Skeletal Rearrangement of N,O-Heterocycles. The Isoxazolinone to Aziridine Transformation Induced by Lithium Aluminum Hydride†

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Abstract: Triphenylisoxazolinone reacts with lithium aluminum hydride to yield either triphenylaziridinic derivatives or open-ring products or both depending on reaction conditions. The structures of the products were ascertained by spectroscopic methods and their stereochemistry was assigned on the basis of lanthanide shift experiments. The main features of the reaction mechanism are also discussed in terms of quantum-mechanical calculations by CNDO/2. The rearrangement under study appears to proceed through a concerted [1,3]-sigmatropic migration of the nitrogen to a carbon of the isoxazolinic enolate system as shown by the HOMO–LUMO interactions possible.

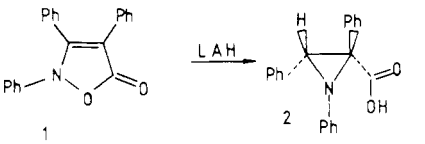
Five-membered N,O-heterocyclic substrates, where a π-electron pair at position 5 of the nucleus is conjugated with the adjacent N–O σ bond, provide a novel functional system which, irrespective of whether the double bond is endo-[2-4] or exocyclic,[5-8] undergoes intramolecular rearrangement processes; such rearrangements can also be applied for synthetic purposes.[9] The overall reaction proceeds via ring opening by N–O bond cleavage and recyclization[2a,4-8] or via other sigmatropic shifts,[2b,3] each of which leads to different products. The conventional source of such N,O-heterocyclic precursors necessitates a preceding 1,3-dipolar cycloaddition of azomethine oxides or equivalent compounds to alkynes,[2-4] allenes,[5,8] and allene-like systems.[6]

An alternative source of similar substrates has now been explored by treating a 3-isoxazolin-5-onic derivatives, i.e., the 2,3,4-triphenyl one (**1**), with lithium aluminum hydride ($LiAlH_4$).[9] This reaction, in which the N,O-heterocyclic precursor undergoes ring contraction to the trans-substituted aziridine (**2**) as shown in Scheme I, widens the range of application of the rearrangement process under investigation. Furthermore, following initial studies on the detailed path and on the possible intermediates of some of these rearrangements,[8] the stereochemistry of some reaction products has been established by lanthanide-induced shift (LIS) analysis. A complete quantum-mechanical investigation at CNDO/2 level on an analogous model system has been performed with the intent of acquiring a better understanding of the chemistry of this particular N,O-heterocyclic nucleus.

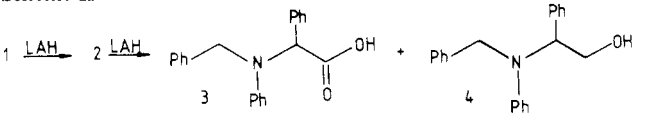
Results

2,3,4-Triphenyl-3-isoxazolin-5-one (**1**), which is easily obtained by adding nitrosobenzene to diphenylcyclopropenone,[10] gives *trans*-2-carboxy-1,2,3-triphenylaziridine (**2**) when refluxed in THF solution with a molar amount of $LiAlH_4$. The structure of aziridine **2** is based on elemental analyses, spectral information (see Table I), and the chemical modification reported in the Experimental Section. Compound **2**, being a zwitterion, is thermally unstable under mass spectrometric experimental conditions and requires careful treatment by the field desorption mode, as reported below. It should be noted that this procedure leads to the conversion of 55% of the starting material only, the remaining product being recovered in the basic extracts of the reaction mixture. On the other hand, if the reaction is prolonged for a total of 3.5 h in conditions identical with those mentioned above, it would appear that not only does product **2** form in greater quantity but it is also successively converted, as a result of hydride action, to the open-ring derivatives **3** and **4**, reported in Scheme II and identified by analytical and spectroscopic means. The overall yield for the latter reaction has been found to be more than 85%. This result, together with an independent treatment of **2** under similar conditions, gives chemical evidence for structural assignment. Furthermore, the major constituent of the reaction mixture, isolated after treatment of **1** with an excess of $LiAlH_4$ in dry ether for 2 h, has been identified as *trans*-2-hydroxymethyl-1,2,3-triphenylaziridine (**5**, Scheme III). The more prominent component **5** corresponds to more than 85% conversion of the isoxazolinone to products, the other significant derivative being **2** (5%).

