NEW METHOD FOR STUDYING THE REACTIVITIES OF α-DIAZO IMINES. INVESTIGATION OF THE CYCLIZATION OF N-SUBSTITUTED 2-DIAZOACETAMIDINES TO 1,2,3-TRIAZOLES

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UDC 547.467.2'791.6.07:543.422.25

N-Substituted diazoacetamidines were generated in the reaction of N-substituted acetamidines with benzenesulfonyl azide. It is shown that their cyclization to isomeric 1,2,3-triazoles characterizes the reactivities of α-diazo imines. The synthesis of 5-amino-1,2,3-triazole derivatives was accomplished, and their ^1H, ^{13}C, and ^{15}N NMR spectra were studied.

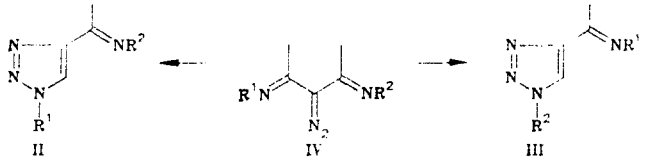
The aza analogs of α-diazo carbonyl compounds — diazo imines — are highly reactive compounds that undergo cyclization to 1,2,3-triazoles under the conditions used to obtain them [1]. They are intermediates in the generation of iminoketenes and iminocarbenes, as well as in the synthesis of triazoles and imidazoles and in rearrangements with the participation of 1,2,3-thiadiazoles and 1,2,3-triazoles [1, 2]. The equilibria between α-diazo imines and the isomeric 1,2,3-triazoles have been studied, and it has been shown that electron-acceptor substituents destabilize the ring and increase the stability of the diazo compounds [3]. The mechanism has been investigated by computational methods, and the energy of activation and the heat of cyclization of 2-diazoethaneimine to 1H-1,2,3-triazoles have been determined [4].

However, no experimental study has thus far been devoted to the reactivities of α-diazo imines in heterocyclization reactions, a knowledge of the characteristics of which makes it possible to predict the synthesis of the final products and direct its selectivity. The study of characteristics of this sort is fraught with significant experimental difficulties, since α-diazo imines are very labile, and in most cases their existence cannot be detected by current spectral physicochemical methods.

I

In this paper we propose and test a method for the study of the reactivities of α-diazo imines I in heterocyclization reactions by determining the direction of cyclization of N-substituted α-diazoacetamidines. We solved this problem by using the method of competitive reactions developed by Ingold as applied to electrophilic substitution reactions in the aromatic series [5].

The essence of the method consists in the investigation of the ratios of isomeric 1,2,3-triazoles II and III formed in the cyclization of the generated diazo compounds IV, which have two imino groups with different substituents attached to the nitrogen atoms. Since the cyclization of diazo imines I to triazoles at low temperatures is irreversible, the ratios of the heterocycles III and IV formed in the reaction characterize the relative reactivities of the two imino groups and, consequently, the change in the reactivities of diazo imines I when one substituent is replaced by another.



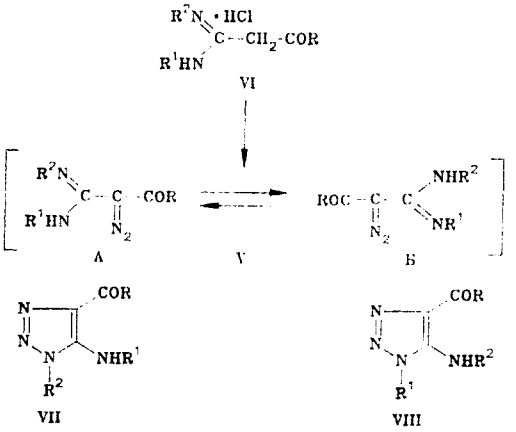
II IV III

As a consequence of the rapid establishment of a prototropic equilibrium between tautomers A and B, diazoacetamidines V can be regarded as compounds that model the properties of diazo imines in heterocyclization reactions.

S. M. Kirov Ural Polytechnical Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 775-782, June, 1991. Original article submitted February 21, 1990.

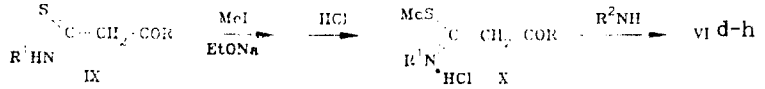
0009-3122/91/2706-0607$12.50

To develop a method for the generation of diazo compounds V we investigated the reaction of acetamidine hydrochlorides VI with benzenesulfonyl azide (BSA, "diazo transfer" to compounds with labile methylene protons).



