YNAZIRIDINES.

METHODS OF SYNTHESIS OF A NEW TYPE OF YNAMINES

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Ways of synthesizing ynaziridines by successive halogenation and dehydrohalogenation of enaziridino esters, the reaction of potassium aziridinide with bromophenylacetylene, the reaction of 1H-aziridines with the methyl ester of bromopropionic acid was studied. The different direction of the reaction of aziridines with bromomethylpropiolate as a function of the nature of the solvent was demonstrated. In methanol the addition of aziridine to the triple bond proceeds stereospecifically with the formation of the E-isomer. When this reaction was conducted in ether, ynaziridines were obtained for the first time. An effective method of synthesis of ynaminoesters was developed.

Ynamines represent an interesting and synthetically important class of organic compounds, the chemistry of which has recently been under intensive development [1, 2]. Thanks to their high reactivity, they have found use in the synthesis of various types of nitrogen-containing compounds [2]. In this work we produced a broad series of ynamines with various assortments of substituents, both at the nitrogen atom and at the carbon of the triple bond.

However, up to this time N-ethynylaziridines — analogs of ynamines which may be called ynaziridines, had been unknown.

Considering the uniqueness of the electronic structure of the aziridine ring, it was of interest to make a comparative study of the chemical behavior and reactivity of N-(1-alkynyl)-aziridines with ynamines, and to detect the effects of mutual influence of the aziridine ring and the triple bond in ynaziridines, and to study the thermal stability of this class of compounds.

Moreover, ynaziridines possess broad possibilities for the production of varied classes of organic compounds, containing an aziridine fragment of practical importance.

The purpose of this work was to seek ways of synthesizing ynaziridines. Analyzing the literature data on the synthesis of ynamines, we took up three methods of synthesis that merit attention. The production of functionally substituted ynamines by successive halogenation and dehydrohalogenation of the corresponding enamines was described in [3, 4]. We were able to synthesize ynaziridines according to this method on the basis of enaziridinoesters Ia, b (see scheme on the following page).

In the bromination of the esters Ia, b in dry chloroform in the presence of triethylamine, Z-enaziridines IIIa, b are formed, while in the absence of a base the enamines IVa, b are obtained. The reaction evidently proceeds through an unstable intermediate dibromide II with the elimination of hydrogen bromide [5], which opens the aziridine ring in the absence of triethylamine. A Z-configuration of compounds IVa, b is supported by the highly polar signal δ_{NH} at 5.25 ppm and the SSCC $J_{=CH,\ NH}$ = 13.0 Hz in comparison with the E-isomers [6, 7]. A comparative analysis of the chemical shifts of the ethylene hydrogen atom in isomeric enaziridines permitted compounds IIIa, b to be assigned to Z-isomers. Moreover, the presence of only one Z-isomer for IVa, b can also serve as a confirmation of the Z-configuration of the enaziridines IIIa, b.

We have shown that when the esters IIIa, b are treated with potassium tert-butoxide under conditions of ynamine synthesis [3, 4], ynaziridines are not formed. Under more rigorous conditions (boiling with THF), the initial enaziridines are resinified. In turn, the enamines IVa, b in the presence of potassium tert-butoxide are readily converted to enaziridines IIIa, b; however, the ynaziridines cannot be obtained.

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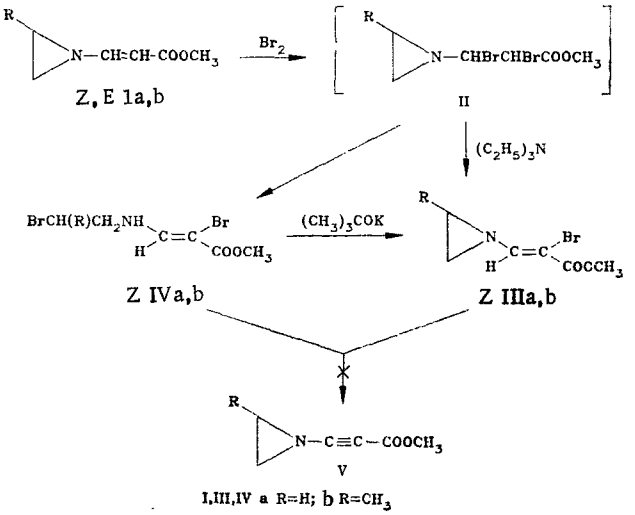
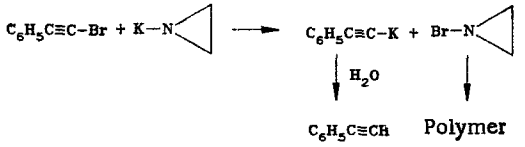


