1-(PHENYLETHYNYL)AZIRIDINE IN REACTIONS WITH AMINES

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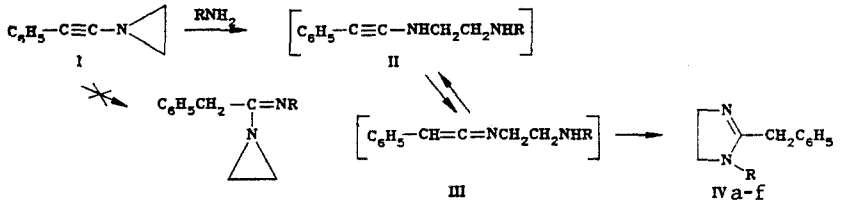
The reaction of 1-(phenylethynyl)aziridine with a primary or secondary amine gave 2-benzylimidazoline-2 or N-aminoethyl substituted phenylacetamidine via nucleophilic attack on the aziridine ring. The mechanism of aziridine ring opening by an amine was studied.

The synthesis of 1-(arylethynyl)aziridines have been reported [1]; these compounds represent a new type of aromatic inamine. The increased pyramidal stability of the nitrogen atom gives rise to a number of differences in the chemical behavior of these compounds in comparison with a aromatic inamines. In the present work we have studied the reactivity of 1-(phenylethynyl)aziridine (I) towards amines.

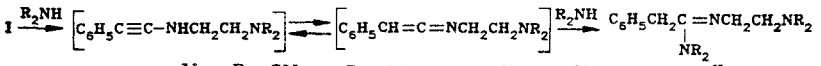
It is known [2] that primary amines combine with the inamine triple bond to give N-alkylamidines. We have shown that in the case of the inaziridine I, the amine attacks the aziridine ring with subsequent formation of the 2-benzylimidazolines-2 (IVa-f).



IV a R=H, b R=CH_3, c R=C_2H_5, d R=$CH_2CH=CH_2$, e R=$CH_2CH_2C_6H_5$, f R=$CH_2C_6H_5$

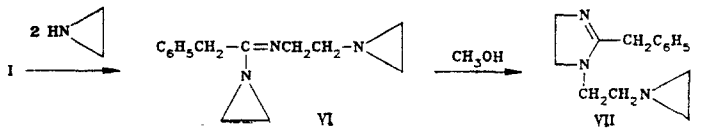
Opening of the aziridine ring by an amine is accompanied by isomerization of the inamine II to the ketenimine III which then undergoes cyclization to the 2-benzylimidazoline-2.

The reaction of 1-(phenylethynyl)aziridine with secondary amines also proceeds with opening of the aziridine ring, but in this case the tautomeric ketenimine combines with the secondary amine molecule to give N-aminoethyl substituted phenylacetamidines (Va-c).



V a R=CH_3, b R=C_2H_5, c R–R=–$(CH_2)_4$–

The reaction of compound I with excess aziridine without a solvent gave the substituted phenylacetamidine VI; when the reaction was carried out in methanol the product of the reaction is the imidazoline VII:



Probably, under conditions of acid catalysis in methanol, the amidine VI isomerizes to the thermodynamically more stable imidazoline VII. The amidine VI is formed as a mixture of E- and Z-isomers in the ratio 5:1; this was confirmed by the presence in the PMR spectrum of two singlets due to the protons at the sp^2 carbon atom of the aziridine ring, and two singlets from the methylene protons of the benzyl group.

In order to explain the mechanism of the inaziridine I ring-opening by an amine, we synthesized a model compound – 1-(phenylethynyl)-2-methylaziridine (VIII) with a marked methyl group on the aziridine ring. The opening of the aziridine ring in compound VIII can be accomplished by direct attack by the amine on the electrophilic aziridine carbon atom by S_N2-substitution [3]. In this case the nucleophile can attack the more electrophilic and sterically less hindered $C_{(3)}$ carbon atom of the aziridine ring. It is also possible that

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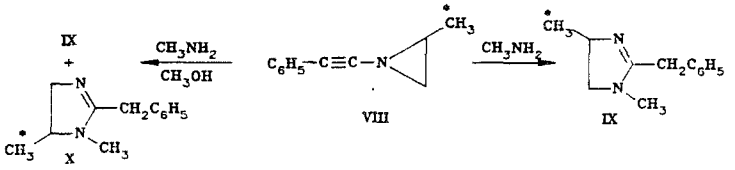
the preliminary protonation of the nitrogen atom of the aziridine ring in compound VIII takes place, with subsequent cleavage of the N–C bond of the ring, and formation of a carbocation by S_N1-substitution [3]. In such a case, the greater stability of the carbocation causes the ring $N–C_{(2)}$ bond to break and the amine to add to the substituted $C_{(2)}$ carbon atom. Consequently, the mechanism of the opening of the aziridine ring in the reaction of the inaziridine VIII with an amine can be determined from the position of the methyl group marker in the final product.