V—VIII a—c R=NH_2, R^1=H, a R^2=Bz, b R^2=Me, c R^2=Py-2; d—f R=OEt, R^1=H, d R^2=Ph, e *p*-C_6H_4Me, f R^2=*p*-C_6H_4Br; g,h R=NHMe, R^1=Me, g R^2=Ph, h R^2=Bz

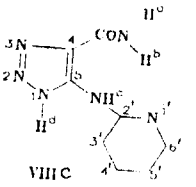
The starting acetamidine hydrochlorides VIa-c were synthesized by the method in [6]. Compounds VId-h were obtained by a method that we developed from acetic acid 2-thiocarbamoyl derivatives IX by their selective methylation with methyl iodide and reaction of the resulting S-methylthioimidates X with the corresponding amines.



IX, Xa R=OEt, R^1=H; b R=NHMe, R^1=Me

According to TLC and ^1H and ^{13}C NMR spectroscopic data (lone signals of protons and carbon atoms, respectively), as a result of "diazo transfer" to amidines VIa-g we obtained individual compounds. Triazoles VIIa, b, d-f and VIIIa, b, d-f have been described in the literature [7-9]. According to the melting points and UV, IR, and PMR spectra, the products of the investigated reaction correspond to 1-N-substituted triazoles VIIa, b, d-f. We also additionally studied their ^{13}C NMR spectra, which confirmed the assigned structures. For aryl-substituted triazoles VIIe, f we also recorded the ^{15}N NMR spectra using pulse succession DEPT (Distortionless Enhancement by Polarization Transfer), in which the signals of the nitrogen atoms of the amino and amido groups appear in the form of triplets at −332.98 (VIIe), −327.13 (VIIf), −281.46 (VIIe), and −280.15 ppm (VIIf), respectively, which attests to their spin-spin coupling (SSC) with two protons and, consequently, confirms the structures of VIIe, f.

The structure of the compound obtained in the reaction of amidine VIc (R = 2-Py) with BSA was determined by ^1H, ^{13}C, and ^{15}N NMR spectroscopy. The assignment of the signals of the pyridyl ring in the PMR spectrum was made on the basis of the use of two-dimensional homonuclear correlation spectroscopy (COSY). The cross peaks in the COSY spectrum indicate SSC of the $H_{(6')}$ proton (δ 8.3 ppm) with the $H_{(5')}$ proton (δ 7.0 ppm), of the $H_{(5')}$ proton with the $H_{(6')}$ and $H_{(4')}$ protons (δ 7.8 ppm), of the $H_{(4')}$ proton with the $H_{(5')}$ and $H_{(3')}$ protons (δ 7.7 ppm), and of the $H_{(3')}$ proton with the $H_{(4')}$ proton. In addition to the indicated signals, on the two-dimensional correlation map we observed cross peaks that indicate SSC of the NH protons with shifts at 7.6 and 8.0 ppm, which makes it possible to unequivocally assign their signals to protons of an amido group. The signal at 9.4 ppm, the integral intensity of which corresponds to one proton, is thus related to a substituted amino group.



VIIIc

To assign the signals in the ^{13}C NMR spectrum we used three additional experiments: recording the monoresonance spectrum of the ^{13}C nuclei, which makes it possible, without information regarding the CH carbon atoms, to unequivocally assign, from the multiplicity of the signals, the doublet of doublets at 152.25 ppm (^3J = 10, 12 Hz) to the $C_{(2')}$ atom, while the other quaternary carbon atoms show up in the form of singlets; correlation heteronuclear (C—H) spectroscopy (HETCOP), which makes it possible, on the basis of the two-dimensional

TABLE 1. Ratios of Isomeric Triazoles VII and VIII in Heterocyclization Reactions of the Corresponding α-Diazoacetamidines V

Diazoacetamidine V	Triazoles, %*		Diazoacetamidine V	Triazoles, %*		Diazoacetamidine V	Triazoles, %*	
	VII	VIII		VII	VIII		VII	VIII
Va	100	0	Vd	100	0	Vg	100	0
Vb	100	0	Ve	100	0	Vh	25	75
Vc	0	100	Vf	100	0			