I,III,IV a R=H; b R=CH$_3$

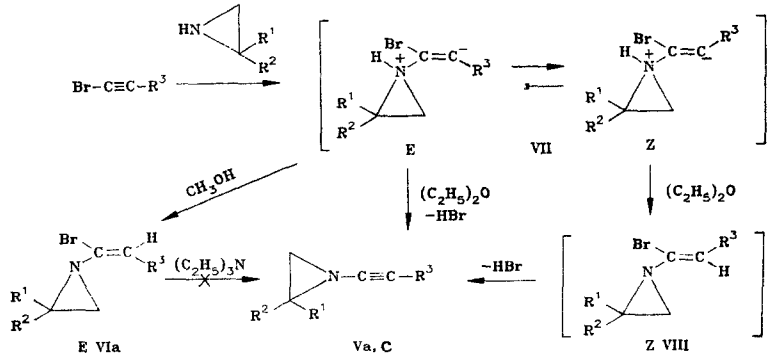
The reaction of 1-haloalkynes with amides of the alkali metals is widely used for the synthesis of ynamines [8]. In the interaction of bromophenylacetylene with potassium aziridinide, instead of the expected nucleophilic substitution product, we obtained phenylacetylene and a product with polymer composition:



The experimental results can be explained by direct attack of the nucleophile on bromine [9] with the formation of the acetylenide ion and N-bromoaziridine, which polymerizes under the conditions of synthesis.

It is known [1] that the ease of nucleophilic substitution of the halogen at the carbon atom decreases in the series $C_{sp^3} > C_{sp^2} > C_{sp}$. It might be expected that the introduction of an electron acceptor substituent into the bromoacetylene molecule increases the mobility of the halogen atom. It was shown [10] that chlorocyanoacetylene forms cyanoynamines with secondary amines.

We studied the interaction of the methyl ester of bromopropiolic acid with aziridines. It was established that the addition of aziridine at the triple bond in methanol occurs stereospecifically with the formation of the E-isomer VIa. Replacement of the solvent radically changes the direction of the reaction. In the reaction of aziridines with methyl bromopropiolate in ether, we obtained ynaziridines Va, c for the first time; their formation

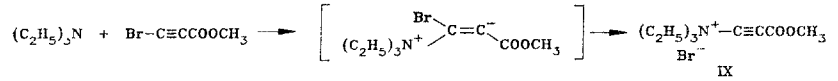


VIa R^3=COOCH$_3$; Va R^1=R^2=H; c R^1=R^2=CH$_3$

is observed at any ratios of aziridine and methyl bromopropiolate; however, the optimum ratio is 2:1. Ynaziridines Va, c are mobile liquids, well preserved in aprotic solvents; they rapidly darken and resinify in the free form. Their structure was demonstrated by the methods of PMR and IR spectroscopy.

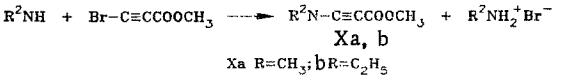
Evidently the intermediate zwitterion VII with an E-configuration [11] is rapidly converted to the enaziridine VIa in methanol, by adding a proton from the solvent. In an

aprotic solvent (ether), in connection with the absence of an external electron donor, isomerization VIIE → VIIZ with the formation of a Z-enaziridine VIII and then dehydrobromination at the ynamine V is possible, or there may be a direct transition VIIE → V according to an addition-elimination mechanism [12]. The latter pathway of the formation of ynaziridines seems preferential. Thus, in a study of the reaction of bromomethyl propiolate with aziridine at −40°C in $CDCL_3$ by a dynamic NMR method, the formation of the Z-enaziridine VIII cannot be registered. Moreover, we demonstrated the possibility of direct replacement of the bromine atom on the example of the reaction of bromomethyl propiolate with triethylamine:



The E-isomer of the enaziridine VIa, formed in methanol, is thermodynamically stable; it cannot be isomerized to the Z-isomer or dehydrobrominated in the presence of triethylamine to an ynaziridine.

