α-ACETYLENIC ETHYLENEIMIDES AND THEIR REACTIONS WITH AMINES

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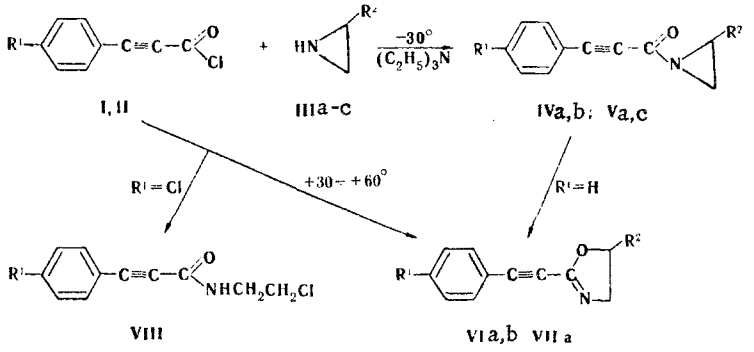
The reaction of aziridines with phenyl and p-chlorophenylpropiolyl chlorides at −30 to 60°C leads only to 1,2-addition products, viz., α-acetylenic ethyleneimides, or their isomerization products, viz., 2-ethynyl-substituted 2-oxazolines. Reactions with amines showed that the p-chlorophenylpropiolic acid ethyleneimides obtained are mild N-acylating agents.

The reactions of aziridines with α-acetylenic aldehydes were studied in [1, 2]. It was found that products of 1,2- or 3,4-addition are formed, depending on the temperature. We continued our study of the reactivities of aziridines in reactions with activated acetylenic compounds in the case of α-acetylenic carboxylic acid chlorides, the molecules of which also have two electrophilic centers.

The study of the reaction of phenylpropargylic chlorides with aziridines was carried out at −30 to 60°C. It was found that α-acetylenic carboxylic acid ethyleneimides (IVa,b-Va,c) are formed in the reaction of chlorides I and II with aziridine (IIIa) and 2-methyl (IIIb) and 2-carbomethoxyaziridine (IIIc) at −30°C in the presence of triethylamine; in the case of I (R^1 = H) the resulting ethyleneimides IVa,b are extremely unstable and are rapidly isomerized to oxazolines VIa,b:



I, IV, VI R^1 = H; II, V, VII, VIII R^1 = Cl; a R^2 = H; b R^2 = CH_3; c R^2 = $COOCH_3$

The PMR spectrum of the product of the reaction of I with aziridine recorded immediately after its isolation from the reaction mixture corresponds to ethyleneimide IVa. The singlet signal of aziridine protons at 2.38 ppm constitutes evidence for rapid (on the NMR time scale) inversion of the nitrogen atom in this compound. However, even during recording of the spectrum product IVa undergoes partial isomerization to oxazoline VIa, as indicated by the appearance of a multiplet at 3.64-3.80 ppm from the proton of the oxazoline ring.

As compared with the ethyleneimides IVa,b described above, chloro-substituted derivatives Va,c are rather stable — appreciable isomerization to oxazolines is not observed in the course of several days.

At the same time, oxazolines VIa and VIIa were obtained as the principal products in the reaction of aziridine IIIa with chlorides I and II at 30-60°C. Under these conditions the reaction proceeds ambiguously, and amide VIII (with R^1 = Cl) and products with polymeric compositions are formed along with oxazolines.

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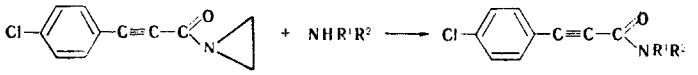
TABLE 1. Characteristics of Va,c and IXa-c*

Compound	mp, °C	IR Spectrum, cm^{-1}			Yield, %
		C≡C	C=O	NH	
Va	73—75	2210, 2230	1665	—	72
Vc	113—115	2210	1660 1750	—	61
IXa	127—129	2220	1630	3275	81
IXb	145—147	2210	1615	—	77
IXc	125—127	2210, 2230	1640	3170, 3300	65

*The results of elementary analysis of Va,c and IXa-c are in agreement with the calculated values.