*The accuracy in the determination of the percentages of the isomers was ~2%.

correlation map, to determine the carbon nuclei and protons that are directly coupled with one another ($^1J_{C-H}$ ~ 160 Hz); recording of the one-dimensional INADEQUATE spectrum, in which only satellites of $^{13}C-^{13}C$ nuclei appear, which makes it possible, from the spin-spin coupling constants (SSCC), to unequivocally determine the order in which the carbon atoms in the molecule are coupled with one another. The ^1H and ^{13}C NMR spectroscopic data are in good agreement and provide evidence in favor of structure VIIIc. We obtained definitive confirmation of the assigned structure by analyzing the ^{15}N monoresonance spectrum. In it we observed signals of three side-chain nitrogen atoms,* the chemical shifts of which were assigned on the basis of the data in [10] in the following way: the nitrogen atom of the pyridyl ring resonates in the form of a multiplet (J ~ 10 Hz) at −106.9 ppm (on the nitromethane scale), the triplet at −277.7 ppm (J = 89.5 Hz) was assigned to the nitrogen atom of the carboxamido grouping, while the doublet at −288.0 ppm (J = 92.7 Hz) belongs to the nitrogen atom of a substituted amino group, which makes it possible to unequivocally identify the compound obtained as 5-(2-pyridyl)amino-1,2,3-triazole-4-carboxamide (VIIIc).

The structure of the triazole obtained as a result of "diazo transfer" to amidine VIg, which contains methyl and phenyl substituents in the amidine grouping, was determined on the basis of ^1H and ^{13}C NMR spectroscopic data. In its ^{13}C NMR spectrum a signal of the carbon atom in the 5 position of the ring shows up in the form of a quartet of doublets at 146.43 ppm (^3J = 164.6, ^5J = 3.7 Hz), which attests to its SSC with the NH proton and the protons of a methyl group located in a substituted amino group in the 3 position of the triazole ring. A signal in the form of a doublet and a singlet of protons of a methyl group at 2.5 ppm is observed in the PMR spectrum of the compound obtained, while for 1-N-methyl-substituted triazoles the protons of the methyl group resonate at weaker field (3.6-4.0 ppm) [10]. In addition, the quartet at 6.55 ppm, which belongs to the NH proton of a substituted amino group, and the singlet of protons of a phenyl ring at 7.6 ppm attest to the presence of a methyl group attached to the nitrogen atom of the amino group in the 5 position and a phenyl substituent in the 1 position of the triazole ring and, consequently, confirm the structure of VIIg.

A mixture of two isomeric compounds VIIh and VIIIh is formed in the reaction of amidine VIIh, which contains methyl and benzyl substituents in the amidino group, with BSA. The PMR spectrum of the mixture contains nine signals, the assignment of which was made on the basis of a comparison of the PMR spectra of the mixture and 1-methyl- and 1-benzyl-substituted triazoles VIIa, b, as well as 5-methyl-substituted triazole VIIg. Thus the doublet and singlet at 2.9 ppm were assigned to the protons of a methyl group attached to the nitrogen atom in the 5 position of the triazole ring. The singlet at 3.8 ppm corresponds to the protons of a methyl group in the 1 position of the ring. The doublet at 4.7 ppm, which belongs to the CH_2 protons of a benzyl grouping, attests to their SSC with one proton, which is possible when there is a benzyl substituent in the amino group in the 5 position of the ring. The aliphatic protons of the other benzyl grouping resonate in the form of a singlet at 5.5 ppm. We assigned the triplet at 6.7 ppm and the quartet at 5.9 ppm to, respectively, the NH protons of the benzyl- and methylamino groups in the 5 position of the ring; the ratio of the VIIh and VIIIh isomers in the mixture, which is 1:3, was determined on the basis of the integral curves in the PMR spectrum, and, consequently, the competition constant *K* for diazo compound Vh (which, in the same sense, is an experimental parameter for the active intermediate particle just as the melting point or the refractive index serves as a characteristic value for a stable compound) is the ratio of the rate constants for the conversion of diazo compound Vh to triazoles VIIh and VIIIh.

Data on the direction of cyclization of diazoacetamidines V are presented in Table 1.

Thus a method for the determination and study of the reactivities of α-diazo imines was developed as a result of a study of the direction of cyclization of N-substituted diazoacetamidines to isomeric 1,2,3-triazoles.

