bonylindolizines (VII-IX) was accomplished by the Hückel MO method with the use of the standard Pullman parameters.

LITERATURE CITED

1. T. S. Loseva, M. S. Goizman, L. M. Alekseeva, O. R. Shvarts, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 6, 802 (1978).
2. E. E. Mikhlina, A. D. Yanina, T. S. Loseva, K. F. Turchin, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 7, 977 (1974).
3. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 2, 209 (1976).
4. T. S. Loseva, A. D. Yanina, E. E. Mikhlina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 348 (1976).
5. L. M. Alekseeva, G. G. Dvoryantseva, M. S. Goizman, T. S. Loseva, A. D. Yanina, E. E. Mikhlina, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 11, 1540 (1976).
6. K. Doerfel, Statistics in Analytical Chemistry [Russian translation], Mir, Moscow (1969).
7. A. Albert and E. Serjeant, Ionization Constants of Acids and Bases, Methuen (1962).

SYNTHESIS OF 6-ALKYLTHIOIMIDAZO[1,2-a]PYRIDINES

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A number of 6-alkylthio(and sulfonyl)-substituted imidazo[1,2-a]pyridines were synthesized by the reaction of 5-alkylthio- and 5-alkylsulfonyl-2-aminopyridines with ω-bromoacetophenone and α-chlorocyclohexanone in order to search for new compounds that have fungicidal activity. 5-Alkylthio-2-aminopyridines were obtained from the double salt of 5-mercapto-2-aminopyridine with $SnCl_2$ and HCl by reaction with alkyl halides or tert-C_4H_9OH and 75% H_2SO_4. 5-tert-Butylthio-2-aminopyridine was oxidized by means of $KMnO_4$ to 5-tert-butylsulfonyl-2-aminopyridine. A double salt was synthesized from 2-aminopyridine-5-sulfonic acid.

It has been shown [1] that 3-alkylthio-substituted imidazo[1,2-a]pyridines have significant fungicidal activity. In our search for more effective compounds of this series we decided to synthesize 6-alkylthioimidazo[1,2-a]pyridines with an alkylthio group in the pyridine ring rather than in the imidazole ring.

Our attempts to replace the bromine atom in 6-bromo-2-phenylimidazo[1,2-a]pyridine by an alkylthio group through the Grignard reaction (by the action of Mg or EtMgBr) or by exchange with Li and by the action of BuLi under various conditions were unsuccessful. In most cases the starting bromo compound was recovered. We were able to solve this problem by a different method, viz., by starting from 2-amino-5-alkylthiopyridines. The key compound — 2-amino-5-mercaptopyridine (I) was obtained in the form of a double salt with $SnCl_2$ and HCl from 2-aminopyridine-5-sulfonic acid. We were unable to obtain 2-amino-5-mercaptopyridine in the base form from salt I. 5,5'-Bis(2-aminopyridyl) disulfide (VIII) was obtained by the action of iodine in an alkaline medium on salt I.

5-Alkylthio-2-aminopyridines (II-IV, Table 1) were obtained by alkylation of salt I with alkyl halides in the presence of alkali. Very small amounts of dialkylated products were formed along with sulfides II-IV; the former were detected by thin-layer chromatography (TLC). In one case this product was isolated and characterized by conversion to the picrate. Its structure can be tentatively expressed by formula V. The indicated impurities are difficult to separate, but their presence does not prevent the use of sulfides II-IV for the preparation of 6-alkylthioimidazo[1,2-a]pyridines.

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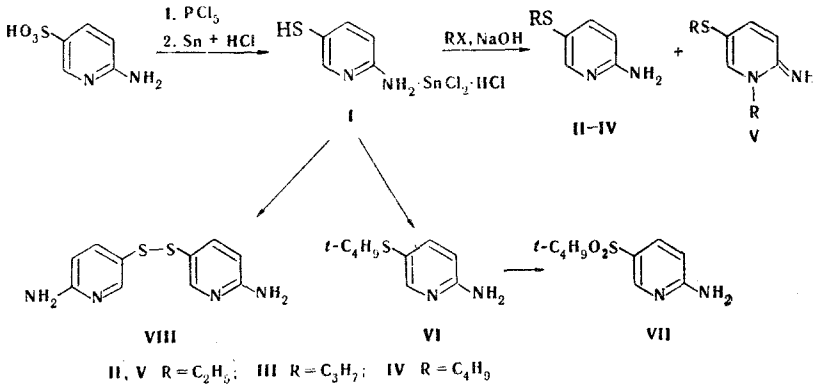
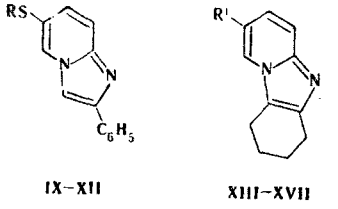


