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SYNTHESIS OF 2-ETHYNYLAZIRIDINES

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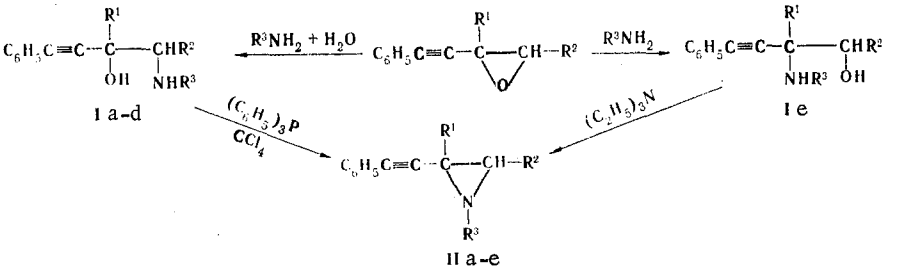
2-Ethynyl-substituted aziridines were obtained by the reaction of acetylenic β-amino and β-azido alcohols with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. The cycloaddition of carbenes and diazomethane to an acetylenic imine was investigated. 2-Ethynylaziridines were obtained in the case of carbonylalkoxycarbenes. The regioselectivity of the cycloaddition of carbenes to an acetylenic imine is demonstrated.

Of the large number of studies dealing with the synthesis and properties of 2-vinylaziridines, thus far only one has been devoted to the synthesis of the corresponding acetylenic aziridine, viz., 2-vinyl-3-ethynylaziridine [1]. At the same time, 2-ethynyl-substituted aziridines are of undoubted interest as valuable intermediates for the preparation of polyfunctional derivatives of aziridine, as well as a number of nitrogen-containing heterocycles.

In the present research we attempted to synthesize compounds of this type on the basis of acetylenic epoxides and acetylenic imines. Methods for the preparation of 2-alkyl- and 2-vinylaziridines by cyclization of the corresponding amino alcohols with triphenylphosphine dibromide or the triphenylphosphine–carbon tetrachloride complex in the presence of triethylamine have been described [1, 2]. We used the latter method for the synthesis of 2-ethynyl-substituted aziridines via the scheme



I, II a $R^1=CH_3$, $R^2=H$, $R^3=C(CH_3)_3$; b $R^1=R^2=CH_3$, $R^3=C(CH_3)_3$; c $R^1=CH_2CH_3$, $R^2=H$, $R^3=CH_2C_6H_5$; d $R^1=H$, $R^2=C\equiv CC_6H_5$, $R^3=C(CH_3)_3$; e $R^1=R^2=CH_3$, $R^3=CH_2C_6H_5$

Starting amino alcohols Ia-e were obtained from acetylenic epoxy compounds and tert-butylamine or benzylamine (Table 1). It should be noted that, depending on the conditions under which the epoxy compounds are opened by amines, two isomers are formed: β-amino alcohols Ia-d are obtained in the presence of small amounts of water, while α-amino alcohol Ie was isolated in the absence of water. The formation of Ie is indicated by resonance ab-

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TABLE 1. Acetylenic Amino Alcohols Ia-e

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
Ia	47—49	77,6	8,9	5,9	$C_{15}H_{21}NO$	77,9	9,1	6,1	75
Ib	40—42	78,1	9,2	5,6	$C_{16}H_{23}NO$	78,4	9,4	5,7	61
Ic	105—107	83,0	7,0	4,3	$C_{22}H_{23}NO$	83,3	7,2	4,4	66
Id	108—109	81,5	7,3	4,7	$C_{19}H_{21}NO$	81,7	7,5	5,0	42
Ie	98—100	81,3	7,4	5,0	$C_{19}H_{21}NO$	81,7	7,5	5,0	45

TABLE 2. PMR Spectra of Aziridines IIa-e and V

Compound	R¹	R²	R³	δ, ppm				
				C_6H_5	R¹	R²	R³	CH
IIa	CH_3	H	$C(CH_3)_3$	7,5—7,1m	1,47s	2,05 d (J=1,8Hz)	1,23	1,69 d (J=1,8 Hz)
IIb	CH_3	CH_3	$C(CH_3)_3$	7,4—7,1m	1,38 s	1,12 d	1,20 s	2,20 q
IIc	CH_2CH_3	H	$CH_2C_6H_5$	7,5—7,1m	2,80 s	7,5—7,1m	1,27 s	2,80 s
IId	H	$C{\equiv}CC_6H_5$	$C(CH_3)_3$	7,5—7,1m	1,60 q (CH_2). 1,02 t (CH_3)	1,91 s	7,1—7,5 m (C_6H_5), 3,86 and 3,64 (type AB, J=16,0 Hz, CH_2)	1,65 s
IIe	CH_3	CH_3	$CH_2C_6H_5$	7,5—7,1m	1,43 s	1,18 d	7,5—7,1 m (C_6H_5), 3,75 and 3,63 (type AB, J=16,5 Hz, CH_2)	1,83 q
V	CH_3	H	H	7,5—7,1 m	1,47 s	2,23 s	1,16 br s	1,74 s