*The signals of the nitrogen nuclei of the triazole ring and of the proton in its 1 position do not show up in the ^{15}N and ^1H NMR spectra, respectively, evidently because of rapid prototropic rearrangement.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-75 spectrometer. The ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded with a Varian VXR-400 spectrometer (399.9, 100.6, and 40.5 MHz, respectively). The ^{1}H and ^{13}C NMR spectra were also obtained with a Bruker WR-80 spectrometer (20.13 and 80.13 MHz, respectively) with tetramethylsilane (TMS) as the internal standard. All of the NMR spectra were obtained from solutions in d_6-DMSO). The UV spectra of solutions in ethanol were recorded with a Beckmann M-26 spectrophotometer. Monitoring of the course of the reactions and the verification of the individuality of the compounds obtained were carried out by means of TLC on Silufol UV-254 plates in an ethanol–chloroform (1:15) system.

The characteristics of the synthesized compounds are presented in Tables 2 and 3. The results of elementary analysis of the substances obtained were in agreement with the calculated values.

2-Carbamoyl-N-benzylacetamidine Hydrochloride (VIa). This compound was synthesized by the method in [6] and had mp 150°C (literature mp 152°C). The yield was 61%.

2-Carbamoyl-N-methylacetamidine Hydrochloride (VIb). This compound was obtained in the same way as VIa.

2-Carbamoyl-N-(2-pyridyl)acetamidine Hydrochloride (VIc). This compound was synthesized in the same way as VIa.

2-Ethoxycarbonyl-N-phenylacetamidine Hydrochloride (VId). A 0.49-ml (5.78 mmole) sample of aniline was added to a suspension of 1.23 g (3.87 mmole) of 2-ethoxycarbonyl-S-methylthioacetimidate hydrochloride (Xa) in 15 ml of dry dioxane, and the mixture was stirred for 4 h at room temperature. The solvent was then removed by distillation at reduced pressure, and the residue was triturated in absolute alcohol, removed by filtration, and reprecipitated from solution in dry ethanol by the addition of dry ether. The yield was 1.13 g.

2-Ethoxycarbonyl-N-(4-tolyl)acetamidine Hydrochloride (VIe). This compound was obtained in the same way as VId.

2-Ethoxycarbonyl-N-(4-bromophenyl)acetamidine Hydrochloride (VIf). This compound was obtained in the same way as VId.

2-(N-Methylcarbamoyl)-N-methyl-N-phenylacetamidine Hydrochloride (VIg). A 0.47-g (20 mmole) sample of sodium was dissolved in 30 ml of absolute ethanol, 3.0 g (20 mmole) of IXb was added, 1.3 ml (20 mmole) of methyl iodide was added to the resulting solution with stirring and cooling, and the reaction mixture was maintained for 24 h at room temperature. A 2.3-ml (20 mmole) sample of aniline was then added, and the mixture was allowed to stand overnight. The mixture was then evaporated at reduced pressure to 2/3 of its original volume, dioxane saturated with HCl was added, and the mixture was maintained for 1 h at 0°C. The precipitate was removed by filtration and washed with ethanol. The filtrate was allowed to stand again at 0-5°C for 2 h, after which the precipitate was removed by filtration and washed with ether. The yield was 2.0 g.

2-(N-Methylcarbamoyl)-N-methyl-N′-benzylacetamidine Hydrochloride (VIh). This compound was obtained in the same way as VIg.

5-Amino-1,2,3-triazole Derivatives VIIa, b, d-h and VIIIc, h (Table 3). A 1000-mmole sample of the corresponding acetamidine hydrochloride VI was suspended in a solution of sodium ethoxide prepared by dissolving 1100 mmole of sodium in 1 liter of absolute ethanol. After 5 min, the precipitate (NaCl) was removed by filtration, 1 mmole of benzenesulfonyl azide was added, and the mixture was stirred for 1 h at room temperature. The precipitate was removed by filtration and crystallized from ethanol. In the case of the mixture of isomers VIIh and VIIIh no precipitate formed, and the reaction mixture was therefore evaporated to the minimum volume and applied to a chromatographic column packed with 40 × 100 silica gel with elution by chloroform. The mixture of isomeric triazoles VIIh and VIIIh emerged in the first fraction, which absorbed in the UV region of the spectrum.

