H 4.6; N 40.4%. $C_7H_{10}N_6S$. Compound Vb underwent decomposition to give starting IV during recrystallization from water.

3-Methylsulfonylpyrido[2,3-e]-asym-triazine (VI). A 0.3 -g (1.46 mmole) sample of IV was suspended in 10 ml of water, after which the suspension was cooled to 0°, and chlorine was bubbled through it with stirring for 20 min. The dihydrochloride was removed by filtration and washed with 2 ml of ether. The free base was isolated by adding the calculated amount of an amine (hydrazine) to a suspension of the dihyrochloride in alcohol. The precipitate was removed by filtration and washed with water.

3-Morpholinopyrido[2,3-e]-asym-triazine (VIIa). A) A 0.1-g (0.35 mmole) sample of the dihydrochloride of VI was suspended in alcohol, and 0.5 g (5.8 mmole) of morpholine was added. The resulting solution was vacuum evaporated to dryness, and the solid residue of triazine VII was crystallized from water.

B) A 0.01-g sample of IV was refluxed for 1 h in alcohol with a small excess of morpholine. Chromatographic study of the reaction mixture attested to the presence of VII along with starting methylthio compound IV.

3-Pyrrolidinylpyrido[2,3-e]-asym-triazine (VIIb). A 0.1-g (0.35 mmole) sample of the hydrochloride of VI was suspended in alcohol, and 0.08 g (1.1 mmole) of pyrrolidine was added. The solvent was vacuum evaporated, and the residue was dissolved in water. The aqueous solution was made alkaline to pH 7-8 and extracted with chloroform. Evaporation of the chloroform gave VIIb, which was crystallized from petroleum ether-dichloroethane.

LITERATURE CITED

1. B. A. Lewis and R. G. Schepherd, US Patent No. 3597427; Chem. Abstr., 75, 110342 (1971).
2. J. A. Carbon, US. Patent No. 3597427; Chem. Abstr., 75, 110342 (1971).
3. J. A. Carbon and S. H. Tobata, J. Org. Chem., 27, 2504 (1962).
4. B. A. Lewis and R. G. Schepherd, J. Heterocycl. Chem., 81, 41 (1971).
5. G. A. Mokrushina, Yu. A. Azev, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 7, 1004 (1975).