According to the data in [3, 4], ethyleneimides of the saturated and ethylene series react with amines to give products of opening of the aziridine ring as a result of nucleophilic attack on the aziridine carbon atom. In contrast to this, we obtained transamination products IXa-c in the reaction of ethyleneimide Va with propylamine, pyrrolidine, and 2-aminomethylaziridine (Table 1):

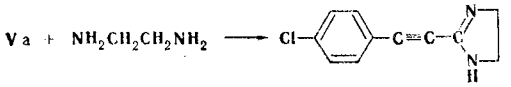


Va IX a-c

IX a R^1=H, R^2=$CH_2CH_2CH_3$; b R^1—R^2=—$(CH_2)_4$—; c R^1=H, R^2=CH_2—NH

The physicochemical properties of ethyleneimides Va,c and IXa-c are presented in Table 1.

In the reaction of Va with ethylenediamine the resulting transamination product undergoes cyclization with splitting out of water to give 2-imidazoline X:



X

The different direction of nucleophilic attack of the amines in the case of ethyleneimides that contain a triple bond can be explained as follows. It is known that the sp-hybridized carbon atom has increased electronegativity as compared with the sp^2- and sp^3-hybridized atoms. For this reason, the triple bond in acetylenic ethyleneimides displays electron-acceptor properties and thus increases the electrophilicity of the carbonyl carbon atom as compared with the electrophilicity of the carbon atom of the aziridine ring.

Thus, as a result of these studies it was established that, in contrast to α-acetylenic aldehydes and ketones, only 1,2-addition products are formed in the reaction of α-acetylenic carboxylic acid chlorides with aziridines under various temperature conditions. The reactions with amines showed that the resulting ethyleneimides are mild N-acylating agents. For example, we were able with their help to accomplish the selective acylation of 2-aminomethylaziridine (IXc) under mild conditions.

EXPERIMENTAL

The PMR spectra of 10% solutions of the compounds in $CDCl_3$ were obtained with a Perkin—Elmer R 12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene or of liquid films were obtained with a UR-20 spectrometer. The individuality of the compounds was monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 [elution with ether—heptane (1:1)].

The starting α-acetylenic acids were obtained by the method in [5], while the corresponding acid chlorides I and II were obtained by the method in [6].

Oxazolines VIa,b. A solution of 0.025 mole of phenylpropiolyl chloride (I) in 20 ml of absolute diethyl ether was added with stirring at −30°C to a mixture of 0.025 mole of aziridine IIIa or IIIb and 0.025 mole of triethylamine in 30 ml of absolute diethyl ether, and the mixture was maintained at this temperature for 20 min. The precipitated triethylamine was removed by filtration, the filtrate was evaporated, and the residue was distilled in vacuo. This procedure gave 2.3 g (54%) of oxazoline VIa with bp 65-66°C (0.01 mm) and mp 42-44°C. IR spectrum: 2210, 2230 (C≡C); 1640 cm^{-1} (C=N). PMR spectrum: 7.3-7.5 (m, 5H, C $_6H_5$); 3.64-3.81 ppm (m, 4H, CH_2CH_2). Found: C 77.0; H 5.4; N 8.5%. $C_{11}H_9NO$. Calculated: C 77.2; H 5.3; N 8.2%: Also obtained by this procedure was 2.8 g (58%) of oxazoline VIb with bp 76-78°C (0.01 mm). IR spectrum: 2230 (C≡C); 1640 cm^{-1} (C=N). PMR spectrum: 7.5 (m, 5H, C_6H_5), 3.87-4.58 (m, 1H, 5-H), 3.87-4.58 (m, 2H, CH_2), and 1.36 ppm (d, 3H, CH_3). Found: C 64.7; H 6.0; N 7.9%. $C_{12}H_{11}NO$. Calculated: C 64.9; H 5.9; N 7.6%.