It is known [3, 4] that the synthesis of functionally substituted ynamines is a multistep, laborious process. According to the data of [13], the reaction of secondary amines with bromoethyl propiolate leads not to ynamines but to gem-enamines. To confirm the ynaziridine structure of compounds Va, c and to develop an effective synthesis of ynamines containing an ester group, we studied the reaction of the methyl ester of bromopropiolic acid with dimethyl- and diethylamines. It was found that under conditions analogous to the synthesis of compound Va, c, methoxycarbonylynamines Xa, b are formed with a good yield (70-80%).



Xa R=CH_3; b R=C_2H_5

The structure of the ynamines that we obtained is strictly demonstrated by the complete coincidence of the physicochemical characteristics of the esters Xa, b with the literature data [4].

Thus, the reaction of aziridines and secondary amines with bromomethyl propiolate is a convenient method of synthesizing ynamino- and ynaziridinoesters.

EXPERIMENTAL

The PMR spectra were recorded on a Perkin-Elmer R 12 A (60 MHz) or Bruker WH-90 spectrometer. The substances were investigated in the form of 10 or 5% solutions in CCl_4 or $CDCl_3$, with TMS as the internal standard. The IR spectra were obtained on a UR-20 instrument in liquid petrolatum, hexachlorobutadiene, or a liquid film. The individuality of the compounds was monitored by thin-layer chromatography (silufol UV-254; ether–hexane, 1:1).

Methyl Ester of Z-2-Bromo-3-(2-bromoethylamino)propenoic Acid (IVa). To a solution of 0.1 mole of compound Ia [14] in 60 ml of dry chloroform, a solution of 0.11 mole of bromine in 35 ml of chloroform was added with mixing at 0°C. The temperature was raised to 20°C, and the reaction mixture was exposed for 3 h. The solution was passed through a column with neutral aluminum oxide. The solvent was evaporated, the residue crystallized from ether. Yield 75%. Mp 71-72°C. IR spectrum: 1620 (C=C), 1690 (C=O), 3360 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 7.65 (1H, d, J = 13 Hz, CH=C), 5.25 (1H, br. s, NH), 3.74 (3H, s, CH_3), and 3.50 ppm (4H, m, CH_2). Found: C 25.4; H 3.1; N 5.2%. $C_6H_9Br_2NO_2$. Calculated: C 25.1; H 3.1; N 4.9%.

The ester IVb was produced analogously. Yield 71%. Mp 83-85°C. IR spectrum: 1625 (C=C), 1695 (C=O), 3365 cm^{-1} (NH). PMR spectrum (CCl_4): 7.67 (1H, d, J = 13.3 Hz, CH=C), 5.30 (1H, br. s, NH), 4.14) 1H, qu, J = 6.6 Hz, CH), 3.74 (3H, s, OCH_3), 3.54 (2H, m, CH_2), and 1.69 ppm (3H, d, J = 6.6 Hz, CH_3). Found: C 28.4; H 3.8; N 5.0%. $C_7H_{11}Br_2NO_2$. Calculated: C 27.9; H 3.7; N 4.7%.

Methyl Ester of 3-Aziridino-2-bromopropenoic Acid (IIIa, b). To a mixture of 0.1 mole of enaziridine Ia or Ib and 0.15 mole triethylamine in 80 ml of dry chloroform, 0.1 mole of bromine in 30 ml of chloroform was added at −30°C with mixing and exposed at this temperature for 0.5 h. The temperature was raised to 20°C. After 2 h the reaction mixture was evaporated; 20 ml of water was added to the residue, and it was extracted with ether. The ether solution was passed through a column with neutral aluminum oxide, the ether evaporated, and the residue redistilled. Yield 44%. Bp 80-83°C (2 mm). IR spectrum: 1635 (C=C), 1710 cm^{-1} (CO). PMR spectrum ($CDCl_3$): 7.81 (1H, s, CH=C), 3.75 (3H, s, CH_3), 2.25 ppm (4H, s, CH ring). Found: C 34.5; H 4.1; N 7.2%. $C_6H_8BrNO_2$. Calculated: 34.8; H 3.9; N 7.3%.