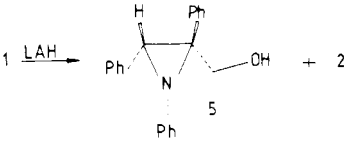
Scheme I



Scheme II



Scheme III



The stereochemistry of product **5** resulting from the $LiAlH_4$ treatment of the isoxazolone **1** has been determined by NMR measurements using the LIS analysis.[11] The signals of the NMR spectrum of **5** can only be assigned to aromatic protons, δ 7.77–6.60 (15 H, m, ArH), to the 3-H proton, δ 4.28 (1 H, s, 3-H), to the methylene protons, δ 3.87 (2 H, d, $-CH_2OH$), and to the hydroxyl one, δ 1.96 (1 H, br s, –OH). Experiments by the LIS technique[11] have been performed using $Pr(fod)_3$ as the lanthanide shift reagent. The choice of the LIS reagent derives from a fair compromise of two factors, i.e., the shift toward high field and the small broadening of resonance signals. Moreover, its contact contribution to the observed shift is negligible; therefore, the interaction of the lanthanide complexes with the molecule under discussion is predominantly pseudocontact and a consistent average geometry for the

† N,O-Heterocyclics. 11. Part 10: G. Cum, P. Giannetto, G. Sindona, and N. Uccella, *Tetrahedron*, in press.

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Table I. Physical and Spectral Data for Products from the Reaction of **1** with $LiAlH_4$ in Various Conditions

compd	mp, °C	molecular formula		anal, % C	anal, % H	anal, % N	IR, cm^{-1}	^1H NMR spectral assignments, chemical shifts, δ	mass spectra, *m/z* (rel intensity)
2	175–176	$C_{21}H_{17}NO_2$	calcd	79.94	5.47	4.44	3060–2200 (br), 1580 (COO^-), 1490, 1410, 1380, 1320, 1290, 1030, 760, 700	7.83–6.33 (15 H, m, ArH), 5.23 (1 H, s, 3-CH)[a]	315 ($M^{+\cdot}$, 33), 227 (14), 226 (100)[d]
			found	80.10	5.37	4.34			
3	134–138	$C_{21}H_{19}NO_2$	calcd	79.47	6.03	4.41	3200–2400 (br), 1700, 1600, 1500, 1260, 1220, 1155, 755, 705, 690	8.26 (1 H, br s, OH), 7.66–6.60 (15 H, m, ArH), 5.72 (1 H, s, 2-CH), 4.50 (2 H, s, 4-CH_2)[b]	317 ($M^{+\cdot}$, 22), 273 (25), 272 (94), 180 (17), 92 (16), (91) (100), 77(42), 65 (19), 51 (14), 43 (36)[e]
			found	79.60	5.98	4.38			
4	224–225	$C_{21}H_{21}NO$	calcd	83.13	6.98	4.61	3590, 3420, 1595, 1505, 1400, 1265, 755, 735, 700	7.90–6.34 (15 H, m, ArH), 5.16 (1 H, m, 2-CH), 4.46 (2 H, s, 4-CH_2), 3.5 (1 H, br s, -OH), 2.43 (2 H, s, CH_2OH)[c]	303 ($M^{+\cdot}$, 11), 278 (100), 180 (22), 92 (10), 91 (80), 77 (35), 65 (12), 51 (8)
			found	82.96	7.06	4.83			
5	133–134	$C_{21}H_{19}NO$	calcd	83.70	6.35	4.65	3405 (OH), 1590, 1480, 1390, 1038, 780, 768, 760, 708, 695	7.77–6.60 (15 H, m, ArH), 4.28 (1 H, s, 3-CH), 3.87 (2 H, d, CH_2OH), 1.96 (1 H, br s, OH)[b]	301 ($M^{+\cdot}$, 60), 300 (100), 283 (11), 282 (16), 261 (7), 260 (44), 259 (11), 211 (19), 210 (83), 182 (30), 181 (18), 180 (64), 167 (56), 165 (33), 152 (15), 104 (27), 91 (56), 77 (70), 337 (10), 324 (6), 306 (6), 302 (26), 301 (100), 208 (10), 183 (7)[e]
			found	83.75	6.31	4.64			
10	79–80	$C_{22}H_{19}NO_2$	calcd	80.22	5.81	4.25	2970, 1780, 1610, 1510, 1470, 1390, 1270, 1260, 1110, 1020, 920, 870, 790, 735, 650	7.0 (15 H, m, ArH), 5.1 (1 H, s, 3-CH), 3.7 (3 H, s, 2-CO_2CH_3)[b]	320 ($M^{+\cdot}$, 5), 273 (3), 272 (12), 270 (3), 269 (4), 243 (4), 242 (30), 241 (45), 196 (33), 183 (50), 182 (100), 152 (21), 118 (11), 105 (34), 104 (63), 103 (11), 91 (37), 89 (45), 77 (90)
			found	80.15	5.87	4.32			