On the basis of the PMR spectroscopic data, we determined that the reaction of VIII with methylamine in aprotic solvents (ether, acetonitrile) gave exclusively a single structural isomer — 2-benzyl-1,4-dimethylimidazoline-2 (IX).



Based on the position of the methyl group marker, it can be shown that in aprotic solvents the opening of the aziridine ring by the amine occurs by S_N2 substitution.

Carrying out the reaction in prototropic solvent (methanol) gave an equimolar mixture of the two structural isomers —IX and X (from GLC data and the presence in the PMR spectrum of two doublets from the methylene protons at δ 1.09 and 1.29 ppm). The formation of a mixture of isomeric imidazolines IX and X when the reaction is carried out in methanol confirms the mixed mechanism of the opening of the aziridine ring in protonic solvent.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 580-B instrument using liquid films. PMR spectra were recorded on a Bruker WH-90 spectrometer using $CDCl_3$ as solvent, and TMS as an internal standard. Mass spectra were taken on an MS-905 spectrometer (70 eV). Gas-liquid chromatography and TLC were used to follow the course of the reaction and to check the purity of the compounds. GLC was carried out using a Biochrome-1 instrument with a flame-ionization detector, a glass column 2.5-3 mm in diameter, 10% ES-30 on chromosorb-750 (30-60 mesh), and helium as carrier gas (25 ml/min). TLC was carried out on Silufol UV-254, (ether-hexane, 1:1).

2-Benzylimidazoline-2 (IVa, $C_{10}H_{12}N_2$*). To a solution of 0.1 g (0.7 mmole) of 1-(phenylethyl)aziridine in 2 ml of methanol at −20°C was added a tenfold excess of ammonia. The reaction mixture was kept at room temperature for 6 days, and the solvent removed by evaporation. The residue was dissolved in ether and filtered through a thin layer of aluminum oxide. Evaporation of the solvent gave 0.07 g (64%) of 2-benzylimidazoline-2 with mp 65-66°C. Literature value [4] mp 66-67°C. IR spectrum: 1620 (C=N), 3200 cm^{-1} (NH). PMR spectrum, δ: 3.30 (1H, broad s, NH); 3.56 (4H, s, ring CH_2); 3.6 (2H, s, $CH_2C_6H_5$); 7.24 ppm (5H, m, C_6H_5).

2-Benzyl-1-methylimidazoline-2 (IVb). To a solution of 0.13 g (0.9 mmole) of compound I in 10 ml of methanol was added 0.28 g (9 mmole) of methylamine, and the reaction mixture was kept at room temperature for 4 days. After evaporation of the solvent, the residue was chromatographed on aluminum oxide (ether hexane 1:1) to give 0.12g (80%) of an oily liquid. IR spectrum: 1615 cm^{-1} (C=N). PMR spectrum, δ: 2.67 (3H, s, NCH_3); 3.31 and 3.67 (2H, m, ring CH_2); 3.58 (2H, s, CH_2); 7.2 ppm (5H, m, C_6H_5). M 174.

2-Benzyl-1-ethylimidazoline-2 (IVc). To a solution of 0.1 g (0.7 mmol) of inaziridine in 10 ml of acetonitrile was added 0.32 g (7.0 mmole) of anhydrous ethylamine, and the reaction mixture was kept at room temperature for 4 days. After evaporation of the solvent, the residue was passed through a column of alumina (ether-hexane, 1:1) to give 0.12 g (95%) of an oily liquid. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 0.93 (3H, t, CH_3); 3.02 (2H, q, CH_2); 3.24 and 3.69 (2H, m, ring CH_2); 3.56 (2H, s, $CH_2C_6H_5$); 7.18 ppm (5H, m, C_6H_5).

1-Allyl-2-benzylimidazoline-2 (IVd). To a solution of 0.1 g (0.7 mmole) of compound I in 5 ml of acetonitrile was added 0.2 g (3.5 mmole) of allylamine. The reaction mixture was worked up as described above (IVc) to give 0.07 g (51%) of an oily liquid. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ; 3.31 and 3.67 (2H, m, ring CH_2); 3.62 (2H, s, $CH_2C_6H_5$); 3.58 (2H, m, CH_2); 5.04-5.51 (3H, m, $CH=CH_2$); 7.2 ppm (5H, m, C_6H_5).

*Elemental analysis data was satisfactory: because of their hygroscopic nature, analytical data for the remainder of the compounds was not reproducible.

