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SYNTHESIS OF 2-AMINO-1-AZIRINES AND THEIR REACTIONS WITH CARBOXYLIC ACIDS

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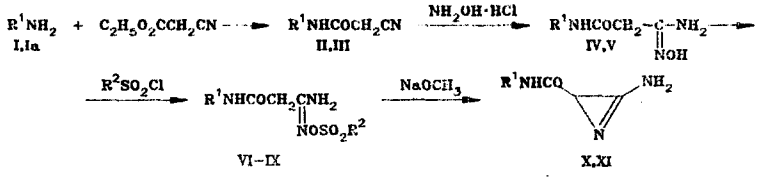
A method was developed for the synthesis of 2-amino-1-azirines under the conditions of a modified Neber reaction. Their reactivities with respect to mono- and dicarboxylic acids and thiocarboxylic acids were investigated.

In recent years a great deal of attention has been directed to the synthesis and study of the reactivities of functionally substituted 1-azirines [1, 2]. Investigations of addition reactions in the 2-alkylamino-1-azirine series that expand the possibilities of the synthesis of acyclic and heterocyclic nitrogen-containing compounds that are difficult to obtain are of particular interest [3-9]. However, the reactions of 2-amino-1-azirines that contain a primary amino group have not been studied at all.

In order to study the reactivities of 2-amino-1-azirines with a primary amino group we synthesized 2-amino-3-phenylcarbamoyl-1-azirines under the conditions of a modified Neber reaction. As the starting compounds we used phenylcarbamoylacetamidoximes IV and V, which were obtained by the reaction of 2-cyanoacetanilides II and III with hydroxylamine in ethanol.



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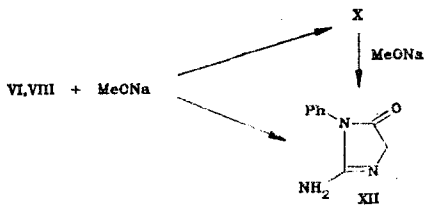
I, II, IV, VI, VIII, X $R^1=C_6H_5$; III, V, VII, IX, XI $R^1=p\text{-}ClC_6H_4$; VI, VII $R^2=p\text{-}CH_3C_6H_4$; VIII, IX $R^2=CH_3$

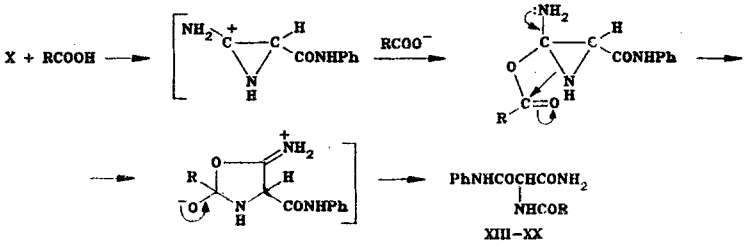
As a result of tosylation and mesylation of amidoximes IV and V we obtained their O-tosylates and O-mesylates VI-IX, which, in turn, undergo rearrangement to 2-amino-1-azirines X and XI under the influence of sodium methoxide in alcohol. Mass-spectrometric analysis of X demonstrates the presence of an M^+ ion with mass 175, which corresponds to the empirical formula of X. A characteristic band of the stretching vibrations of the C=N bond of the azirine ring (1820 cm^{-1}) is present in the IR spectra of azirine X. A singlet of the proton of the azirine ring (2.64 ppm) is observed in the ^1H NMR spectra.



The conditions under which the synthesis is carried out are of great significance in the direction that the reaction takes. In the case of excess sodium methoxide the principal reaction product is imidazolone XII, which is probably formed as a result of rearrangement of azirine X under the influence of the base; this is confirmed by the reaction of azirine X with sodium methoxide, in the course of which, instead of the corresponding alkoxyaziridine — the product of alcoholysis of azirine X — only imidazolone XII [10] was isolated.

According to the literature data, N,N-dialkylaminoazirines react with electrophilic reagents with opening of the N—C_3 bond [11-13] or the C=N bond [14], depending on the character of the electrophile.

Acylaminomalonic acid amides XIII-XX are formed in the reaction of azirine X with mono- and dicarboxylic acids in absolute acetone at room temperature or with heating, as in the case of acetic acid.