II, V $R=C_2H_5$; III $R=C_3H_7$; IV $R=C_4H_9$

The synthesis of a tertiary sulfide — 5-tert-butylthio-2-aminopyridine (VI) — was also realized starting from salt I but in this case by reaction with tert-C_4H_9OH and 75% sulfuric acid by the method in [2]. Sulfide VI was oxidized by means of $KMnO_4$ in acetic acid to 5-tert-butylsulfonyl-2-aminopyridine (VII).

2-Phenyl-6-alkylthioimidazo[1,2-a]pyridines (IX-XII) were synthesized by reaction of amino sulfides II-IV and VI with ω-bromoacetophenone, while 2,3-tetramethylene-6-alkylthioimidazo[1,2-a]pyridines (XIII-XVII) were obtained by heating amines II-IV, VI, and VII with excess α-chlorocyclohexanone without a solvent [3] at 180-200°C.



IX $R=C_2H_5$; X $R=n$-C_3H_7; XI $R=n$-C_4H_9; XII $R=t$-C_4H_9; XIII $R^1=C_2H_5S$;
XIV $R^1=n$-C_3H_7S; XV $R^1=n$-C_4H_9S; XVI $R^1=t$-C_4H_9S; XVII $R^1=t$-$C_4H_9SO_2$

The yields and constants of the synthesized compounds are presented in Tables 2-4. Their structures, which follow from the method of synthesis, find confirmation in the spectral data presented in the experimental section.

It is interesting to note that the oxidation of sulfide XVI under various conditions leads to 5-tert-butylsulfonyl-2-aminopyridine (VII) rather than to sulfone XVII. This sort of behavior of imidazo[1,2-a]pyridines toward oxidizing agents has been previously observed [4]. Thus sulfonyl-substituted imidazo[1,2-]pyridines cannot be prepared by oxidation of the corresponding sulfides but only from the sulfonyl derivatives of aminopyridine.

TABLE 1. 5-Alkylthio-2-aminopyridines

Compound	mp, °C (crystallization solvent)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	S		C	H	S	
II	20*	54,4	6,5	20,5	$C_7H_{10}N_2S$	54,5	6,5	20,8	63
III	51—51,5 (hexane—ether)	57,3	7,0	18,7	$C_8H_{12}N_2S$	57,1	7,2	19,1	39
IV	53,5—54,5 (hexane—ether)	59,2	7,6	17,5	$C_9H_{14}N_2S$	59,3	7,7	17,6	52
VI	85,0—85,5 † (hexane)	59,2	7,7	17,8	$C_9H_{14}N_2S$	59,3	7,7	17,6	75

*This compound had bp 166-169°C (15 mm); its picrate had mp 238-240°C (alcohol). Found: N 18.1%. $C_7H_{10}N_2S \cdot C_6H_3N_3O_7$. Calculated: N 18.3%.

†The hydrochloride had mp 142-143°C (benzene). Found: C 49.3; H 6.9; Cl 16.3%. $C_9H_{14}N_2S \cdot HCl$. Calculated: C 49.4; H 6.9; Cl 16.2%.

TABLE 2. Hydrobromides of 2-Phenyl-6-RS-imidazo[1,2-a]pyridines

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Br	S		C	H	Br	S	
IX	241—243	53,3	4,4	23,1	9,2	$C_{15}H_{14}N_2S \cdot HBr$	53,7	4,5	23,8	9,6	56
X	238—240	54,6	4,8	22,3	9,0	$C_{16}H_{16}N_2S \cdot HBr$	55,0	4,9	22,9	9,2	70
XI	203—204,5	56,3	5,4	21,6	8,7	$C_{17}H_{18}N_2S \cdot HBr$	56,2	5,3	22,0	8,8	46
XII	265—267	56,3	5,3	22,3	8,9	$C_{17}H_{18}N_2S \cdot HBr$	56,2	5,3	22,0	8,8	61

