YNAZIRIDINES AND THEIR REACTIONS WITH AMINES

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On the basis of the results of IR and UV spectroscopy, a considerable decrease in the efficacy of the conjugation of the unshared pair of the nitrogen atom with a carbonyl group in ynaziridines as compared with ynamines has been shown. The difference in the electronic structures of these compounds finds its reflection in their chemical behavior: the electrophilicity of the triple bond in an ynaziridine is higher than that in the analogous ynamine in reactions with amines.

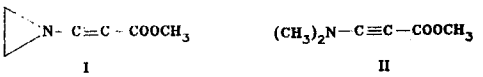
In a preceding paper [1], we reported the synthesis of previously unknown ynaziridines — new types of ynamines containing an aziridine fragment in their molecule. Thanks to their high reactivity, ynamines have found use in the synthesis of various classes of organic compounds [2]. Since the ynaziridines are analogs of the ynamines, it appeared of interest to study their physicochemical properties and chemical behavior in comparison with those of the ynamines.

The chemistry of the ynamines can be discussed on the basis of the idea of two resonance structures [3]:

Experimental results [3] suggest that the inductive effect of the nitrogen atom is completely compensated by its mesomeric effect, as a consequence of which the ketene imine structure plays a predominanting role. According to this, ynamines are, in the chemical respect, strong nucleophiles [3].

The replacement of an amino group by an aziridine residue, where the nitrogen atom has an increased s-nature of the orbital of the unshared pair of electrons, should lead to a fall in the efficacy of the conjugation of the nitrogen atom in the ynaziridines with the system of unsaturated bonds.

We have made a comparative study of the spectroscopic characteristics (IR, UV) of two model compounds: the ynaziridine (I) and the ynamine (II).



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In actual fact, a fall in the degree of conjugation in the ynaziridine was shown by the hypsochromic shift, as compared with the ynamine (II), of the absorption band of the n-π* transition in the UV spectrum of the ynaziridine (I) by 27 nm (Fig. 1). A similar conclusion can be deduced from an analysis of the IR spectra of compounds (I) and (II). The lowering of the efficacy of conjugation in the ynazaridine (I) led to a high-frequency shift of the absorption bands of the C≡C and C=O bonds (2230, 1710 cm^{-1}) in comparison with those for the ynamine (II) (2195 and 1695 cm^{-1}).

The difference in the electronic structures of these compounds finds its reflection in their chemical behavior: the electrophilicity of the triple bond in the ynaziridines is higher than in the ynamines. This is shown by the experimental results obtained in reactions with amines.

It is known [3, 4] that acid catalysis and fairly severe conditions are necessary for the successful interaction of amines with ynamines. On the other hand, the ynazaridines

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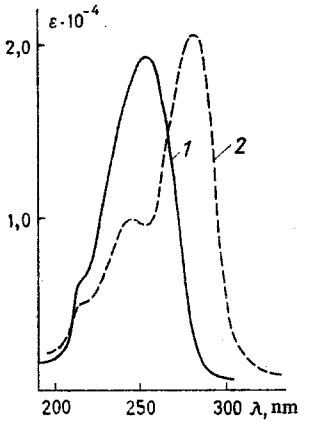
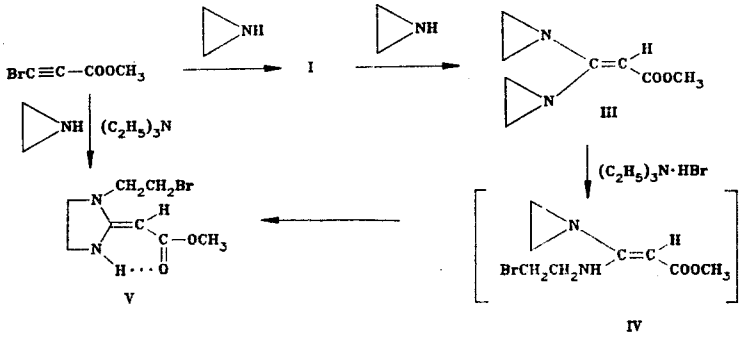


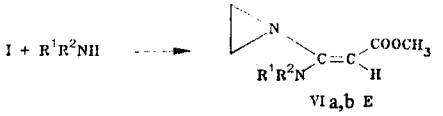
Fig. 1. Absorption spectra: 1) methyl aziridinopropynoate; 2) methyl dimethylaminopropynoate in hexane.

readily take part in reactions with amines. Thus, even under the mild conditions of the synthesis of the ynaziridine (I) (reaction of methyl bromopropiolate with an excess of aziridine at −20°C [1]) the addition of a second molecule of aziridine at the C≡C bond of (I) was observed with the formation of the enaziridine (III). This makes it difficult to obtain compound (I) in the pure form.