2-Benzyl-1-phenethylimidazoline-2 (IVe). To a solution of 0.1 g (0.7 mmole) the inaziridine I in 5 ml of acetonitrile was added 0.08 g (0.7 mmole) of phenylethylamine and the mixture stirred for 30 h at 60°C. After evaporation of the solvent, the residue was chromatographed on alumina (ether-hexane, 1:1) to give 1.2 g (55%) of an oily liquid. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 2.56 and 3.24 (2H, t, J=8 Hz, $CH_2CH_2C_6H_5$); 3.27 and 3.67 (2H, m, ring CH_2); 3.44 (2H, s, $CH_2C_6H_5$); 6.96 and 7.2 ppm (5H, m, C_6H_5).

1,2-Dibenzylimidazoline-2 (IVf). To a solution of 0.1 g (0.7 mmole) of compound I in 5 ml of methanol was added 0.07 g (0.7 mmole) of benzylamine and the mixture allowed to stand for 30 h at 60°C. After evaporation of the solvent, the residue was chromatographed on alumina (ether-hexane, 1:1) to give 0.14 g (80%) of an oily liquid. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 3.27 (4H, m, ring CH_2); 3.49 and 3.67 (2H, s, $CH_2C_6H_5$); 7.2 ppm (10H, m, C_6H_5).

N^1,N^1-Dimethyl-N^2-(2-diethylaminomethyl)phenylacetamidine (Va). To a solution of 0.1 g (0.7 mmole) of compound I in 5 ml of dry diethyl ether was added 0.31 g (7 mmole) of anhydrous dimethylamine, and the reaction mixture kept at room temperature for 2 days. The solvent was removed by evaporation, the residue was dissolved in chloroform and transferred onto alumina. The product of the reaction was eluted with ether to give 0.075 g (50%) of an oily liquid. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 2.2 and 2.87 [6H, s, $N(CH_3)_2$]; 2.44 and 3.36 (2H, m, CH_2); 3.77 (2H, s, $CH_2C_6H_5$); 7.2 ppm (5H, m, C_6H_5).

N^1,N^1-Diethyl-N^2-(2-diethylaminoethyl)phenylacetamidine (Vb). To a solution of 0.1 g (0.7 mmole) of the inaziridine I in 5 ml of dry diethyl ether was added 0.7 g (9.6 mmole of diethylamine. The mixture was kept for 24 h at 30°C, the solvent evaporated, and the residue chromatographed on an alumina column (ether) to give 0.1 g (50%) of an oily liquid. IR spectrum: 1610 cm^{-1}(C=N). PMR spectrum, δ: 0.98 (6H, t, CH_3); 1.2 (6H, t, CH_3); 2.4 (6H, m, CH_2); 3.24 (6H, m, CH_2); 3.7 (2H, s $CH_2C_6H_5$); 6.9 ppm (5H, m, C_6H_5).

N^2-(2-Pyrrolidinoethyl)-N^1,N^1-tetramethylenephenylacetamidine (Vc). To a solution of a 0.1 g (0.6 mmole) of compound I in 5 ml of acetonitrile was added 0.058 ml of (0.6 mmole) of pyrrolidine. The mixture was stirred for 4 hours at 70°C, then cooled to room temperature and the solvent evaporated. The residue was dissolved in chloroform and transferred onto an alumina column. The reaction product was eluted with diethyl ether to give 0.1 g (50%) of an oily liquid. IR spectrum: 1615 cm^{-1} (C=N). PMR spectrum, δ: 1.76 (8H, m, ring CH_2); 2.51 (4H, m, ring CH_2); 2.68 and 3.38 (2H, t, NCH_2); 3.33 (4H, m, ring CH_2); 3.78 (2H, s, $CH_2C_6H_5$); 7.24 ppm (5H, m, C_6H_5).

Reaction of aziridine with 1-(phenylethynyl)aziridine. A. A mixture of 0.1 g (0.07 mmole) of 1-(phenylethynyl)aziridine was allowed to stand at room temperature for 48 h. A yield of 0.13 g (80%) of N^2-(2-aziridinoethyl)-N^1,N^1-ethylenephenylacetamidine (VI) as a mixture of E-, and Z-isomers in the ratio of 5:1 was obtained. IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 1.13 and 1.69 (2H, t, aziridine CH_2); 2.0 (4H, s, aziridine CH_2, E-isomer); 2.1 (4H, s, aziridine CH_2, Z-isomer); 2.24 and 3.5 (2H, t, NCH_2); 3.62 and 3.76 (2H, s, $CH_2C_6H_5$); 7.28 ppm (5H, m, C_6H_5).