TABLE 3. 2-Phenyl-6-RS-imidazo[1,2-a]pyridines

Compound	mp, °C	Found, %			Empirical formula	Calc., %		
		C	H	S		C	H	S
IX	135—136	71,0	5,6	12,4	$C_{15}H_{14}N_2S$	70,9	5,5	12,6
X	106,5—107,5	72,1	6,2	11,8	$C_{16}H_{16}N_2S$	71,6	6,0	11,9
XII	151—152	72,1	6,4	11,5	$C_{17}H_{18}N_2S$	72,3	6,4	11,3

TABLE 4. Hydrochlorides of 2,3-Tetramethylene-6-R^1-imidazo-[1,2-a]pyridines

Compound	mp, °C (crystallization solvent)	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	Cl	S		C	H	Cl	S	
XIII	183—184 (dioxane + alcohol)	58,2	6,4	13,4	12,1	$C_{13}H_{16}N_2S \cdot HCl$	58,1	6,4	13,2	11,9	44
XIV	176—177 (dioxane + alcohol)	59,3	6,6	12,5	11,3	$C_{14}H_{18}N_2S \cdot HCl$	59,5	6,8	12,5	11,3	65
XV	157—159 (dioxane + alcohol)	60,6	7,2	11,7	10,6	$C_{15}H_{20}N_2S \cdot HCl$	60,7	7,1	11,9	10,8	48
XVI	205—206,5 (dioxane)	60,6	7,1	11,6	10,5	$C_{15}H_{20}N_2S \cdot HCl$	60,7	7,1	11,9	10,8	60

EXPERIMENTAL

The melting points were determined with a Boetius apparatus. Thin-layer chromatography (TLC) was carried out on a loose layer of Al_2O_3 with elution by benzene—alcohol (9:1). The PMR spectra of the compounds were recorded with a DA-60-IL spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard; the chemical shifts are presented on the δ scale relative to tetramethylsilane.

Double Salt of 2-Amino-5-mercaptopyridine (I). A ground mixture of 22.6 g (0.13 mole) of 2-aminopyridine-5-sulfonic acid [5] and 36 g (0.17 mole) of PCl_5 was heated for 4 h in the presence of a few drops of $POCl_3$ on an oil bath at 120-130°C, after which the temperature was lowered to room temperature and 144 ml of concentrated HCl and 57 g of granulated tin were added. After the resulting vigorous reaction, during which cooling was necessary, the mixture was heated on a boiling-water bath for 1 h. The hot mixture was then filtered through a glass filter; and the crystalline precipitate that formed when the filtrate was cooled was separated, squeezed on the filter, and washed with ether to give 35.4 g (83%) of 2-amino-5-mercaptopyridine in the form of a double salt with $SnCl_2$ and HCl (I) with mp 265-267°C. Found: C 16.6; H 2.0; Cl 30.1; S 9.1%. $C_5H_6N_2S \cdot SnCl_2 \cdot HCl$. Calculated: C 17.0; H 2.0; Cl 30.3; S 9.1%.

5-Ethylthio-2-aminopyridine (II). A 10.9-g (0.07 mole) sample of ethyl iodide was added in the course of 2 h to a suspension of 21.1 g (0.06 mole) of salt I in 50 ml of a 30% alcohol solution of KOH, and the mixture was refluxed for 18 h. It was then diluted with 100 ml of water and extracted repeatedly with ether and benzene. The extract was washed successively with a 10% solution of NaOH and water and dried over KOH granules. The residue that remained after removal of the solvent was distilled twice to give 6.5 g of sulfide II with bp 166-169°C (15 mm), which, according to the TLC data, contained small amounts of 5-ethylthio-N-ethylpyridoneimine (V). Column chromatography on Al_2O_3 (elution with ether) yielded sulfide II, with mp 20°C, and pyridoneimine V (2.8% of the theoretical value). The

picrate had mp 129-130°C (from alcohol). Found: N 16.7; S 7.4%. $C_9H_{14}N_2S \cdot C_6H_3N_3O_7$. Calculated: N 17.0; S 7.8%. Sulfides III and IV were obtained by a method similar to that used to prepare sulfide II (Table 1).

5-tert-Butylthio-2-aminopyridine (VI). A 23-ml sample of tert-butyl alcohol was added at 0°C to a mixture of 79 ml of concentrated H_2SO_4 and 45 ml of water; after 30 min at the same temperature, 52.8 g (0.15 mole) of salt I was added, and the mixture was stirred at 0°C for 30 min and at 20°C for 18 h. It was then diluted with 500 ml of water and extracted with ether. The aqueous solution was neutralized with sodium carbonate, and the mixture was made alkaline with 40% NaOH and extracted with ether and chloroform. The combined extracts were dried, and the solvents were removed in vacuo to give 21 g (75%) of 5-tert-butylthio-2-aminopyridine (VI) with mp 85-85.5°C (from hexane) (Table 1).