p-Chlorophenylpropiolic Acid Ethyleneimides (Va,c). A solution of 0.025 mole of p-chlorophenylpropiolyl chloride in 20 ml of diethyl ether was added with stirring at −30°C to a mixture of 0.025 mole of aziridine IIIa or IIIc and 0.025 mole of triethylamine in 30 ml of absolute diethyl ether, and the reaction mixture was maintained at this temperature for 20 min. The precipitated triethylamine salt was removed by filtration, and the filtrate was evaporated. This procedure gave 3.7 g (72%) of ethyleneimide Va (Table 1). PMR spectrum: 7.2-7.6 (m, 4H, C_6H_4); 2.36 ppm [s, 4H, $N(CH_2)_2$]. Also obtained by this procedure was 4.0 g (61%) of ethyleneimide Vc (Table 1). PMR spectrum: 7.23-7.56 (m, 4H, C_6H_4), 3.78 (s, 3H, $COOCH_3$), 3.3 (m, 1H, CH), and 2.72 ppm (m, 2H, CH_2).

Reaction of Aziridine (IIIa) with α-Acetylenic Carboxylic Acid Chlorides (I, II). A 0.01-mole sample of acid chloride I or II in 20 ml of dry benzene was added with stirring at 30-60°C to a mixture of 0.01 mole of IIIa and 0.01 mole of triethylamine in 30 ml of absolute benzene, and the mixture was maintained at this temperature for 0.5 h. It was then cooled, and the triethylamine hydrochloride and resinous products were separated. The benzene solution was evaporated. a) The residue was distilled *in vacuo* to give 0.65 g (38%) of a white crystalline product with bp 64-66°C (0.01 mm) and mp 42-44°C. The data from the IR and PMR spectra were in agreement with the data for oxazoline VIa. b) The residual oily yellow liquid was chromatographed with a prefabricated preparative plate with silica gel (Merck) [elution with ether—pentane (1:3)], as a result of which two components were isolated. The first component was 0.46 g (19%) of amide VIII as light-yellow crystals with mp 39-41°C. IR spectrum: 1640 (C=O), 2220 (C≡C), and 3280 cm^{-1} (NH). PMR spectrum: 7.29 (m, 4H, C_6H_4), 6.62 (br s, 1H, NH), and 3.57 ppm (d, 4H, CH_2CH_2). The second component was 0.76 g (37%) of oxazoline VIIa as a viscous oily liquid. IR spectrum: 2205, 2235 (C≡C); 1635 cm^{-1} (C=N). PMR spectrum: 7.4 (m, C_6H_4); 3.8-4.5 ppm (m, 4H, CH_2CH_2).

p-Chlorophenylpropiolic Acid N-Propylamide (IXa). A solution of 0.004 mole of propylamine in 5 ml of ether was added with stirring at room temperature to a solution of 0.004 mole of ethyleneimide Va in diethyl ether, and the mixture was refluxed for 2 h. The solvent was evaporated, and the residue was crystallized from diethyl ether to give 0.72 g (81%) of amide IXa (Table 1). PMR spectrum: 7.27 (m, 4H, C_6H_4), 6.16 (br s, 1H, NH), 3.25 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), and 0.96 ppm (t, 3H, CH_3).

p-Chlorophenylpropiolic Acid N-Pyrrolidinylamide (IXb). A 0.004-mole sample of pyrrolidine in 10 ml of ether was added with stirring at 10°C to a solution of 0.004 mole of ethyleneimide Va in 10 ml of diethyl ether, and the mixture was maintained at room temperature for 3 h. The solvent was evaporated, and the residue was crystallized from ethanol to give 0.58 g (77%) of amide IXb (Table 1). PMR spectrum: 7.34 (m, 4H, C_6H_4), 3.58 (m, 4H, α-CH_2), and 1.92 ppm (m, 4H, β-CH_2).

p-Chlorophenylpropiolic Acid N-(2-Aziridinyl)methylamide (IXc). A 0.12-mole sample of 2-aminomethylaziridine in 20 ml of ethanol was added with stirring at 0 to −5°C to a solution of 0.12 mole of ethyleneimide Va in 50 ml of ethanol, and the mixture was maintained at this temperature for 1 h, after which the temperature was raised to room temperature and allowed to stand for 12 h. The ethanol was evaporated, and the residue was crystallized from ethyl acetate to give 1.9 g (65%) of amide IXc (Table 1). PMR spectrum: 7.3 (m, 4H, C_6H_4), 7.0 (br s, 1H, NH), 3.60 (m, 2H, CH_2), 2.32 (m, 1H, ring CH), 1.87 (d, J = 5.2 Hz, 1H, ring H_{trans}), and 1.49 ppm (d, J = 3.2 Hz, 1H, ring H_{cis}).