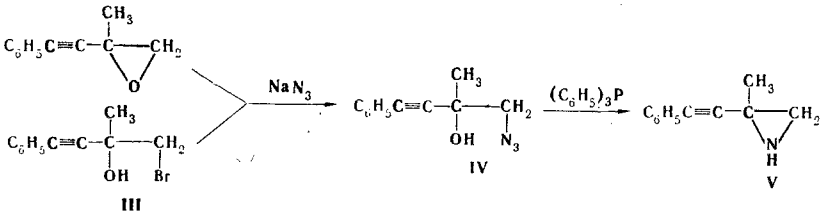
sorption from the CH proton at δ 3.65 ppm, which, in contrast to β-amino alcohols (δ_{CH} 2.5-2.8 ppm), is shifted ∿1 ppm to weak field. When the epoxides are opened under more severe conditions (100-110°C), in addition to acetylenic amino alcohols, products of their subsequent cyclization, viz., the corresponding pyrroles, are formed [3].

We obtained 2-ethynyl-substituted aziridines IIa-c, e by the reaction of acetylenic amino alcohols Ia-c, e with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. In the case of amino alcohol Ia a mixture of aziridine IIa and 2,5-dimethyl-1,4-di-tert-butyl-3,6-diphenylethynylpiperazine is formed as a result of cyclization, and the ratio of the reaction products varies as a function of the temperature. When the reaction is carried out at −5°C, the amount of piperazine in the reaction mixture is very small.

2,3-Diethynylaziridine IId was synthesized by the same method from amino alcohol Id, obtained by cleavage of the diacetylenic epoxide [4].

The IR spectra of IIa-e contain absorption bands of a triple bond at 2220 and 2250 cm^{-1} and aziridine ring C—H stretching vibrations at 3090 cm^{-1}. The data from the PMR spectra also confirm the structures of the compounds obtained (Table 2).

A method for the synthesis of 1H-aziridines from azido alcohols and triphenylphosphine has been described [5]. In order to obtain N-unsubstituted 2-ethynylaziridine we used acetylenic azido alcohol IV, which is formed in the reaction of sodium azide with the acetylenic epoxy compound or the corresponding bromohydrin III:



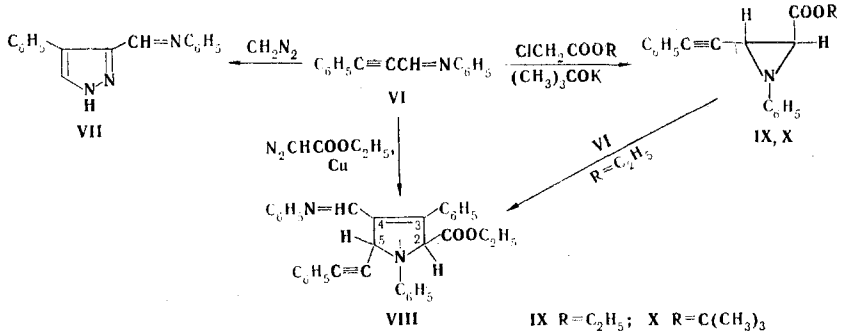
2-Methyl-2-phenylethynylaziridine (V) is formed when azido alcohol IV is treated with triphenylphosphine. The IR spectrum of V contains bands of stretching vibrations of a triple bond at 2200 cm^{-1}, of the aziridine ring at 3080 cm^{-1}, and of stretching vibrations of

an N—H bond at 3300 cm^{-1}. The signals of protons in the PMR spectrum at δ 7.29 (5H, m, C_6H_5), 2.23 and 1.74 (2H, broad s, aziridine ring CH_2), 1.47 (3H, s, CH_3), and 1.16 ppm (1H, broad s, NH) also constitute evidence for the formation of aziridine V.