[a] Spectra obtained in acetone-d_6. [b] Spectra obtained in $CDCl_3$. [c] Spectra obtained in Me_2SO-d_6. [d] FD spectrum. [e] FI spectrum.

substrate **5** can result from the application of the appropriate equation for the pseudocontact interaction, relating isotropic shifts with geometrical parameters of the complex and thus of the substrate.[12]

The aziridine **5** coordinates with $Pr(fod)_3$ at the hydroxyl group. The analysis of the aromatic pattern has been found initially complicated by the extensive overlapping of the signals of the three phenyl groups on the aziridine ring system. A good separation has been possible through the simplification induced by the LIS reagent when a molar ratio of Ln/substrate in the range of 0.05–0.3 is used.

Signals belonging to different phenyl moieties are recognized by means of decoupling experiments. Limiting shifts have been derived by a mean square fitting on experimental shift values obtained from ten solutions of different molar ratios, assuming an equilibrium for 1:1 complex between substrate and paramagnetic reagent; this is also confirmed by the linear behavior of the measured shifts against the ratio Ln/sample. All possible stereoisomers of the reaction product have been tested by least-squares analysis to fit the experimental limiting shifts; meanwhile, this procedure allows us also to be confident of the proper assignment of each NMR transition. The geometrical interpretation of spectral parameters and the correct assignment of signals have been performed according to the LISCA program.[13] From the initial investigation of those limiting shifts related to the different phenyl moieties, two of the six possible attributions of the three aromatic signal groups with the phenyl rings have been selected. In fact, owing to the vicinal paramagnetic interaction, one of the phenyl groups is the most influenced and thus assigned with ease to that close to the coordination site. In order to define the stereochemical configuration of the compound under investigation, six possible stereomodels have been analyzed. The occurrence of a defined spectral pattern, due to only one compound, permits us to consider two possible situations as far as the nitrogen atom is concerned; i.e., the trivalent nitrogen of the aziridine nucleus can undergo a fast inversion compared to the NMR time scale or can be blocked in a preferential conformation by a high energy barrier. In the first case two stereoisomers are possible and in the second one four different stereochemical ones are expected. All six isomers have been tested in order to fit the experimental LIS data, verifying at the same time the two different combinations of phenyl signals. The molecule under examination has been treated as a set of five rigid units, connected to one another by a rotatable bond and without restriction, giving the system the largest degrees of freedom possible allowed by the LISCA approach. Calculations have been carried out for the different models optimizing rotatable bonds, the Ln/substrate bond length, and the Ln–O–CH_2 bond angle. Geometrical parameters of the aziridine ring have been taken from previous data[14] referring to a N-unsubstituted molecule. Because the system studied bears an aryl-substituted nitrogen, possible molecular modifications of the ring parameters might be occurring. Therefore, as the LISCA program does not permit direct correction of the above cited parameters, the fitting procedure of the examined models has been performed varying stepwise also bond lengths and angles of the aziridine system.

Only one of the possible isomers has met the experimental LIS data with confidence also on the precise aromatic signal assignment. The results thus obtained allow the stereochemistry to be assigned to the substituted aziridine **5**, as shown in Scheme III. In Table II, experimental isotropic LIS ratios for the protons of **5** and the relative calculated LIS ratios for the trans configuration with the lowest total quasi-*R* factor (TQRF) are reported. The ortho protons of the 1-phenyl group of **5** have been taken as "standard" nuclei. The TQRF found for the assigned configuration **5** is 0.16, while all other examined configurations show a value greater than 0.5, allowing the program to make all possible modifications of bonds and angles. The stereochemical configuration found for the molecule under study can be thus confidently established by the evaluation above described. The results obtained clearly indicate that the substituted aziridine formed from **1** by $LiAlH_4$ treatment lies in a potential well controlled by a sufficiently high energy barrier which prevents rapid inversion at the nitrogen atom. This is in agreement with previous conclusions on the equilibrium between invertomers at the nitrogen.[15,16]

Table II. Aziridine ^{1}H Data, Pr LIS Ratios, 1-Ortho-H Standard

nucleus	exptl shift ratios (SR)	calcd SR trans isomer
H-CH_2	4.123	4.160
H-3	1.277	1.256
H-ortho-1[a]	1.000	0.860
H-meta-1	0.208	0.304
H-para-1	0.164	0.185
H-ortho-2	1.436	1.403
H-meta-2	0.286	0.392
H-para-2	0.286	0.248
H-ortho-3	1.158	1.150
H-meta-3	0.135	0.162
H-para-3	0.135	0.056
TQRF[b]		0.160

[a] Ortho and meta H's are almost equivalent. [b] Weighted TQRF.