2-(p-Chlorophenylethynyl)imidazoline (X). A 0.004-mole sample of ethylenediamine in 10 ml of ether was added with stirring at room temperature to a solution of 0.004 mole of ethyleneimide Va in 20 ml of diethyl ether, and the reaction mixture was allowed to stand for 30 min. The ether was evaporated, and the residue was crystallized from ether by cooling to

give 0.43 g (63%) of the 2-imidazoline with mp 122-124°C, Found; C 64.5; H 4.2; N 13.9%, $C_{11}H_9N_2Cl$. Calculated: C 64.7; H 4.4; N 13.7%, IR spectrum: 1630 (C=N), 2220 (C≡C), and 3260 cm^{-1} (NH). PMR spectrum: 7.56 (m, 4H, C_6H_4), 7.49 (br s, 1H, NH), and 3.27 ppm (m, 4H, CH_2CH_2).

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INTRAMOLECULAR REARRANGEMENT OF N-ACETYLINDOXYL OXIME

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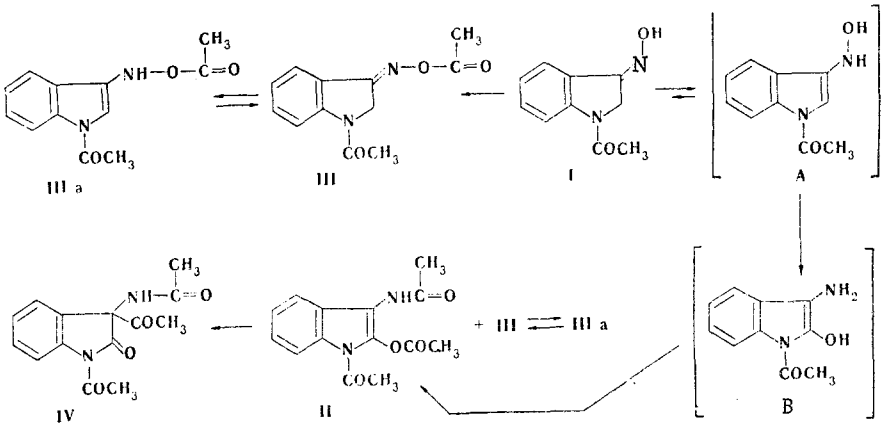
It was established that N-acetylindoxyl oxime is converted to N-acetylindoxyl acetyloxime when it is heated to 50°C in a mixture of acetic acid and acetic anhydride. If the reaction is carried out by refluxing, N-acetyl-2-acetoxy-3-acetamidoindole, which undergoes rearrangement to 1,3-diacetyl-3-acetamidooxindole when it is heated, is also formed.

We have previously demonstrated that N-acetylindoxyl arylhydrazones undergo a rearrangement of the o-benzidine type and form indolo[1,2-c]quinazolines [1].

In the present research we studied the behavior of N-acetylindoxyl oxime (I) under similar conditions, i.e., in the case of heating a solution of oxime I in acetic acid in the presence of acetic anhydride to the boiling point. As a result, we obtained N-acetyl-2-acetoxy-3-acetamidoindole (II) and N-acetylindoxyl acetyloxime (III).



In acidic media oxime I in tautomeric form A evidently undergoes a rearrangement of the type that phenylhydroxylamines undergo, in which the hydroxy group migrates to the α position of the indole ring to give N-acetyl-2-hydroxy-3-aminoindole (B). Under the reaction conditions rearrangement product B is acetylated to give II.

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