2-(N-Methylthiocarbamoyl)-N-methylacetamide (IXb). A 400-ml sample of ethanol saturated with 110 g (3550 mmole) of methylamine was added to 130 g (880 mmole) of ethyl 2-thiocarbamoylacetate (IXa) [12], and the reaction mixture was maintained for 20 days at room temperature. It was then evaporated to 2/3 of its original volume, and the precipitate was removed by filtration and crystallized from acetonitrile. The yield was 63 g.

2-Ethoxycarbonyl-S-methylthioacetamidate Hydrochloride (Xa). A 0.32-g (14 mmole) sample of sodium was dissolved in 20 ml of absolute ethanol, 2.0 g (14 mmole) of ethyl 2-thiocarbamoylacetate (IXa) was added, 1.66 ml (28 mmole) of methyl iodide was added with stirring and cooling to the resulting suspension, and the mixture was stirred for 3 h at room temperature. The solvent was removed by distillation at reduced pressure, the residue was dissolved in water, and the aqueous solution was extracted with ether (3 × 50 ml). The ether extracts were dried over $CaCl_2$ and evaporated to 2/3 of the original volume, 15 ml of dioxane saturated with HCl at 0°C was added with cooling to the resulting solution, and the precipitate was removed by filtration and washed with ether. The yield was 1.88 g.

TABLE 2. Characteristics of the 2-Carbamoylacetic Acid Derivatives

Compound	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
VIb	142	3375, 3250, 3180 (NH), 3080, 2930 (CH), 1670 (C=O)	2,9 (3H, s, Me); 3,4 (2H, s, CH_2)	89
VIc	185	3350, 3185 (NH), 3025, 2940, 2860 (CH), 1690 (C=O)	3,4 (2H, s, CH_2); 7,2...8,5 (4H, m, Py); 8,9 (H, s, NH); 9,2 (H, s, NH)	64
VId	63	3220, 3065 (NH), 3020, 2915 (CH), 1730 (C=O)	1,3 (3H, q, J=5,5 Hz, CH_3); 4,0 (2H, s, CH_2); 4,2 (2H, q, J=5,5 Hz, CH_2); 7,1...7,7 (5H, m, Ph); 9,0 (1H, s, NH); 9,3 (1H, s, NH)	75
VIe	113	3210 (NH), 3005, 2850 (CH), 1735 (C=O)	1,3 (3H, q, J=5,5 Hz, CH_2); 2,4 (3H, d, J=2,5 Hz, Me); 3,5 (2H, s, CH_2); 4,2 (2H, m, J=5,5 Hz, CH_2); 7,1...7,6 (4H, m, C_6H_4); 8,3 (1H, s, NH)	70
VIf	147	3375, 3340, 3170 (NH), 3000, 2860, 2830, 2785 (CH), 1725 (C=O)	1,3 (3H, q, J=5,5 Hz, Me); 3,5 (2H, s, CH_2); 4,1 (2H, q, J=5,5 Hz, CH_2); 7,2...7,9 (4H, m, C_6H_4); 9,1 (1H, , NH)	82
VIg	185...187	3270 (NH), 3045, 2895 (CH), 1630 (C=O)	2,5 (3H, s, NMe); 3,0 (3H, s, q, CONMe); 3,4 (2H, s, CH_2); 7,1...7,7 (5H, m, Ph); 7,9 (1H, s, CONH); 10,0 (1H, s, NHPh)	40
VIh	175...177	3375 (NH), 2870 (CH), 1685 (C=O)	2,5 (3H, s, NMe); 3,0 (3H, s, q, CONMe); 3,5 (2H, s, CH_2); 4,6 (2H, s, CH_2); 7,4 (5H, s, C_6H_5); 8,3 (1H, s, CONH); 9,8 (1H, s, NHBz)	33
IXb	132...133	3235 (NH), 3100, 3025, 2950, 2930 (CH), 1640 (C=O)	2,6 (3H, s, q, CSNMe); 3,0 (3H, s, q, CSNMe); 3,5 (2H, s, CH_2); 7,9 (1H, s, CONH); 10,1 (1H, s, CSNH)	49
Xa	135	3065, 2915, 2780 (CH), 1710 (C=O)	1,1 (3H, q, J=5,5 Hz, Me); 2,3 (3H, s, SMe); 4,0 (2H, q, J=5,5 Hz, CH_2); 4,4 (2H, s, CH_2); 7,6 (1H, s, NH)	70