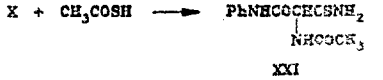
XIII-XX

XIII R=COOH; XIV R=Ph; XV R=$PhCH_2$; XVI R=PhC≡C; XVII R=HOOCCH=CH; XVIII R=CH_3; XIX R=CH_2=CH; XX R=PhCH=CH

The resulting aminoaziridinium cation probably reacts readily with the nucleophilic carboxylate anion to give the corresponding aminoaziridines, which, in turn, undergo 1,2 cleavage of the ring with simultaneous transfer of the aryl group or its vinylog to give triamides XIII-XX.

An analysis of the ^1H NMR spectra of triamides XIII-XX showed that the signals of the NH_2 protons of the terminal amide fragment are overlapped with the resonance signals of the phenyl protons. Consequently, it is difficult to establish the conformation of this fragment. The central amide group is represented in the ^1H NMR spectra of amides XIII-XV and XVII-XX by a doublet of NH protons at 10 ppm as a consequence of their vicinal spin-spin coupling with the α-carbon proton with ^3J = 8 Hz. The existence of preferably the Z conformation, which predominates in secondary amides [15], can be proposed for amides XIII-XV and XVII-XX.

Thioamide XXI is formed in the reaction of azirine X with thioacetic acid.



XXI

TABLE 1. Spectral Characteristics of II-XII

Compound	PMR spectrum, δ, ppm				IR spectrum, ν, cm^{-1}	
	Ar–H	CH_2	NH_2	NH	C=O	NH
II	7,14—7,68	3,93	—	10,34	1630, 1670	3090, 3260 ($\nu_{C\equiv N}$ 2280)
III	7,18—7,64	3,78	—	10,38	1635, 1670	3080, 3260 ($\nu_{C\equiv N}$ 2280)
IV	7,00—7,73	3,11	5,48	10,03	1650, 1680	3180—3460
V	7,14—7,62	3,04	5,37	10,30	1630, 1675	3200—3450
VI	7,05—7,65	3,27	6,85	10,07	1640, 1670	3200—3460
VII	7,28—7,62	3,21	6,82	10,17	1630, 1680	3180—3480
VIII	7,01—7,81	3,08	6,81	9,97	1650, 1680	3180—3450
IX	7,27—7,78	3,05	6,79	10,05	1650, 1680	3180—3460
X*	7,07—7,65	—	—†	9,95	1630, 1650	3050—3330 ($\nu_{C\equiv N}$ 1820)
XI	7,07—7,65	—	—†	9,94	1630, 1650	3060—3330 ($\nu_{C\equiv N}$ 1820)
XII	7,01—7,48	3,72	—†	—	1660, 1689	3020—3290

*The ^{13}C NMR spectrum indicates the presence of C≡N (149.95 ppm) and C=O (171.52 ppm) groups.
†The signals of the protons of the NH_2 group are overlapped with the resonance signals of the Ph protons.

TABLE 2. Characteristics of II-XXI

Compound	mp, deg C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
II	157—159	67,5	5,0	17,5	$C_9H_8N_2O$	67,5	5,0	17,5	98
III	198—199	55,6	3,6	14,4	$C_9H_7ClN_2O$	55,5	3,6	14,4	96
IV	155—156	55,9	5,7	21,7	$C_6H_{11}N_3O_2$	55,9	5,7	21,8	62
V	148—149 (subl.)	47,5	4,4	18,4	$C_9H_{10}ClN_3O_2$	47,5	4,4	18,5	65
VI	120—121	50,2	5,4	17,6	$C_{10}H_{13}N_3O_4$	50,2	5,4	17,6	72
VII	126—128	43,9	4,4	15,3	$C_{10}H_{12}ClN_3O_4$	43,9	4,4	15,4	69
VIII	119—120	60,9	5,4	13,3	$C_{16}H_{17}N_3O_4$	60,9	5,4	13,3	67
IX	164—165	54,9	4,6	12,0	$C_{16}H_{16}ClN_3O_4$	54,9	4,6	12,0	70
X	146—147	61,7	5,1	24,0	$C_9H_9N_3O$	61,7	5,1	24,0	73
XI	158—160	51,5	3,8	20,1	$C_9H_8ClN_3O$	51,6	3,8	20,1	79
XII	240	61,7	5,1	24,0	$C_9H_9N_3O$	61,7	5,1	24,0	89
XIII	121—122	49,8	4,2	15,8	$C_{11}H_{11}N_3O_5$	49,8	4,2	15,8	88
XIV	321 (subl.)	64,7	5,1	14,1	$C_{16}H_{15}N_3O_3$	64,7	5,1	14,1	76
XV	189	65,6	5,5	13,5	$C_{17}H_{17}N_3O_3$	65,6	5,5	13,5	70
XVI	185	68,1	5,1	12,5	$C_{19}H_{17}N_3O_3$	68,0	5,1	12,5	56
XVII	193	53,6	4,5	14,4	$C_{13}H_{13}N_3O_5$	53,6	4,5	14,4	64
XVIII	176	56,2	5,5	17,9	$C_{11}H_{13}N_3O_3$	56,2	5,5	17,9	68
XIX	162	58,3	5,3	17,0	$C_{12}H_{13}N_3O_3$	58,3	5,3	17,0	67
XX	257—258	66,8	5,3	13,0	$C_{18}H_{17}N_3O_3$	66,8	5,3	13,0	54
XXI	230	52,6	5,2	16,7	$C_{11}H_{13}N_3O_2$	52,6	5,2	16,7	70