The ester IIIb was produced analogously. Yield 39%. Bp 93-95°C (2 mm). IR spectrum: 1630 (C=C), 1715 cm^{-1} (CO). PMR spectrum ($CDCl_3$): 8.25 (1H, s, CH=C), 3.77 (3H, s, OCH_3), 2.40 (1H, m, 2-H), 2.23 (1H, d, J = 6.0 Hz, 3-H_{cis}), 2.07 (1H, d, J = 4.0 Hz, 3-H_{trans}), and 1.38 ppm (3H, d, J = 5 Hz, CH_3). Found: C 38.5 H 4.2 N 6.6%. $C_7H_{10}BrNO_2$. Calculated: C 38.2; H 4.5; N 6.4%.

Interaction of Potassium Aziridinide with Bromophenylacetylene. To a solution of 2 g (0.05 mole) potassium in 15 ml of aziridine, 50 ml of absolute ether was added, and then 0.5 g (0.025 mole) bromophenylacetylene in 20 ml of absolute ether was added at −30°C with mixing. The temperature was raised to 20°C, and the reaction mixture was exposed for 1 h. It was filtered, the ether solution washed with 20 ml of water, and dried with anhydrous sodium sulfate. The ether was evaporated and the residue redistilled. Yield 1.7 g (67%) of phenylacetylene. Bp 49-50°C (15 mm). IR spectrum: 2260 (C≡C), 3285 cm^{-1} (≡CH). PMR spectrum ($CDCl_3$): 7.32 (5H, m, C_6H_5), and 3.08 ppm (1H, s, ≡CH). After the phenylacetylene was distilled off, a resinous product with a polymer structure remained in the flask.

Methyl Ester of 3-Aziridinopropynoic Acid (Va). To a solution of 0.01 mole of the methyl ester of bromporopiolic acid in 50 ml of absolute ether, a solution of 0.02 mole aziridine or 2,2-dimethylaziridine in 20 ml of absolute ether was added with mixing at −10°C. The temperature was raised to 20°C, and the reaction mixture was passed through a column with neutral aluminum oxide. The solvent was evaporated, yielding a freeflowing liquid that was distilled off under vacuum. Yield 75%. Bp 25-27°C (0.01 mm). IR spectrum: 1710 (C=O), 2230 cm^{-1} (C≡C). PMR spectrum ($CDCl_3$): 3.65 (3H, s, OCH_3), and 2.29 ppm (4H, s, CH ring). Found: C 57.2; H 5.7; N 11.5%. $C_6H_7NO_2$. Calculated: C 57.6; H 5.6; N 11.2%.

The ester Vc was produced analogously. Yield 52%. Bp 34-36°C (0.01 mm). IR spectrum: 1710 (C=O), 2225 cm^{-1} (C≡C). PMR spectrum ($CDCl_3$) 3.70 (3H, s, OCH_3), 2.20 (2H, s, CH_2), and 1.45 ppm (6H, s, CH_3). Found: C 63.0; H 7.1; N 9.4%. $C_8H_{11}NO_2$. Calculated C 62.7; H 7.2; N 9.1%.

Methyl Ester of 3-Aziridino-3-bromopenoic Acid (VIa). To a solution of 1.6 g (0.01 mole) of the methyl ester of bromopropiolic acid in 30 ml of methanol, a solution of 0.43 g (0.01 mole) aziridine in 20 ml of methanol was added at −10° C with mixing. The temperature was raised to 20°C, the reaction mixture exposed for 2 h, the methanol evaporated, and the residue washed with pentane. The pentane solution was passed through a column with neutral aluminum oxide, the pentane evaporated, and 1.6 g (78%) of a colorless oily liquid was obtained. Bp 60-62°C (2 mm). IR spectrum: 1730 (C=O), 1660 cm^{-1} (C=C). PMR spectrum ($CDCl_3$) 5.71 (1H, s, C=CH), 3.65 (3H, s, OCH_3), and 2.27 ppm (4H, s, CH ring). Found: C 35.2; H 3.8; N 7.0%. $C_6H_8BrNO_2$. Calculated: C 35.0; H 3.9; N 6.8%.