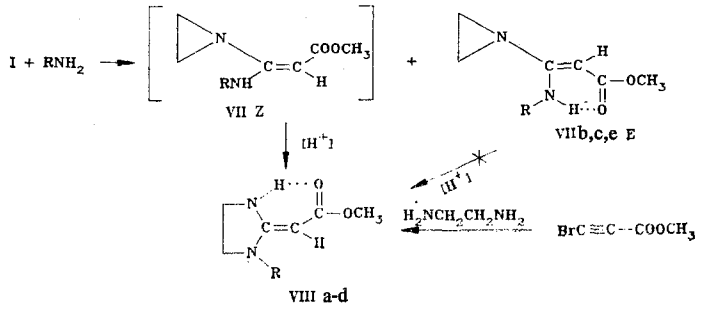
In order to eliminate this undesirable reaction, we made an attempt to synthesize the ynaziridine (I) in the presence of triethylamine with HBr as acceptor. However, instead of the expected ynaziridine (I) we isolated a compound with the empirical formula $C_8H_{13}BrN_2O_2$ (this was confirmed by mass spectrometry). Its IR spectrum showed an absorption band at 3350 cm^{-1} which is characteristic for an intramolecularly bound NH group, and also the band of C=O stretching vibrations at 1645 cm^{-1}. The PMR spectrum of the reaction product lacked the resonance signal of the protons of an aziridine ring while there were multiplets and a singlet with δ 3.49 and 3.57 ppm, each with an intensity of 4 protons, and also a singlet with an intensity of 1 H at 4.02 ppm and a broad signal from a proton at 7.47 ppm taking part in deuterium exchange. On the basis of the spectral results it may be concluded that the reaction of aziridine with bromopropiolate in the presence of triethylamine leads to the imidazolidine (V). Apparently, the enaziridine (III) also formed in this reaction is converted in the presence of a triethylamine salt into the intermediate enamine (IV) which then undergoes intramolecular alkylation to give the imidazolidine (V). The proposed scheme was confirmed by the formation of the imidazolidine (V) under similar conditions in an independent experiment by the action of triethylamine hydrobromide on the enaziridine (III).

Just as in the reaction with aziridine, in the absence of a catalyst the ynaziridine (I) readily interacts with other secondary amines, giving the enamines (VI).



VI a $R^1=R^2=CH_3$, b $R^1—R^2=—(CH_2)_4—$

The reaction of the ynaziridine (I) with primary amines takes place in a more complex manner, leading, in the majority of cases, to the formation of an enamine (VII) and an imidazolidine (VIII) in various ratios. Exceptions are the reactions with ammonia and aniline, giving only the corresponding imidazolidines. Compounds (VIIb, c, e) and (VIIIb, c, e) were isolated in the individual form with the aid of column chromatography. A possible scheme of their formation can be represented in the following way:



a R=H; b R=C_2H_5; c R=—$CH_2CH{=}CH_2$; d R=C_6H_5; e R=$C_6H_5CH_2$

On the interaction of primary amines with the ynaziridine (I), apparently, the two isomers (E and Z) of the enamine (VII), differing in their reactivities, are first formed. In the intermediate Z stereoisomer of (VII) the basicity of the aziridine nitrogen atom is higher than in the E isomer in view of the less effective conjugation of the unshared electron pair on this nitrogen atom with the carboxy group. As a result of this, the opening of the aziridine ring in the Z isomer under the action of acidic reagents (for example, catalytic amounts of hydrobromides of primary amines) takes place considerably more readily than for the E isomer and leads to the formation of imidazolidines. The imidazolidine structure of compounds (VIIIa-d) was established on the basis of the results of IR, PMR, and mass spectroscopy and, in the case of compound (VIIIa), was also confirmed by independent synthesis. In an independent experiment we also showed that the E stereoisomer of (VII), with the trans orientation of the aziridine residue and the ester group, is chemically and thermodynamically stable under the conditions of the synthesis of the imidazolidines (VIII).