The reactions of carbenes, carbenoids, and diazo compounds with imines are known methods for the preparation of aziridines [6]. Proceeding from this, we studied the possibilities of the synthesis of 2-ethynylaziridines in reactions involving the cycloaddition of diazomethane and carbenes to an acetylenic imine. The presence of two reaction centers in imine VI, viz., the conjugated acetylenic and imine bonds, makes it possible to expect the formation of various addition products.

We obtained a compound with the general formula $C_{16}H_{13}N_3$ (the empirical formula was confirmed by mass spectroscopy) by reaction of diazomethane with imine VI. Bands of a C=N bond at 1635 cm^{-1} and an NH bond at 3450 cm^{-1} are observed in the spectrum of the product, and absorption of a triple bond is absent. A singlet of an azomethine proton at δ 8.57 ppm and a multiplet of two groups of phenyl protons are present in the PMR spectrum of the reaction product. According to the literature data [7, 8], the 1,3-cycloaddition of diazoalkanes to a triple bond that is activated by an electron-acceptor substituent proceeds regioselectively to give pyrazoles with an electron-acceptor group in the 3 position of the ring. Proceeding from this and on the basis of the spectral data, it may be assumed that pyrazole VII is formed in the reaction of diazomethane with imine VI.

We isolated VIII as the principal product in the reaction of imine VI with ethyl diazoacetate in the presence of catalytic amounts of powdered copper. Bands of stretching vibrations of C=N and C=O bonds at 1635 and 1735 cm^{-1} are present in its vibrational spectrum. A singlet of an azomethine proton and a multiplet of aromatic protons with a relative intensity of 20 H, which indicates the presence of four phenyl rings, as well as a triplet and a quartet of an ethyl group, are observed in the ^1H NMR spectrum. The pyrroline structure is confirmed by the presence in the spectrum of two doublets at δ 6.20 and 5.75 ppm with J = 6.0 Hz, which, according to [9], are related to the 2- and 5-H protons of the pyrroline ring. The J value of 6.0 Hz corresponds to a trans orientation of the protons in the ring [9]. The ^{13}C NMR spectrum of VIII contains two singlets at 85.6 and 87.7 ppm, which can be related only to the resonance of the carbon atoms of a triple bond. Mass-spectroscopic analysis of the product reveals the existence of M^+ 496, which corresponds to empirical formula VIII (also confirmed by the results of elementary analysis).



The formation of pyrroline VIII is possible through intermediate aziridine IX, which undergoes reaction with a second molecule of imine VI with opening of the aziridine ring. The formation of pyrroline VIII in an independent experiment in the reaction of aziridine IX with imine VI constitutes evidence in favor of this reaction scheme.

We were able to synthesize 1-phenyl-2-alkoxycarbonyl-3-phenylethynylaziridine (IX, X) from imine VI and chloroacetic acid esters in the presence of potassium tert-butoxide. In the case of ethoxycarbonylcarbene the products are aziridine IX and its structural isomer, viz., ethynyl-substituted enamine $C_6H_5NH—C(C{\equiv}CC_6H_5){=}CHCOOC_2H_5$ (XI). It is noteworthy that the cycloaddition of carbenes to imine VI takes place regioselectively without involvement of the triple bond. An analysis of the PMR spectra of IX and X and the literature data [10] makes it possible to conclude that the aziridines obtained are trans isomers ($^3J_{HH'}$ = 2.5 Hz).

TABLE 3. Aziridines IIa-e and V

Compound	IR spectrum, cm⁻¹		Found, %			Empirical formula	Calculated, %			Yield, %
	C≡C	ring CH	C	H	N		C	H	N	
IIa	2230	3090	84,3	9,1	6,8	$C_{15}H_{19}N$	84,5	8,9	6,6	39
IIb	2220 2250	3090	84,2	9,1	6,1	$C_{16}H_{21}N$	84,6	9,2	6,2	35
IIc	2230	3080	87,9	7,2	4,6	$C_{22}H_{21}N$	88,3	7,0	4,7	41
IId	2230	3080	87,1	7,0	5,3	$C_{19}H_{19}N$	87,3	7,3	5,4	46
IIe	2225 2260	3090	87,0	7,1	5,5	$C_{19}H_{19}N$	87,3	7,3	5,4	63
V	2220 2250	3080	84,0	6,8	9,0	$C_{11}H_{11}N$	84,1	7,0	8,9	32

EXPERIMENTAL

The NMR spectra of 10% and 5% solutions of the compounds in $CDCl_3$ and CCl_4 were recorded with Perkin-Elmer R 12 A (60 MHz) and Bruker WH-90 spectrometers with tetramethylsilane as the internal standard. The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene and liquid films were obtained with a UR-20 spectrometer. The individuality of the compounds was monitored by thin-layer chromatography (TLC) on Silufol UV-254 with ether–hexane (1:1).