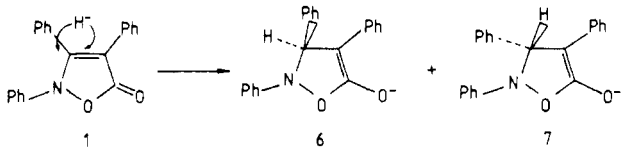
The nitrogen inversion barrier is, in fact, dependent on the substituent groups of the ring system. Particular nitrogen substituents, i.e., alkoxy, amino, or halide, induce a higher inversion barrier,[15] as also happens in the case of crowding on the carbon atoms of the aziridine ring.[16] In the latter, the steric effect influences the conformation of the molecule; thus the most stable invertomer form is that with the nitrogen substituent in a position where less steric interactions occur.[16] In the case of compound **5**, the occurrence of three substituent groups on the carbon atoms, as well as that on the nitrogen one, supports the conclusion that only one invertomer form is stable under normal conditions. The chemical procedure used in the preparation of **5** from **2** also makes it possible to establish the stereochemistry of the precursor molecule **2**.

Discussion

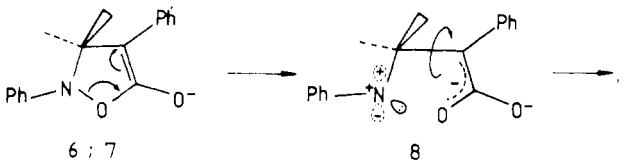
The present rearrangement of the substituted isoxazolidinone **1** to aziridine can be interpreted as a multiple-step process which implies an intermediate formation of two initial adducts induced by the reaction of $LiAlH_4$ with the substrate. Initial 1,4-hydride attack takes place from both sides of the double bond, thus generating two enantiomeric 4-isoxazolinic systems of structures **6** and **7**, as reported in Scheme IV if nitrogen is rapidly flipping. These stereoisomers could be split into four conformational isomers at the nitrogen atom and then successively distinguished as eight ones if the ring conformational equilibrium among them is considered (vide infra). However, the pyramidal inversion at nitrogen of **6** and **7** is greatly influenced by the conjugative effect which tends to lower the energetic barrier for the process. In fact, an adjacent aromatic group, as in the systems considered here, in some cases reduces the barrier to inversion at nitrogen to as little as 10 kcal/mol.[12] Therefore, even if all the invertomers of **6** and **7** will be again considered for the sake of clarity, these reaction intermediates must be regarded as undergoing fast nitrogen inversion during the course of the rearrangement.

There is no direct proof that the enolates in Scheme IV are intermediates in the process under investigation, since these kinds of molecules are thermally unstable and undergo structural modification, but their intervention is in agreement with analogous transformation.[1-3] Thus a rational explanation of the reaction path can be given. Moreover, the fact that only one isomer of the aziridine, i.e., **2** and **5**, has been isolated from the reaction mixture should result in the hydride attack occurring preferentially from one side of the double bond, giving rise to