5-tert-Butylsulfonyl-2-aminopyridine (VII). A solution of 33.2 g (0.21 mole) of $KMnO_4$ in 1660 ml of water was added with stirring at 20°C in the course of 1.5 h to a solution of 22.1 g (0.12 mole) of sulfide VI in 85 ml of acetic acid, and stirring was continued for another 25 h. The mixture was then treated with 250 ml of alcohol and heated to the boiling point. The resulting precipitate was removed by filtration, and the filtrate was extracted repeatedly with ether and chloroform. The extract was evaporated to give 11 g (72%) of 5-tert-butylsulfonyl-2-aminopyridine (VII) with mp 190-191°C [after sublimination at 200°C (10 mm) and recrystallization from benzene]. Found: C 50.6; H 6.5; S 15.0%. $C_9H_{14}N_2O_2S$. Calculated: C 50.4; H 6.5; S 15.0%.

5,5'-Bis(2-aminopyridyl) Disulfide (VIII). A total of 20 ml of 10% NaOH solution was added to 3.6 g (10.2 mmole) of salt I, the mixture was filtered, 1.3 g (5.1 mmole) of finely ground iodine was added, and the mixture was allowed to stand at 20°C for 3 days. The resulting precipitate was removed by filtration and recrystallized from alcohol to give 0.45 g (36%) of disulfide VIII with mp 189-190°C. Found: C 47.9; H 3.9; S 25.2%. $C_{10}H_{10}N_4S_2$. Calculated: C 48.0; H 4.0; S 25.6%.

Hydrobromides of 2-Phenyl-6-alkylthioimidazo[1,2-a]pyridines (IX-XII). A 0.1-mole sample of the amino sulfide (II-IV, VI) was heated with 0.1 mole of ω-bromoacetophenone by refluxing in alcohol solution for 11 h, after which the mixture was cooled and the resulting precipitate was removed by filtration and recrystallized from alcohol. The yields and constants of the resulting hydrobromides of IX-XII are presented in Table 2. The bases (IXa-XIIa) were obtained by treatment of the hydrobromides with 10% NaOH solution, extraction with ether, and subsequent crystallization from alcohol (Table 3).

Hydrochlorides of 2,3-Tetramethylene-6-alkylthioimidazo[1,2-a]pyridines (XIII-XVI). A 0.1-mole sample of α-chlorocyclohexanone was added with stirring and maintenance of the temperature at 190°C to 0.1 mole of the amine (II-IV, VI). After maintenance at this temperature for 10 min, the melt was cooled and recrystallized from a suitable solvent. The yields and constants of the compounds obtained are presented in Table 4.

2,3-Tetramethylene-6-tert-butylthioimidazo[1,2-a]pyridine (XVIa). This compound, with mp 173°C (from aqueous alcohol), was obtained after brief heating of the hydrochloride of XVI with 20% NaOH solution and extraction with benzene. Found: C 69.1; H 7.9; S 12.3%. $C_{15}H_{20}N_2S$. Calculated: C 69.2; H 7.7; S 12.3%. PMR spectrum (CD_3OD): 1.27 s (9H, t-Bu); 1.93 m (4H); 2.75 m [4H, $(CH_2)_4$]; 7.20 q (1H, 8-H); 8.09 t ppm. (1H, 5-H); $J_{7,8} = 9.4$; $J_{5,7} = 1.7$; $J_{5,8} = 1.2$ Hz.

2,3-Tetramethylene-6-tert-butylsulfonylimidazo[1,2-a]pyridine (XVII). A 19.8-g (0.15 mole) sample of α-chlorocyclohexanone was added gradually at 185-190°C to 10.7 g (0.05 mole) of sulfone VII, and the mixture was stirred at this temperature for 10 min. It was then cooled and dissolved in dilute HCl, and the acid solution was washed several times with ether, made alkaline, and saturated with potassium carbonate. The resulting precipitate was removed by filtration and crystallized twice from benzene to give 7.2 g (49%) of imidazopyridine XVII with mp 191.5-192.5°C. Found: C 61.6; H 7.0; S 10.9%. $C_{15}H_{20}N_2O_2S$. Calculated: C 61.6; H 6.9; S 11.0%. PMR spectrum (CD_3OD): 1.33 s (9H, t-Bu); 1.95 m (4H), 2.80 m [4H, $(CH_2)_4$]; 7.48 (1H, 7-H); 7.57 (1H, 8-H); 8.55 ppm (1H, 5-H); $J_{7,8} = 9.35$; $J_{5,7} = 1.6$; $J_{5,8} = 1.2$ Hz. The picrate had mp 248-249°C (from alcohol). Found: N 13.6%. $C_{15}H_{20}N_2O_2S \cdot C_6H_3N_3O_7$. Calculated: N 13.4%.