B. To a solution of 0.1 g (0.7 mmole) of 1-(phenylethynyl)aziridine in 3 ml of methanol was added 0.3 g (7.0 mmole) of aziridine, and the mixture kept at room temperature for 3 days. Evaporation of the solvent to gave 0.13 g (81%) of 1-(2-aziridinoethyl)-2-benzylimidazoline-2 (VII). IR spectrum: 1610 cm^{-1} (C=N). PMR spectrum, δ: 1.0 and 1.64 (2H, t, aziridine CH_2); 2.1 (2H, t, J = 6Hz, β-CH_2); 3.18 (2H, t, J = 6Hz, NCH_2); 3.3 (2H, m, ring CH_2); 3.6 (2H, s, $CH_2C_6H_5$); 3.78 (2H, m, ring CH_2): 7.2 ppm (5H, m, C_6H_5).

Reaction of 1-Phenylethnyl-2-methylaziridine [1] with Methylamine. A. To a solution of 0.16 g (1.0 mmole) of 1-phenylethynyl-2-methylaziridine in 3 ml of diethyl ether was added 0.13 g (10 mmole) of anhydrous methylamine and the mixture stirred at room temperature for 10 days. The reaction product was separated by column chromatography on alumina (ether-hexane, 1:1) to give 0.16 g (87%) of 2-benzyl-1,4-dimethylimidazoline-2 (IX). IR spectrum: 1615 cm^{-1} (C=N). PMR spectrum, δ: 1.27 (3H, d, CH_2); 2.6 (3H, s, NCH_2); 2.78 and 3.4 (1H, t, ring CH_2); 3.6 (2H, d, $CH_2C_6H_5$); 3.96 (1H, m, ring CH); 7.2 ppm (5H, m, C_6H_5).

B. To a solution of 0.16 g (1.0 mmole) of 1-phenylethynyl-2-methylaziridine in 5 ml of methanol was added to 0.13 g (10 mmole) of anhydrous methylamine. The reaction mixture was kept for 25 days at room temperature. The reaction product was separated by column chromatography on alumina (chloroform) to give 0.18 g (95%) of a mixture of the two isomers: 2-benzyl-1,4-dimethylimidazoline (IX) and 2-benzyl-1,5-dimethylimidazoline (X) in the ratio 1:1.

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ELECTROPHILIC ADDITION OF PHENOLS TO 1-VINYL-4,5,6,7-TETRAHYDROINDOLE

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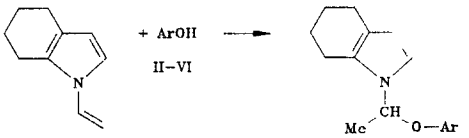
Both uncatalyzed and acid-catalyzed (CH_3COOH) addition of phenols to 1-vinyl-4,5,6,7-tetrahydroindole gave 1-(1-aroxyethyl)-4,5,6,7-tetrahydroindoles. With increasing acidity of the phenol and in the presence of CF_3COOH the yield of adducts was lowered because of the oligomerization of 1-vinyl-4,5,6,7-tetrahydroindole.

The addition of phenols to 1-vinylpyrroles has received little attention, although this reaction gives a promising method of modifying the biological action of a series of complex phenol-like compounds by the introduction of a pyrrole ring. This reaction is also interesting because of the competition between the two nucleophilic centers — the α-position to the pyrrole nucleus and the vinyl group.

It is known that 1-vinylpyrroles [1, 2], in the presence of both protonic acids and Lewis acids (or combinations of the two) add alcohols to give the corresponding 1-(1-alkoxyethyl)pyrroles. With acids, 1-vinylpyrroles [3] form dimers and oligomers [4] — products of the electrophilic substitution of hydrogen in the pyrrole ring by an immonium cation, formed from another molecule.

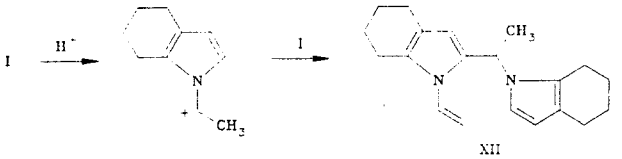
In the present work, using 1-vinyl-4,5,6,7-tetrahydroindole (I) as an example, the mechanism of the uncatalyzed and acid-catalyzed addition of phenols II-VI to 1-vinylpyrrole to give the previously unknown 1-(1-aroxyethyl)-4,5,6,7-tetrahydroindoles (VII-XI) has been studied (Table 1).



I VII–XI

II, VII Ar=C_6H_5; III, VIII Ar=4-MeC_6H_4; IV, IX Ar=2-ClC_6H_4; V, X Ar=4-ClC_6H_4; VI, XI Ar=4-FC_6H_4

The discrepancy between the conversion of the starting pyrrole I (Table 1) and the yield of adduct was due to the fact that as well as addition of phenols to 1-vinyl group there also occurs the dimerization of the vinylpyrrole I to give 1-vinyl-2-[1-(1,4,5,6,7-tetrahydroindolyl)ethyl]-4,5,6,7-tetrahydroindole (XII) (from TLC data) [3].



XII

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