Scheme IV



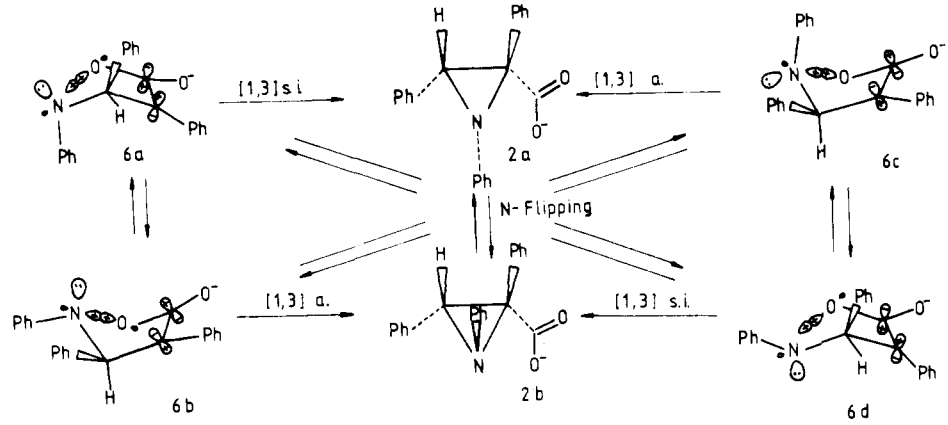
Scheme V



one of the two isomers **6** and **7**. This intermediate could then rearrange to only one product via a specific mechanism. This assumption is, however, unrealistic, since it implies a stereospecific hydride addition, which does not appear to be justified. On the contrary, it seems reasonable to postulate that both stereoisomeric heterocycles occur in the reaction process and that the successive rearrangement develops through discrete steps where free rotation around some bonds is allowed, the steric effect thus determining the product configuration, or via a concerted mode, where the symmetry of the molecular orbitals controls the final stereochemistry of the aziridine. The possible routes to be considered from the precursor isoxazolone **1** to compound **2** are those involving biradical, zwitterionic, or concerted mechanisms. The first approach has already been suggested and discussed extensively.[4] It has been discarded on the basis of stereochemical considerations of similar reacting systems.[4] This also appears to be the case for the isoxazolinic intermediate mentioned here. Since the reaction of N,O-heterocyclics **6** and **7** of Scheme IV occurs by N-O bond cleavage, the process may imply a heterolytic rupture of this bond, thus leading to a nitrenium ion **8**, whose stability is somewhat increased by the resonance effect induced by the aromatic ring; the enolate counterpart is also delocalized.[2b,5-8] In the case under study and reported in Scheme V, the process can be considered even less likely than those previously suggested for similar reacting molecules, where the N,O-heterocyclic nucleus contained either the exo[5-8] or the endo double bond.[2b] In fact, in the suggested intermediate **8** there would have to be a high charge repulsion in the O-containing chain, because two negative charges are delocalized on the same group of atoms as shown in Scheme V. Formation of a unique product **2** from **8** could have been explained by considering the free rotation around C-3 and C-4 of the precursors **6** and **7** shown in Scheme V. The two opposite rotational modes, needed to explain the occurrence of only one product from the two stereoisomeric precursors **6** and **7**, could also be justified by the steric effect of the substituents on the original molecule which determines an increment of the activation energy for the production of *cis*-aziridine. Therefore, even if the zwitterionic intermediate **8** is associated with several energetic restrictions particularly stringent in the present case, it appears that such a mechanism cannot in principle be ruled out.[5,6]

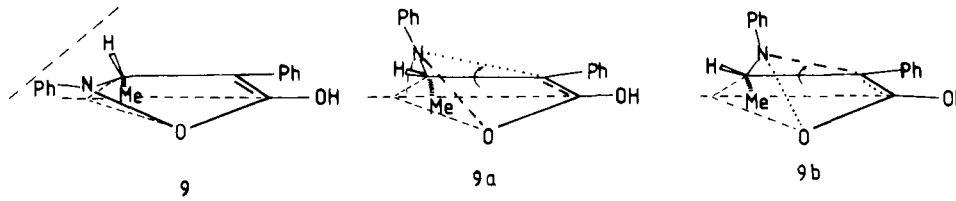
A third possibility involves a [1,3]-sigmatropic rearrangement in which a nitrogen atom, linked by a σ bond to an oxygen, moves across the conjugated π bond between C-4 and C-5 of the precursors **6** and **7** to the new site at C-4, leading to the formation of the aziridine nucleus, as outlined in Scheme VI. Although the migrating atom may cause consistent perturbation to the overall transformation where stereoselection is concerned,[17] a frontier orbital approach[18] can be applied to the interpretation of the reaction reported in Scheme VI, where the possible conformational precursors **6** are reported. Since intermediates **6** and **7** are characterized by two asymmetric centers and, as mentioned above, it is assumed that the nitrogen one undergoes fast inversion, there is no a priori need to postulate preferential conformations of the envelope-shaped ring of the isoxazolinic enolates in question. Therefore, the rearrangement process from **6** leading to **2** can be explained by the interaction of the HOMO of the σ N-O bond with the LUMO of the π bond between C-4 and C-5. This kind of interaction is favored when the overlap of the nitrogen migrating orbital

Scheme VI



a = antarafacial; s.i. = suprafacial with inversion.

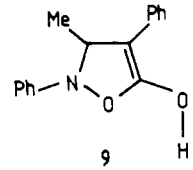
Scheme VII



with that of C-4 occurs in the suprafacial mode with inversion of configuration at the migrating center as is the case for **6a** to **2a** and for **6d** to **2b**, and in the alternative process allowed which requires an antarafacial shift. The latter pathway can be said to take place from the precursors **6b** and **6c**, in both cases the final system being **2b** and **2a**, respectively (see Scheme VI).