TABLE 3. Spectral Characteristics of XIII-XXI

Compound	PMR spectrum, δ, ppm				IR spectrum, ν, cm^{-1}	
	NH(CH) (d)	NH (s)	CH (d)	Ar—H (m)	C=O	NH
XIII	8,51	10,06	5,00	7,21—7,67	1530—1720 (ν_{OH} 2600—2710)	3120—3420
XIV	8,59	10,23	5,30	7,16—7,90	1555—1695	3125—3390
XV	9,36	10,45	5,67	7,01—7,67	1550—1695	3120—3400
XVI	8,85	10,10	5,11	7,11—7,55	1550—1695 ($\nu_{C\equiv N}$ 2210)	3150—3403
XVII	9,15	10,13	5,11	7,07—7,53	1550—1720 (ν_{OH} 2580—2725)	3150—3420
XVIII	8,26	10,07	5,00	7,23—7,63	1530—1685	3140—3460
XIX	8,53	10,12	5,14	7,07—7,56	1550—1690	3120—3420
XX	8,56	10,21	5,26	7,18—7,69	1530—1692	3190—3350
XXI*	8,27	10,25	5,46	7,18—7,68	1530—1665 ($\nu_{C=S}$ 1110; 1530)	3180—3340

*A signal of CH_3 protons is located at 2.0 ppm, and signals of $H_2N(C=S)$ protons are found at 9.58 ppm.

In the course of the investigations it was established that the reactivity of 2-amino-1-azirine with carboxylic acids is similar to that observed for 2,2-dialkylamino-1-azirines.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol were recorded with a Specord 75-IR spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Bruker WH-90 spectrometer with tetramethylsilane (TMS) as the internal standard. The ^{13}C NMR spectra of solutions in d_6-DMSO were recorded with a Bruker WH-90 spectrometer at 22.63 MHz. The compositions of the reaction mixtures and the purity of the products were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates.

The characteristics of the compounds obtained are presented in Tables 1-3.

2-Cyanoacetanilide (II). A solution of 18.6 g (200 mmole) of aniline and 22.6 g (200 mmole) of ethyl cyanoacetate was heated at 180-190°C until the liberation of ethanol ceased, after which the reaction mixture was cooled, and the precipitate was washed with 100 ml of ether and recrystallized from ethanol to give 31.4 g (98%) of II.

2-Cyano-4-chloroacetanilide (III). This compound was similarly obtained.

Phenylcarbamoylacetamidoxime (IV). An aqueous solution of 3.4 g (32 mmole) of hydroxylamine hydrochloride and a mixture of 2.2 g (32 mmole) of sodium carbonate in 20 ml of 50% ethanol were added with stirring to a solution of 4 g (25 mmole) of anilide II in 130 ml of ethanol, and the mixture was heated at 70°C for 45 min and allowed to stand at room temperature overnight. The solvent was evaporated, and the precipitate was washed with water and recrystallized from ethanol to give 3.0 g (62%) of amidoxime IV.

p-Chlorophenylcarbamoylacetamidoxime (V). This compound was similarly obtained.