The acetylenic amino alcohols were obtained by the method in [11]. Their constants are presented in Table 1.

3-Benzylamino-3-phenylethynylbutan-2-ol (Ie, Table 1). A mixture of 0.1 mole of 1,2-dimethyl-1-phenylethynyloxirane and 0.3 mole of benzylamine was heated at 110°C for 20 h, after which the unchanged starting substances were evaporated *in vacuo*, and the residue was crystallized from hexane by cooling. PMR spectrum: 1.31 (d, J = 6.5 Hz, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.16 (broad s, 1H, NH), 2.16 (broad s, 1H, OH), 3.65 (q, J = 6.5 Hz, 1H, CH), 3.94 and 4.20 (system of the AB type, J = 13.5 Hz, CH_2), and 7.34 ppm (m, 5H, C_6H_5).

Aziridines IIa-e (Table 3). A mixture of 0.02 mole of amino alcohol Ia-e, 0.028 mole of triphenylphosphine, 0.028 mole of carbon tetrachloride, and 0.028 mole of triethylamine in 1 ml of acetonitrile was maintained at −3°C for 2 days, after which the precipitate was removed by filtration, the filtrate was evaporated, and the residue was washed with pentane. The pentane solution was evaporated, and the residue was chromatographed with a column filled with neutral aluminum oxide by elution with pentane.

1-Azido-2-methyl-4-phenylbut-3-yn-2-ol (IV). This compound was obtained as a colorless liquid in 66% yield by the method in [12]. IR spectrum: 2110 (N_3), 2230 (C≡C), and 3400 cm^{-1} (OH). PMR spectrum: 1.48 (s, 3H, CH_3), 3.40 and 3.28 (system of the AB type, J = 14.0 Hz, CH_2), 3.35 (broad s, 1H, OH), and 7.2 ppm (m, 5H, C_6H_5).

1-Methyl-1-phenylethynylaziridine (V). A solution of 2 g (0.01 mole) of azido alcohol IV in 15 ml of ether was added to a solution of 2.6 g (0.01 mole) of triphenylphosphine in 15 ml of absolute ether (nitrogen was liberated), and the mixture was stirred at room temperature for 2 h and refluxed for 1 h. The precipitate was removed by filtration, the ether was evaporated, and the residue was chromatographed with a column filled with Al_2O_3 by elution with ether to give 1.56 g (42%) of V. Found: C 84.5; H 7.2; N 9.2%. $C_{11}H_{11}N$. Calculated: C 84.1; H 7.0; N 8.9%.

3-Phenyliminomethyl-4-phenylpyrazole (VII). A solution of 1 g (0.024 mole) of diazomethane in 200 ml of absolute ether was added at 0°C to a solution of 3.5 g (0.017 mole) of imine VI in 30 ml of absolute ether, and the mixture was maintained at this temperature for 48 h. The solvent was evaporated, and the residual oil was washed with hexane and crystallized in diisopropyl ether to give 2.2 g (51%) of pyrazole VII with mp 215-217°C. PMR spectrum: 8.57 (s, 1H, CH=N), 7.97 (s, 1H, ring CH), and 7.4 ppm (m, 10H, C_6H_5); the resonance absorption from the proton of the NH group is found under the multiplet of aromatic protons. Found: C 77.4; H 4.9; N 17.0%. $C_{16}H_{13}N_3$. Calculated: C 77.7; H 5.2; N 17.0%.

1,3-Diphenyl-2-ethoxycarbonyl-4-phenyliminomethyl-5-phenylethynyl-3-pyrroline (VIII). A solution of 2.3 g (0.02 mole) of ethyl diazoacetate in 50 ml of hexane was added slowly at 80°C to a solution of 4.1 g (0.02 mole) of imine VI in 150 ml of hexane and 100 ml of tetrahydrofuran (THF) in the presence of 0.1 g of powdered copper, and the mixture was re-