The proposed mechanism can, therefore, give a rational interpretation for the formation of aziridine **2**, but at this point it is essential that both **2a** and **2b** invertomers be initially obtained. On the basis of the foregoing arguments on conformational equilibrium which is rapidly reached under the reacting condition of the rearrangement under study, the apparent discrepancy between the proposed mechanism and the isolated products can be easily reconciled by assuming that the reaction conformation of **6** is only that yielding **2a** or that **2b** once formed inverts immediately to **2a**. In both cases steric restrictions may be in operation, thus directing the reaction to the thermodynamic preferred product. Identical considerations apply to the isomers **7** which lead to the enantiomers of **2a,b**. In the latter case, **7a** and **7d**, stereoisomers of the corresponding **6** forms, should react in an antarafacial manner giving rise to the enantiomer of **2a** in the racemic mixture of **2**, while **7b** and **7c**, via a suprafacial manner with inversion shift, lead to the enantiomer of **2b**. The rotatory dispersion experiment indicates clearly that the reaction product **5** is a racemic mixture, being optically inactive.

A detailed quantum-mechanical treatment of a model system of type **9** should give a deeper insight into the mechanistic problem arising out of the rearrangement processes so far observed.[2-4,9] In order to elucidate the behavior of the five-membered-ring system with the N–O bond linked to a trigonal carbon atom at position 5, some theoretical investigations at the CNDO/2 level[19] have been performed on **9**, since to consider **1** would be prohibitive both cost- and timewise owing to



9

the number of internal coordinates and basis functions involved. Model **9** was chosen in that its electronic and steric characteristics are the closest possible to the real system **1**. In fact, structure **9** is characterized by phenyl groups on both nitrogen and C-4 atom aimed at ascertaining the possible stabilization effect of the aromatic moiety onto the diradical or the zwitterionic intermediate, while a phenyl at C-3 has been replaced by a methyl assuming that some steric interaction is operative. In order to remove partially the effect of a full negative charge on the oxygen of the enolate **9** which in solution should be balanced with the cations from the $LiAlH_4$, a hydrogen atom has been added to the negative oxygen. The molecular conformation of **9** has thus been obtained according to the partitioned energy model preserving the van der Waals term with R6-R12 functions and the electrostatic one[20] so that conformational energy could be derived from parameters depending only on interacting atoms.[21] A very general Fortran V program[22] has been employed, while the geometrical parameters used for calculations on **9** have been found in previous reports.[23,24] The aromatic group at the nitrogen of the ring has been placed in a medium position since it can undergo rapid conformational equilibrium; this should give a better stabilization to the nitrenium intermediate and is, therefore, suitable for the zwitterionic mechanism. On the other hand, the methyl group of **9** is in an axial position in order to relieve steric hindrance.

The N–O cleavage process develops along the reaction coordinate which has been assumed to be the puckering of nitrogen with the ring plane (ϕ angle), together with the decrease of the bond angle (θ) at C-3. Various values of both angles have been taken into consideration, ϕ and θ being respectively 20 and 100° for **9a** and 40 and 95° for **9b**, as shown in Scheme VII, with all the other constants. Results have been analyzed in terms of net charges[19] and Mulliken populations.[25] As shown in Table III, as long as nitrogen moves from the ring oxygen to carbon 4, there is a net loss of negative charge on the nitrogen and an increase on the ring oxygen as well as on the exo oxygen of the formal enolate moiety, while C-3 becomes more positive. On the other hand, the situation, as far as the carbon atom at 4 is concerned, initially reveals a net charge conservation and then a change to charge gain; this occurs in synchronism with the bond-order variation. In fact, as also

Table III. Net Charges on the Atoms and Mulliken Population of the Bonds in the Model System **9**

	9	9a	9b
O1	−0.2368	−0.2394	−0.2445
N2	−0.0881	−0.0749	−0.0500
C3	0.1649	0.1549	0.1424
C4	−0.1308	−0.1309	−0.1364
C5	0.3090	0.3092	0.3191
O5′	−0.1924	−0.1956	−0.2246
O1-C5	1.3804	1.3796	1.3782
C5-C4	2.0856	2.0852	2.0816
C4-C3	1.4520	1.4408	1.4198
C3-N1	1.4958	1.4818	1.4496
N1-O5′	0.9058	0.8762	0.4942
O5′-C5	1.1788	1.1710	1.1664
N1-C4	−0.0008	0.0046	0.0308

reported in Table III, the bond between N and O of the ring decreases as that between N and C-4 increases. The latter from antibonding in **9** becomes gradually more bonding in **9a,b,** whereas that between C-4 and C-5 remains substantially unaltered.