Phenylcarbamoylacetamidoxime O-Mesylate (VI). A 1.48-g (13 mmole) sample of methanesulfonyl chloride was added gradually dropwise at −20°C to a solution of 1.93 g (10 mmole) of amidoxime IV in 35 ml of absolute pyridine, after which the mixture was maintained at −20°C for 15 min and at 0°C for 20 min. It was then poured into 200 ml of cold water, and the precipitate was removed by filtration, washed with cold water, and recrystallized from ethanol to give 1.7 g of mesylate VI.

O-Mesylate VII and O-Tosylates VIII and IX. These compounds were similarly obtained.

2-Amino-3-phenylcarbamoyl-1-azirine (X). A solution of 1.2 g (21 mmole) of sodium methoxide in 50 ml of absolute ethanol was added slowly dropwise with stirring at 25°C to a mixture of 4.6 g (20 mmole) of mesylate VI in 150 ml of absolute ethanol, after which the mixture was maintained at 25°C for 1 h. The precipitate was removed by filtration and washed with water and chloroform to give 2.5 g (73%) of azirine X.

2-Amino-3-(p-chlorophenyl)carbamoyl-1-azirine (XI). This compound was similarly obtained.

2-Amino-1-phenylimidazol-5-one (XII). A solution of 0.55 g (10 mmole) of sodium methoxide in 20 ml of absolute ethanol was added dropwise at 25°C to a solution of 1.75 g (10 mmole) of azirine X in 150 ml of absolute ethanol, after which the precipitate was removed by filtration, washed with water, and recrystallized from ethanol to give 1.65 g (89%) of imidazolone XII.

N-Oxaloaminomalonic Acid N-Phenyldiamide (XIII). An acetone solution of 0.14 g (1.6 mmole) of oxalic acid was added dropwise at 0°C to a solution of 0.25 g (1.4 mmole) of azirine X in 30 ml of absolute acetone, after which the mixture was allowed to stand at room temperature for 24 h. The precipitate was removed by filtration and washed with a small amount of alcohol to give 2.3 g (88%) of XIII.

N-Benzamidomalonic Acid N-Phenyldiamide (XIV). An acetone solution of 0.18 g (1.5 mmole) of benzoic acid was added dropwise at 0°C to a solution of 0.25 g (1.4 mmole) of azirine X in 30 ml of absolute acetone, after which the mixture was maintained at room temperature for 4 days, and the solvent was then evaporated. Ether was added to the residue, and the resulting precipitate was removed by filtration and recrystallized from ethanol to give 0.3 g (76%) of XIV.

Compounds XV-XVII and XIX-XXI. These compounds were similarly obtained.

N-Acetamidomalonic Acid N-Phenyldiamide (XVIII). An acetone solution of 0.09 g (1.5 mmole) of acetic acid was added dropwise at 15°C to a solution of 0.25 g (1.4 mmole) of azirine X in 30 ml of absolute acetone, after which the reaction mixture was heated at 50°C for 1 h. It was then cooled, and the solvent was evaporated. The precipitate was recrystallized from ethanol to give 0.22 g (68%) of XVIII.

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MECHANISM OF THE FISCHER REACTION. EFFECT OF ELECTRONIC FACTORS ON THE KINETICS OF THE REARRANGEMENT OF m-SUBSTITUTED CYCLOHEXANONE ARYLHYDRAZONES TO TETRAHYDROCARBAZOLES

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The kinetics of the thermal and acid-catalyzed Fischer indolization of m-substituted cyclohexanone arylhydrazones were studied. It was shown that substituents with different natures ($-CH_3$, $-Cl$) and the polarity of the solvent have little effect on the rate of the rearrangement. The results obtained were interpreted within the framework of a concerted mechanism for the formation of the carbon—carbon bond ([3,3]-sigmatropic rearrangement).

In a previous paper we reported the results of kinetic [in the case of cyclohexanone N-methylphenylhydrazone and N,N'-di-methyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine] and quantum-chemical (for the model compound divinylhydrazine) investigations of the mechanism of the Fischer reaction [1]. It was shown that both the experimental data for the thermal and acid-catalyzed indolization of the indicated arylhydrazone and enehydrazine and theoretical calculations satisfactorily describe the mechanism in terms of the concerted formation of a carbon—carbon bond ([3,3]-sigmatropic rearrangement for step II → III in scheme 1). In addition, the data obtained from quantum-chemical calculations predicted an increase in the rate of the I → IV + V rearrangement when electron-donor substituents are introduced into the molecule undergoing cyclization and slowing down of the reaction when electron-acceptor substituents are present [1].

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