Thus, in the case of the E and Z stereoisomers of (VII) we have an example of a stereocontrolled aziridine ring opening reaction.

Sasaki and Kojima [4] have shown that reactions of secondary amines with ynamines lead to mixtures of Z and E isomers. We studied the stereoisomerism of the products of the addition of amines to the ynaziridine (I) with the aid of the PMR method. It was found that one isomer was formed predominantly in the reaction with a secondary amine. To determine the configurations of compounds (VIa, b) we used, as model compound, the enaziridine (III) in the PMR spectrum of which the singlets of the protons of the aziridine ring in the trans and cis positions relative to the ester group are located at 2.14 and 2.38 ppm, respectively. In the PMR spectra of the enamines (VIa) and (VIb), the protons of the aziridine ring resonated at 2.33 and 2.31 ppm, which showed the cis arrangement of the aziridine fragment and the carboxy group and corresponded to the Z configuration of the isomers.

An analysis of the PMR spectra of the imidazolidines (VIIIb-d) also indicated the formation of only one isomer in each case. The PMR spectrum of the imidazolidine (VIIIa) contained a weak-field signal of the N—H proton at δ 7.47 ppm, which is characteristic for an intramolecular hydrogen bond, and the signal of an unbound N—H proton at 4.40 ppm. The presence in the PMR spectrum of each of the other imidazolidines (VIIIb-d) of only one weak-field signal of the N—H proton in the 7.47-7.78 region is evidence in favor of the Z configuration of these compounds.

The resonance absorption of the aziridine protons at 2.13-2.15 ppm in the enamines (VIIb, c, e) showed the trans arrangement of the aziridine residue and the carboxy group (starting from the enaziridine (III)) and permitted these compounds to be assigned to the E isomers. Also in favor of the E configuration was the weak-field chemical shift of the N—H proton at 8.15-8.25 ppm due to the presence of an intramolecular hydrogen bond.

TABLE 1. Characteristics of Compounds (III) and (V-VIII)

Compound	mp, °C [bp, °C (mm)]	IR spectrum, ν, cm⁻¹		Found, %			Empirical formula	Calculated, %			Yield, %
		νCO	νNH	C	H	N		C	H	N	
III	[80 (0,01]	1700		57,3	7,2	16,8	$C_8H_{12}N_2O_2$	57,1	7,1	16,7	90
V	92—94	1645	3350	38,3	5,2	11,0	$C_8H_{13}BrN_2O_2$	38,6	5,2	11,2	65
VIa		1670		56,4	8,3	16,6	$C_8H_{14}N_2O_2$	56,5	5,2	16,5	51
VIb	76—78	1680		61,4	8,4	14,4	$C_{10}H_{16}N_2O_2$	61,2	8,2	14,3	79
VIIb		1655	3280	56,7	8,4	16,5	$C_8H_{14}N_2O_2$	56,5	8,2	16,5	65
VIIc		1655	3360	59,4	7,7	15,5	$C_9H_{14}N_2O_2$	59,3	7,7	15,4	23
VIIe		1655	3260	67,4	6,8	12,4	$C_{13}H_{16}N_2O_2$	67,2	6,9	12,1	68
VIIIa	98—99	1640	3240, 3410	50,6	7,1	19,7	$C_6H_{10}N_2O_2$	50,7	7,0	19,7	80
VIIIb		1650	3355	56,7	8,3	16,6	$C_8H_{14}N_2O_2$	56,5	8,2	16,5	5
VIIIc	73—75	1650	3350	59,5	7,9	15,7	$C_9H_{14}N_2O_2$	59,3	7,7	15,4	48
VIIId	122—124	1650	3355	66,4	6,5	12,9	$C_{12}H_{14}N_2O_2$	66,1	6,4	12,8	71

The ease of addition of amines to the ynaziridine (I), and also the fact that (I) does not take part in the hydrogenation reaction characteristic for ynamines indicates a lower nucleophilicity of ynaziridines on the whole as compared with ynamines and agrees well with the features of their electronic structure that have been discussed above.

EXPERIMENTAL

UV spectra were taken in a Unicam SR-1800 instrument, and IR spectra on a Perkin-Elmer 580 B instrument in Nujol or CCl_4. PMR spectra were recorded on a Bruker WH-90 spectrometer in $CDCl_3$ with TMS as internal standard. ^{13}C NMR spectra were recorded on the Bruker WH-90 spectrometer at 22.63 MHz with TMS as internal standard. Mass spectra were obtained on a MS-905 spectrometer (70 eV).