Oxidation of Sulfide XVI to 2-Amino-5-tert-butylsulfonylpyridine (VII). A 1.5-g (5.8 mmole) sample of sulfide XVI in 60 ml of CH_3COOH was shaken at 20°C with 2.25 g (14.2 mmole) of $KMnO_4$ in 90 ml of water for 20 h, after which alcohol was added, and the mixture was

heated to the boiling point. The precipitated MnO_2 was removed by filtration, and the filtrate was made alkaline and extracted with ether. The residue remaining after removal of the solvent consisted of starting XVI and sulfone VII (TLC). Several crystallizations from benzene yielded sulfone VII with mp 186-187.5°C, which was identical to an authentic sample according to the result of a mixed-melting-point determination and its chromatographic characteristics.

LITERATURE CITED

1. A. Ya. Malkina, S. N. Godovikova, V. F. Gladkikh, É. V. Sazonova, and G. L. Astakhova, Vestn. Dermatol. Venerol., 4, 44 (1967).
2. R. G. Karpenko, F. M. Stoyanovich, and Ya. L. Gol'dfarb, Zh. Org. Khim., 5, 2000 (1969).
3. N. Campbell and E. B. McCall, J. Chem. Soc., 2411 (1951).
4. Ya. L. Gol'dfarb and S. N. Godovikova, Izv. Akad. Nauk SSSR, Ser. Khim., 1671 (1965).
5. F. Korte, Ber., 83, 1019 (1952).

CYCLOADDITION OF AZODICARBOXYLIC ACID ESTERS TO VINYLPYRIDINES

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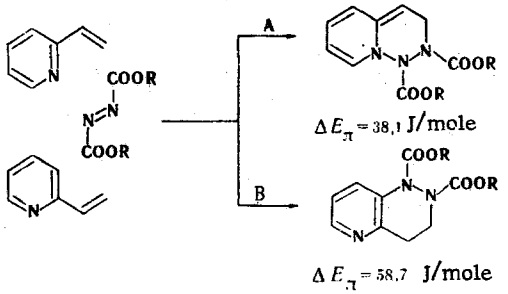
The reaction of methyl or ethyl esters of azodicarboxylic acid with 3-, 4-, 5-, or 6-alkyl-2-vinylpyridines proceeds via the scheme of the diene synthesis with the participation of the pseudocarbodiene system of vinylpyridines and leads to the formation of 1,2,3,4-tetrahydro-5-azacinnoline derivatives. In addition to these "monoadducts," 4-[N,N'-bis(methoxycarbonyl)hydrazino] derivatives are formed in large amounts. The structures of all of the reaction products were proved by the IR, UV, PMR, and mass spectra. The possibility of the application of the computational methods of MO perturbation theory for the prediction of the probability of the formation of various regioisomers is demonstrated.

2-Vinylpyridines, like styrene [1, 2], are capable of undergoing 1,4-cycloaddition with N-phenyl-1,3,4-triazoline-2,5-dione to give the 5-azacinnoline system [3]. In experiments with 2-(1-alkoxyvinyl)pyridines [4] it was found that methyl and ethyl azodicarboxylates (Ia, b) give both cycloaddition products and vinyl substitution products; this is probably a consequence of the increased nucleophilicity of the terminal methylene carbon atom owing to the strong +M effect of the alkoxy group. We therefore investigated the reaction of esters Ia, b with unsubstituted 2-vinylpyridine (IIa) and with its isomeric alkyl(hetaryl)-substituted derivatives (IIb-i) and observed that the reaction proceeds only via a 1,4-cycloaddition scheme in all cases.

In the case of this reaction pathway one might have expected the addition of ester I to both the C=C—C=C— and —C=C—C=N— pseudodiene systems of vinyl pyridine:



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