TABLE 3. ^{1}H, ^{13}C, and ^{15}N NMR Spectra of the Synthesized 1,2,3-Triazoles

Compound	mp, °C		NMR spectrum, δ, ppm (J, Hz)			Yield, %
	our data	lit. data	^{1}H*	^{13}C*	^{15}N**	
VIIa	230	229 [7]	5,5 (2H, s, CH_2); 6,5 (2H, s, NH_2); 7,2...7,3 (5H, m, C_6H_5); 7,1; 7,4 (2H, s, s, $CONH_2$)	48,30 (CH_2); 121,57 ($C_{(4)}$); 127,36 ($C_{(2')}$); 127,58 ($C_{(4')}$); 128,47 ($C_{(3')}$); 135,85 ($C_{(1')}$); 144,75 ($C_{(5)}$); 164,21 ($CONH_2$)		74
VIIb	239	243 [7]	3,8 (3H, s, NMe); 6,3 (2H, s, NH_2); 7,1; 7,4 (2H, s, s, $CONH_2$)	32,46 (3H, q, J=142, Me); 121,77 ($C_{(4)}$); 145,03 ($C_{(5)}$); 164,39 ($CONH_2$)		73
VIId	123	126 [8]	1,3 (3H, t, J=5,5, Me); 4,3 (2H, q, J=5,5, CH_2); 6,5 (2H, s, NH_2); 7,6 (5H, s, Ph)			94
VIIe	143	147,5 [9]	1,3 (3H, t, J=5,6, Me); 2,5 (3H, s, Me); 4,3 (2H, q, J=6,8, CH_2); 6,5 (2H, s, NH_2); 7,4 (4H, m, C_6H_4)	14,34 (3H, q, t, ^{1}J=127,0; ^{3}J=3,2, Me); 20,66 (3H, q, J=127,0, Me); 59,55 (2H, t, q, J=148,0; ^{3}J=4,5, CH_2); 119,00 ($C_{(4)}$); 124,39 ($C_{(2')}$); 130,12 ($C_{(3')}$); 131,96 ($C_{(1')}$); 138,98 ($C_{(4')}$); 146,11 ($C_{(5)}$); 161,69 ($C_{(6)}$)	−281,5 (2H, t, J=88,0, $CONH_2$); −333,0 (2H, t, J=86,0, NH_2)	76
VIIf	163	166 [9]	1,3 (3H, t, J=7,2, Me); 4,3 (2H, q, J=7,2, CH_2); 6,6 (2H, s, NH_2); 7,5...7,8 (4H, m, C_6H_4)	14,34 (3H, q, t, ^{1}J=127,0; ^{3}J=2,6, Me); 59,59 (2H, t, q, ^{1}J=148,0; ^{3}J=4,5, CH_2); 119,06 ($C_{(4)}$); 122,27 ($C_{(4')}$); 126,70 ($C_{(2')}$); 132,67 ($C_{(3')}$); 133,71 ($C_{(1')}$); 146,24 ($C_{(5)}$); 161,60 ($C_{(6)}$)	−327,11 (2H, t, J=89,0, NH_2)	82
VIIg	160		2,5 (3H, s, d, J=2,2, Me^1); 2,8 (3H, s, d, J=4,7, Me^2); 6,6 (H, q, J=5,3, $NHMe^2$); 7,6 (5H, s, Ph); 8,2 (H, q, J=4,8, $NHMe^1$)	25,14 (3H, q, d, ^{1}J=138,0; ^{3}J=2,4, Me^2); 31,50 (3H, q, d ^{1}J=138,0; ^{3}J=2,4, Me^1); 122,44 ($C_{(4)}$); 125,95 ($C_{(2')}$); 129,29 ($C_{(3')}$); 129,59 ($C_{(1')}$); 136,07 ($C_{(4')}$); 146,43 ($C_{(5)}$); 162,49 (C=O)		45
VIIh			2,7 (3H, s, d, J=2,2, Me^1); 2,9 (3H, s, d, J=3,3, Me^2); 5,5 (2H, s, CH_2); 5,9 (H, m, $NHMe^2$); 7,3 (5H, s, Ph); 8,1 (H, q, J=3,8, $NHMe^1$)			
VIIIc	281 (dec)		7,0 (H, t, J=6,0, $H_{(5')}$); 7,6 (H, s, NH^b); 7,7 (H, d, J=8,0, $H_{(3')}$); 7,8 (H, t, J=7,2, $H_{(4')}$); 8,0 (H, s, NH^a); 8,3 (H, d, J=4,8, $C_{6'}$); 9,4 (H, s, NH^c)	110,49 ($C_{(3')}$); 116,52 ($C_{(5')}$); 124,99 ($C_{(4)}$); 139,39 ($C_{(4')}$); 144,3 ($C_{(5)}$); 146,61 ($C_{(6')}$); 152,25 ($C_{(2')}$); 163,96 (C=O)	−106,9 (H, m, $J \approx 10,0$, $N_{(1')}$); −277,7 (2H, t, J=89,5, $CONH_2$); −288,0 (H, d, J=92,7, NH^c)	83
VIIIh			2,7 (3H, s, d, J=2,2, Me^1); 3,8 (3H, s, Me); 4,7 (2H, d, J=4,1, CH_2); 6,7 (H, t, $NHCH_2$); 7,3 (5H, s, Ph); 8,1 (H, q, J=3,8, $NHMe^1$)			
VIIh+ +VIIIh	143...145					56