The characteristics of compounds (III) and (V-VIII) are given in Table 1.

Methyl 3,3-Bis(aziridino)propenoate (III). At −20°C with stirring, a solution of 0.84 g (19.5 mmole) of aziridine in 10 ml of absolute ether was added dropwise over 0.5 h to a solution of 1.06 g (6.5 mmole) of methyl bromopropiolate in 50 ml of absolute ether. The temperature of the reaction mixture was raised to room temperature and it was kept for 4 h. The resulting precipitate was filtered off, the filtrate was evaporated, and the residue was distilled in vacuum. This gave 0.98 g of the enaziridine (III). PMR spectrum, δ, ppm: 4.83 (1 H, s, =CH); 3.65 (3 H, s, OCH_3); 2.38 (4 H, s, ring CH); 2.14 (4 H, s, ring CH).

1-(2-Bromoethyl)-2-(methoxycarbonylmethylene)imidazolidine (V). A. At −30°C with stirring, a solution of 0.22 g (5 mmole) of aziridine and 0.5 g of triethylamine in 10 ml of absolute ether were added dropwise over 0.5 h to a solution of 0.82 g (5 mmole) of methyl bromopropiolate in 50 ml of absolute ether. The temperature was raised to room temperature and the reaction mixture was left to stand for 2 days. Then it was filtered, the filtrate was evaporated, and the residue was washed with pentane and was crystallized from ether with cooling. This gave 0.81 g of the imidazolidine (V). PMR spectrum, δ, ppm: 7.47 (1 H, br.s, NH); 4.02 (1 H, s, =CH); 3.62 (CH, s, OCH_3); 3.57 (4 H, s, CH_2CH_2Br); 3.49 (4 H, m, ring CH). Mol. wt. 248.

B. A mixture of 0.6 g (3.6 mmole) of the enaziridine (III), 0.98 g (5.4 mmole) of triethylamine hydrobromide, and 20 ml of ether was kept at room temperature for 3 days. Then it was filtered, the filtrate was evaporated, and the crystalline residue was washed with ether—hexane (2:1) and recrystallized from ether. This gave 0.75 g of the imidazolidine (V).

Methyl 3-Aziridino-3-dimethylaminopropenoate (VIa). A solution of 0.39 g (3.1 mmole) of the ynaziridine (I) [1] in 30 ml of absolute ether cooled at −20°C was treated with 0.68 g (15 mmole) of dimethylamine, and the mixture was kept at the given temperature for 3 h. Then the temperature was slowly raised to room temperature and it was allowed to stand for another 2 h. The resulting precipitate was filtered off, the filtrate was evaporated, and the residue was distilled in vacuum. This gave 0.23 g of the enaziridine (VIa). PMR spectrum, δ, ppm: 4.29 (1 H, s, =CH); 3.62 (3 H, s, OCH_3); 2.92 [6 H, s, $N(CH_3)_2$], 2.33 (4 H, s, ring CHs).

Methyl 3-Aziridino-3-pyrrolidinopropenoate (VIb). At −20°C with stirring, a solution of 0.65 g (9.2 mmole) of pyrrolidine in 10 ml of absolute ether was added to a solution of 0.76 g (6.1 mmole) of the ynaziridine (I) in 40 ml of absolute ether. The temperature was slowly

raised to room temperature and the mixture was left for 20 h. Then it was filtered through a small layer of alumina, and the filtrate was evaporated. The crystalline residue was washed with pentane and was recrystallized from petroleum ether–diethyl ether (1:1). This gave 0.94 g of the enaziridine (VIb). PMR spectrum, δ, ppm: 4.18 (1 H, s, =CH); 3.60 (3 H, s, OCH_3); 3.33 (4 H, m, CH_2); 2.31 (4 H, s, aziridine CH); 1.89 (4 H, m, NCH_2).