Analysis of the data reported in Table III clearly shows that the pentacyclic ring opening via N-O bond cleavage takes place with the shift of these bond electrons to the oxygen, together with a transfer of charge density to the C-4 and C-5 bond, followed by an accumulation of negative charge on C-4. This rearrangement process develops, however, with the initial formation of bonding between nitrogen and carbon 4 which decreases the electron density on C-4 and weakens the double bond of the enolate. In fact, the analysis of bond Mulliken population and net charge data (see Table III) indicates that a filling of the antibonding orbitals on the $O_5O_1C_5C_4$ moiety occurs, thus giving rise to a decrease of the bond order and to an increase of the electron density on the same group of atoms, as expected according to a HOMO-LUMO interaction.

It can be concluded from the overall behavior of the reaction investigated that, even in the best possible conformational conditions, the zwitterionic species similar to **8** is not a plausible intermediate as had been suggested by calculations. Furthermore, the theoretical data obtained infer that a distinction should be made between stepwise or concerted pathways, since it can be seen from the above-mentioned results that the latter operates with a nonsymmetrical charge distribution.

A final question remains to be commented on in connection with the apparent difference in reaction products obtained according to the reaction condition used to induce chemical modification of **1** by $LiAlH_4$, as indicated above. The isolated derivatives, i.e., **2–5,** depend on the different degree of competition among all the possible $LiAlH_4$ reactions and the intramolecular rearrangement from the isoxazolinic system to the aziridine one, e.g., the [1,3]-sigmatropic migration, the carboxylic group reduction from **2** to **5,** and the aziridine ring opening to **3** and then to **4.** The first process appears to be slower than the second one at a low temperature and with a low $LiAlH_4$ concentration, while the reduction of the carbonylic group requires lower energetic restrictions compared with the other reaction observed. At a higher temperature, i.e., in THF solution, the thermally allowed sigmatropic rearrangement becomes predominant, although the low yield of product **2** after a short reaction time indicates a slow rate for the process which is overcome by the aziridine ring opening to **3** when the treatment is prolonged. This consideration confirms that the skeletal modification from **6** and **7** to **2** is thermally controlled and is probably characterized by a stringent activation entropy. Furthermore, the trans geometrical isomers **2** and **5,** always obtained using also different reaction conditions, must be the kinetic controlled products. In fact, the trans configuration of the aziridine nucleus is acquired at lower and higher temperature reaction, when ether and THF are used, respectively, and is therefore independent of both time and temperature of reaction. Moreover, cis-trans isomerization via an ylide intermediate can be excluded, otherwise the open-chain products **3** and **4** would be always trapped in the presence of excess $LiAlH_4$.

Conclusion

The addition of hydride to a 3-isoxazolin-5-onic system yields a 4-isoxazolinic one which then rearranges thermally to an aziridine derivative. This process is explained in terms of a dominant interaction occurring between the HOMO of the N-O bond and the LUMO of the enolate double bond, as can be seen in a perturbational model, giving rise to a [1,3]-sigmatropic migration of a nitrogen atom. This general reaction has its source at the N-O bond in the molecular framework which is weaker because of its low bond-electron density, and is not exclusively due to a simple core-core repulsion[2a] between N and O.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Analyses were performed on a Perkin-Elmer 240 elemental analyzer. IR spectra were measured on a Perkin-Elmer 377 instrument, and NMR on a Varian EM 360 using tetramethylsilane as internal standard. Experimental paramagnetic shifts were obtained on a Varian XL-100, operating in FT mode with ^2H internal lock at room temperature. Spectra of dried $CDCl_3$ solutions of the organic material with Me_4Si (ca. 0.5%) added as internal standard were recorded at a constant substrate concentration (ca. 0.2 M), using molar ratios of shift reagent to substrate in the range 0–0.3. Each aliphatic resonance was monitored and the shift to the higher field was found to be directly proportional to the molar fraction of the complex present for all signals. Mass spectra were measured on a Varian MAT CH-5 DF spectrometer, equipped with a Varian Spectro System SS-100 computer, operating at 70 eV, 3 kV, and an ion source temperature of 200 °C. Samples were introduced via the direct inlet system, the insertion probe temperature being in the region of the melting points of the products. The FD spectra were obtained with an EI/FD combined ion source at 7.5 kV, 15 mA, and source temperature 100 °C; the sample was applied by the dipping technique to a wire emitter activated at a high temperature.[26] Calculations were carried out using the standard CNDO/2 program.[22]