*With tetramethylsilane (TMS) as the internal standard.

**With $MeNO_2$ as the external standard.

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HEXAHYDROPYRIDAZINE DERIVATIVES.

3.* SYNTHESIS OF HEXAHYDRO-4-PYRIDAZINONES

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UDC 547.852.2

The reaction of azodicarboxylic acid esters with 2-methoxy- or 2-trimethylsilyloxy-1,3-butadienes gave a number of 1,2-bis(alkoxycarbonyl)-4-methoxy(trimethylsilyloxy)-1,2,3,6-tetrahydropyridazines, which were hydrolyzed to the corresponding hexahydro-4-pyridazinones.

The Diels—Alder reaction is widely used for the synthesis of six-membered heterocycles [2, 3]. Various combinations of heterodienes and heterodienophiles have been proposed [4, 5]. The possibilities of this reaction for the synthesis of heterocycles are far from having been exhausted.

We have previously reported the synthesis of 1,2-bis(methoxycarbonyl)-4-piperidazines by the [4 + 2]-cycloaddition of azodicarboxylic acid esters to 2-methoxy-1,3-butadiene with subsequent hydrolysis of the resulting 1,2-bis(alkoxycarbonyl)-4-methoxy-1,2,3,6-tetrahydropyridazines [1, 6]. To obtain new ketones of the hexahydropyridazine series with various substituents we studied the reaction of a number of other dienes (Ia-e) with azodicarboxylic acid esters IIa, b. In particular, 1,2-bis(ethoxycarbonyl)-4-methoxy-5-methyl-1,2,3,6-tetrahydropyridazine (III) was obtained from 2-methyl-3-methoxy-1,3-butadiene (Ia) [7]. The most convenient starting compounds for the synthesis of 6-substituted hexahydropyridazines are 2-trimethylsilyloxybutadienes Ib-d, which are readily accessible from α,β-unsaturated ketones [8-10]. The 1,2-bis(alkoxycarbonyl)-4-trimethylsilyloxy-1,2,3,6-tetrahydropyridazines IV-VII obtained in the reaction of Ib-d with esters IIa, b, like pyridazine III, are readily hydrolyzed by dilute hydrochloric acid at room temperature to give ketones VIII-XI in high yields. Evidence for this is provided by the absence in the PMR spectra of signals of OCH_3 and $OSi(CH_3)_3$ groups and the presence of 5-CH (VIII) and 5-CH_2 (VIII-XI) signals, as well as by the retention of the signals of protons of CO_2CH_3 (IX, X) and $CO_2C_2H_5$ (VIII, XI) groups (Table 1) (see scheme below).

1-Ethoxy-3-trimethylsilyloxy-1,3-butadiene (Ie) [11] behaves somewhat differently in this reaction. The 1,2-bis(alkoxycarbonyl)-3-ethoxy-5-trimethylsilyloxy-1,2,3,6-tetrahydropyridazines (XIIa, b) formed in the cyclization of Ie with azodicarboxylic acid esters IIa, b cannot be isolated. Fractional distillation of the reaction products gave 1,2-

*See [1] for Communication 2.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 783-785, June, 1991. Original article submitted November 28, 1989; revision submitted October 30, 1990.