Reaction of the Ynaziridine (I) with Ethylamine. At −10°C, 0.54 g (6 mmole) of ethylamine was added to a solution of 0.63 g (5 mmole) of the ynaziridine (I) in 50 ml of absolute ether. The reaction mixture was kept for 1 h and then the temperature was raised to room temperature and it was allowed to stand for 2 days, after which it was filtered through a small layer of alumina and evaporated. The residue was chromatographed on a column of alumina (ether–hexane (1:1)). This gave 0.55 g of methyl 3-aziridino-3-ethylaminopropenoate (VIIb) in the form of a colorless oily liquid [R_f 0.67 (Silufol UV-254, ether). PMR spectrum, δ, ppm: 8.28 (1 H, br.s, NH); 4.22 (1 H, s, =CH); 3.65 (3 H, s, OCH_3); 3.43 (2 H, q, CH_2); 2.13 (4 H, s, ring CH); 1.30 (3 H, t, CH_3)], and also 0.04 g of 1-ethyl-2-(methoxycarbonylmethylene)imidazolidine (VIIIb) [R_f 0.17 (Silufol UV-254, ether). PMR spectrum, δ, ppm: 7.58 (1 H, br.s, NH): 4.06 (1 H, s, =CH); 3.76 (4 H, m, ring CH); 3.61 (3 H, s, OCH_3); 3.07 (2 H, q, CH_2); 1.20 (3 H, t, CH_3).

Compounds (VIIc and d) and (VIIIc) were obtained similarly.

Methyl 3-allylamino-3-aziridinopropenoate (VIIc). Colorless oily liquid. R_f 0.83 (Silufol UV-254, ether). PMR spectrum, δ, ppm: 8.42 (1 H, br.s, NH); 5.91 (1 H, m, =CH); 5.20 (2 H, m, $=CH_2$); 4.24 (1 H, s, =CHCO); 4.00 (2 H, m, CH_2NH); 3.60 (3 H, s, OCH_3); 2.09 (4 H, s, ring CH).

1-Allylamino-2-(methoxycarbonylmethylene)imidazolidine (VIIIc). PMR spectrum, δ, ppm: 7.49 (1 H, br.s, NH); 5.73 (1 H, m, =CH); 5.21 (2 H, m, $=CH_2$); 4.06 (1 H, s, =CHCO); 3.70 (2 H, m, CH_2N); 3.62 (3 H, s, OCH_3); 3.47 (4 H, m, ring CH). Mol. wt. 182.

Methyl 3-Aziridino-3-benzylaminopropenoate (VIIe). Colorless oily liquid. R_f 0.60 [Silufol UV-254; ether–hexane (1:1)]. PMR spectrum, δ, ppm; 8.69 (1 H, br.s, NH); 7.29 (5 H, m, C_6H_5); 4.58 (2 H, d, CH_2NH); 4.27 (1 H, s, =CH); 3.61 (3 H, s, OCH_3); 2.07 (4 H, s, ring CHs).

2-(Methoxycarbonylmethylene)imidazolidine (VIIIa). A. A solution of 0.39 g (3.1 mmole) of the ynaziridine (I) in 30 ml of tetrahydrofuran cooled to −20°C was treated with 5 ml of ammonia. The mixture was kept in a sealed tube at room temperature for 3 days and was evaporated. The residue was crystallized from ether with cooling. This gave 0.35 g of the imidazolidine (VIIIa). PMR spectrum, δ, ppm: 7.47 (1 H, br.s, NH...O); 4.40 (1 H, br.s, NH); 4.11 (1 H, s, =CH); 3.62 (3 H, s, OCH_3); 3.53 (4 H, m, ring CHs). Mol. wt. 142.

B. At −20°C with stirring, a solution of 0.53 g (8.8 mmole) of ethylenediamine in 10 ml of absolute ether was slowly added to a solution of 0.72 g (4.4 mmole) of methyl bromopropiolate in 50 ml of absolute ether. The temperature was raised to room temperature and was kept there for 1 h. The resulting precipitate was filtered off, the filtrate was evaporated, and the residue was crystallized from ether at −10°C. This gave 0.55 g (88%) of the imidazolidine (VIIIa).

2-(Methoxycarbonylmethylene)-1-phenylimidazolidine (VIIId). A mixture of 0.7 g (5.6 mmole) of the ynaziridine (I), 0.51 g (5.6 mmole) of aniline, and 40 ml of absolute ether was boiled for 12 h. Then it was evaporated, and the residue was washed with hexane and crystallized from ether. This gave 0.87 g of the imidazolidine (VIIId). PMR spectrum, δ, ppm: 7.78 (1 H, br.s, NH); 7.24 (5 H, m, C_6H_5); 4.27 (1 H, s =CH); 3.78 (4 H, s, ring CHs); 3.60 (3 H, s, OCH_3). Mol. wt. 218.

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