2,3,4-Triphenyl-3-isoxazolin-5-one (1). A solution of diphenylcyclopropenone (4.9 mmol) and nitrosobenzene (4.7 mmol) in benzene (20 mL) was heated, in a neutral glass tube closed under nitrogen, at 80 °C for 2 h. Then more nitrosobenzene (4.7 mmol) was added to the reaction mixture, which was kept at 80 °C for another 2 h. After cooling, a solid began to precipitate. The precipitate, together with that recovered from the mother liquors (4.7 mmol, 95%), was recrystallized from methanol to yield compound **1,** mp 201–202 °C, as white crystals.[10]

Reaction of 1 with $LiAlH_4$. *trans*-2-Hydroxymethyl-1,2,3-triphenylaziridine (5). A solution of isoxazolinone **1** (313 mg) in dry ether (30 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (114 mg) in dry ether (30 mL). The mixture was then refluxed for 2 h, cooled, and decomposed by the cautious addition of NaOH (1 N) solution. The alkaline solution was extracted with ether. The combined extract was dried (Na_2SO_4) and left to concentrate slowly. On standing, 266 mg (85%) of product was recovered and recrystallized to yield *trans*-2-hydroxymethyl-1,2,3-triphenylaziridine (**5**), mp 133–134 °C, as a colorless solid.

***trans*-2-Carboxy-1,2,3-triphenylaziridine (2).** A procedure similar to that described above was applied for the reaction of **1** (939 mg) in dry THF (70 mL) and $LiAlH_4$ (114 mg) in the same solvent (20 mL), refluxed for 1 h. The alkaline extracts gave starting material (400 mg) which solidified on standing. Recrystallization of the product from methanol gave **2** as yellow needles, mp 175–176 °C.

***trans*-2-Carbomethoxy-1,2,3-triphenylaziridine (10).** Product **2** (3.3×10^{-2} mmol) was allowed to react with an excess of diazomethane ethereal solution for 2 h. After evaporation of the solvent an oil was recovered which crystallized under pentane treatment to give **10** as white crystals, mp 79–80 °C.

Prolonged Treatment of 1 with $LiAlH_4$. The same method as above

was used (THF, 1:1 $LiAlH_4$) with a reaction time of 3.5 h. The alkaline extracts gave a yellow oil (35%), which recrystallized from ether to furnish compound **4** as colorless crystals, mp 224–225 °C. The acid extracts (pH ~2) produced a pale yellow solid (55%), which after recrystallization from ether yielded compound **3**, mp 134–138 °C, as white crystals.

Reaction of 2 with $LiAlH_4$. The sodium salt of **2** (167 mg) was added in small amounts to a stirred suspension of lithium aluminum hydride (57 mg) in dry ether (30 mL). The mixture was then refluxed for 2 h and worked up as described for the preparation of **5**. The isolated product (130 mg) was identified as *trans*-2-hydroxymethyl-1,2,3-triphenylaziridine (**5**).

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Electrophilic Heteroaromatic Substitutions. 2.[1] Mechanism of the Side-Chain Halogenation of Polysubstituted α-Methylpyrroles with Molecular Chlorine

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Abstract: The mechanism of the α-side-chain chlorination with molecular chlorine in dichloromethane or chloroform solution at low temperatures and in the dark of polysubstituted α-methylpyrroles **1–4** has been investigated with regard to the nature of the reagent and to the fate of the attacking as well as the substituent halogen in the reaction products. Careful product analysis was carried out by radiochemical measurements (chlorine exchange), NMR spectra, standard halide ion titration, and preparative layer chromatography (PLC) techniques. The results suggest that the overall process consists of two main steps, i.e., the electrophilic nuclear attack and the subsequent rearrangement of the halogen to the side chain. Halogen migration from nucleus to side chain may occur from either the adjacent β or the vinylogous α′ position. The present data provide a considerable extension of the concept of nonconventional electrophilic halogenation of aromatic molecules into the field of pyrroles.

Introduction

Side-chain halogenations of polysubstituted α-methylpyrroles have been known for a long time[3–5] and have been recognized as intermediate steps in the preparation of a number of pyrrole oligomers such as dipyrrylmethanes, dipyrrylmethines, and porphyrins.[1,5–7] However, very little attention has been paid to the mechanism of these reactions. In one instance, the side-chain chlorination with sulfuryl chloride was assumed to occur by a free-radical mechanism.[8]

In view of the relevance of these reactions for a deeper understanding of the chemistry of pyrroles we have undertaken a systematic investigation related to their course and mechanism. Some striking analogies[9] with the nonconventional electrophilic substitutions of highly activated methyl-substituted benzenes,[10] naphthalenes,[11] benzothiophenes, and benzofurans[12] have led us to the hypothesis that similar reaction mechanisms also apply to appropriately substituted pyrroles under suitable conditions.

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