fluxed for 20 h. The copper was separated, the solvent was evaporated, and the residual oil was washed with pentane and crystallized in ether. Recrystallization from ether gave 4.2 g (42%) of pyrroline VIII with mp 94-95°C. IR spectrum: 1640 (C=N) and 1735 cm^{-1} (C=O). PMR spectrum: 8.26 (s, 1H, CH=N), 6.70-7.55 (m, 20H, C_6H_5), 6.20 (d, J = 6.0 Hz, 1H, 2-H), 5.75 (d, J = 6.0 Hz, 5-H), 3.97 (q, 2H, CH_2), and 0.84 ppm (t, 3H, CH_3). ^{13}C spectrum ($CDCl_3$): 171.1 (CO); 153.6 (C=N); 152.7 and 131.9 (C=C); 145.7, 144.6, 137.2, 132.3, 130.2, 129.7, 129.3; 128.6, 123.8, 121.4, 118.9, and 144.3 (aromatic hydrocarbons); 87.7 and 85.6 (C≡C); 72.7 (C_2); 61.9 (C_5); 58.6 (OCH_2); 14.2 ppm (CH_3). Found: C 81.9; H 5.8; N 5.6%. $C_{34}H_{28}N_2O$. Calculated: C 82.3; H 5.6; N 5.6%.

Reaction of Aziridine IX with Acetylenic Imine VI. A solution of 3.6 g (0.012 mole) of aziridine IX and 2.5 g (0.012 mole) of imine VI in 60 ml of hexane and 30 ml of THF was refluxed in the presence of traces of copper for 20 h, after which the solvent was evaporated, and the residual oil was washed with hexane and crystallized from ether by cooling to give 2.1 g (38%) of a crystalline product with mp 93-95°C. The data from the IR and PMR spectra of this compound were in agreement with the previously described pyrroline VIII.

1-Phenyl-2-tert-butoxycarbonyl-3-phenylethynylaziridine (X). A solution of 0.05 mole of imine VI in 100 ml of THF and a solution of 0.07 mole of tert-butyl monochloroacetate in 50 ml of THF were added simultaneously with stirring at −40°C to 0.07 mole of potassium tert-butoxide in 100 ml of THF, and the mixture was maintained at this temperature for 2 h and then at room temperature for 12 h. The mixture was filtered and evaporated, and the residue was washed with pentane. The pentane solution was passed through a column filled with aluminum oxide, the solvent was evaporated, and the residual oil was crystallized from pentane and recrystallized from acetone to give 8.5 g (55%) of aziridine X with mp 105-107°C. IR spectrum: 1740 (C=O) and 2235 cm^{-1} (C≡C). PMR spectrum: 7.10 (m, 10H, C_6H_5), 3.42 (d, J = 2.5 Hz, 1H, 2-H), 2.97 (d, J = 2.5 Hz, 1H, 3-H), and 1.44 ppm [s, 9H, $C(CH_3)_3$]. Found: C 79.1; H 6.4; N 4.5%. $C_{21}H_{21}NO_2$. Calculated: C 78.9; H 6.6; N 4.4%.

1-Phenyl-2-ethoxycarbonyl-3-phenylethynylaziridine (IX). A solution of 0.05 mole of imine VI in 100 ml of THF and a solution of 0.07 mole of ethyl monochloroacetate in 50 ml of THF were added simultaneously with stirring at −40°C to 0.07 mole of potassium tert-butoxide in 100 ml of THF, and the mixture was maintained at this temperature for 2 h and then at room temperature for 12 h. The mixture was filtered and evaporated, and the residue was washed with pentane. The pentane solution was passed through a column filled with aluminum oxide, the solvent was evaporated, and the residual oil was chromatographed with a column filled with aluminum oxide by elution with hexane. Two components were isolated. The first component was 1.4 g (10%) of ethynyl-substituted enamine XI with mp 49-51°C. IR spectrum: 1740 (C=O), 2225 (C≡C), and 3300-3500 cm^{-1} (NH). PMR spectrum: 10.28 (broad s, 1H, NH), 7.33 (m, 10H, C_6H_5), 5.19 (s, 1H, CH), 4.15 (q, 2H, CH_2), and 1.26 ppm (t, 3H, CH_3). Found: C 78.4; H 6.1; N 4.5%. $C_{19}H_{17}NO_2$. Calculated: C 78.4; H 5.8; N 4.8%. The second component was 3.5 g (25%) of aziridine IX with mp 80-82°C. IR spectrum: 1740 (C=O) and 2230 cm^{-1} (C≡C). PMR spectrum: 7.15 (m, 10H, C_6H_5), 4.2 (q, 2H, OCH_3), 3.50 (d, J = 2.5 Hz, 1H, 2-H), 3.08 (d, J = 2.5 Hz, 1H, 3-H), and 1.26 ppm (t, 3H, CH_3). Found: C 78.1; H 5.9; N 4.7%. $C_{19}H_{17}NO_2$. Calculated: C 78.4; H 5.8; N 4.8%.

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