N-(Methoxycarbonylethynyl)triethylammonium Bromide (IX). To a solution of 0.01 mole of the methyl ester of bromopropiolic acid in 30 ml of absolute ether, a solution of 0.01 mole triethylamine in 20 ml of absolute ether was added at −30°C with mixing. The precipitate formed was filtered off rapidly (the salt formed is unstable) and dissolved in chloroform. Yield 62%. IR spectrum ($CHCl_3$): 1735 (C=O), 2180 cm^{-1} (C≡C). PMR spectrum ($CDCl_3$): 3.87 (3H, s, OCH_3), 2.54 (2H, qu, CH_2), and 1.02 ppm (3H, t, CH_3).

Methyl Ester of 3-(Diethylamino) propynoic Acid (Xa). To a solution of 0.82 g (0.005 mole) of the methyl ester of bromopropiolic acid in 30 ml of absolute ether, a solution of 0.58 (0.013 mole) dimethylamine in 20 ml of absolute ether was added with mixing at −10°C. The reaction mixture was exposed at 20°C for 1 h. The precipitate was filtered off, the filtrate evaporated, and the residue crystallized from ether. Yield 0.5 g (78%) of the ynamine Xa. Mp 35-37°C [4]. IR spectrum: 1695 (C=O), 2195 cm^{-1} (C≡C). PMR spectrum ($CDCl_3$) 3.72 (3H, s, OCH_3), 2.96 ppm (6H, s, CH_3). Found: C 56.1; H 7.3; N 11.2%. $C_6H_9NO_2$. Calculated: C 56.4 H 7.1 N 11.0%.

Methyl Ester of 3-(Dimethylamino)propynoic Acid (Xb). To a solution of 0.82 g (0.005 mole) of the methyl ester of bromopropiolic acid in 30 ml of absolute ether, 0.95 g (0.013 mole) diethylamine in 20 ml of absolute ether was added with mixing at −10°C. The reaction mixture was exposed for 1 h at 20°C. The precipitate formed was filtered off, the filtrate evaporated, and the residue redistilled under vacuum. Yield 0.58 g (75%) of the ynamine Xb. Bp 60°C (0.01 mm). IR spectrum: 1690 (C=O), 2175 cm^{-1} (C≡C). PMR spectrum ($CDCl_3$): 3.76 (3H, s, OCH_3), 3.16 (2H, qu, CH_2), and 1.27 ppm (3H, t, CH_3). Found: C 61.8; H 8.7; N 9.3%. $C_8H_{13}NO_2$. Calculated: C 61.9; H 8.4; N 9.0%.

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COMPARATIVE ANALYSIS OF THE ELECTRONIC STRUCTURE OF POSITIONAL ISOMERS: INDOLE—ISOINDOLE

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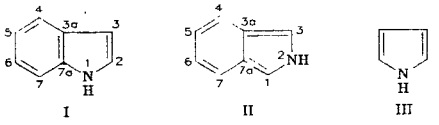
On the basis of an analysis of the canonical and localized molecular orbitals of indole and isoindole, calculated in the SCF and CNDO/2 approximations, as well as an x-ray crystallographic investigation of 2-methyl-isoindole, a comparison of the electronic structure of the positional isomers was made. The 10π-electronic system of isoindole is more integral than for indole: isoindole is a single 10π-electronic system with an appreciable localization of the bonds in the carbocyclic portion of the bicycle; the electronic structure of indole can be represented in a first approximation as the aggregate of three weakly interacting π-subsystems: the benzene ring, the double bond between the α- and β-carbon atoms, and the free electron pair of the nitrogen atom.

The electronic structure of indole (I) and isoindole (II) has been the subject of several investigations, in which methods of quantum chemistry were used to study the differences in the ground state [1-4], peculiarities of the reactivity [5, 6], and photophysical properties [3, 7, 8]. Despite the existence of a number of studies, there is no unanimity on the electronic structure and factors determining the stability of systems I and II [9].



I II III

In all the theoretical investigations conducted until recently, conclusions concerning the differences in the ground state of the structures I and II were drawn on the basis of an analysis of the basis of the canonical molecular orbitals (MO), the properties of the symmetry of which determine their substantial delocalization, which hinders a comparison of the characteristics of individual chemical bonds in related structures.

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