

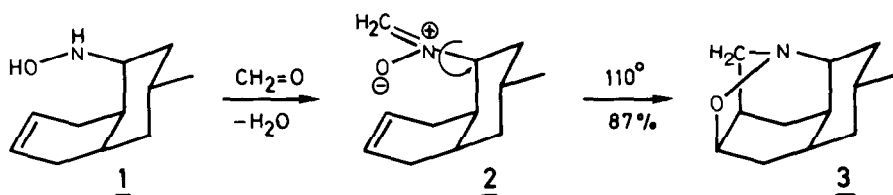
THE REGIOCHEMISTRY OF INTRAMOLECULAR N-ALKENYLNITRONE ADDITIONS:
 PREPARATIVE AND MECHANISTIC IMPLICATIONS

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Summary. The opposite regiochemistry, observed for the reactions $\underline{7a} \rightarrow \underline{8a}$ and $\underline{7d} \rightarrow \underline{8d}$, as compared with additions $\underline{7b} \rightarrow \underline{9b}$, $\underline{7c} \rightarrow \underline{9c}$ and $\underline{7e} \rightarrow \underline{9e}$, supports the hypothesis that in the transition state of nitron-olefin additions the new C,C bond is more advanced than the C,O bond. Further examples show the superimposition of substituent effects on this intramolecular control.

Recently we have reported an efficient synthesis of luciduline,¹ based on the unidirectional 1,3-dipolar addition² $\underline{2} \rightarrow \underline{3}$ with exclusive attack of the dipole-carbon at the nearer centre



of the non-polarized olefinic bond. In contrast, highly selective C,C bond formation with the more remote olefinic carbon was described for the conversion $\underline{7} \rightarrow \underline{9}$, $n=1$, $R^1=R^2=H$, $R^3=Ph$.³ We now present a systematic study of intramolecular N-alkenylnitrone additions with the aim to understand and to predict their regiochemistry. In order to exclude secondary steric and electronic factors the thermolyses of straight chain N-3-butenyl-, N-4-pentenyl- and N-5-hexenyl-nitrones $\underline{7a}$ to $\underline{7e}$, containing a "symmetric" olefinic bond, were first investigated (Table 1). The nitrones $\underline{7}$ were readily obtained *in situ* by condensation of the hydroxylamines $\underline{6}^4$ with aldehydes. In order to avoid the cyclizations of $\underline{6}$ to N-hydroxy pyrrolidines, (*e.g.* the smooth reaction $\underline{6i} \rightarrow \underline{10}^5$), the hydroxylamines $\underline{6}$ were liberated from their stable hydrogenoxalates at 0° under argon and condensed immediately with the requisite aldehyde (*e.g.* by introducing a stream of gaseous formaldehyde at 0°) in toluene in the presence of anhydrous Na₂SO₄; the resulting nitron solutions were then heated at reflux for several hours. Under these conditions $\underline{6a}$ furnished $\underline{9a}$ as the sole adduct *via* the non-isolated nitron $\underline{7a}$, whereas the addition of the higher homologue $\underline{7b}$ proceeded with completely reversed regioselectivity. Increasing the distance between the dipole and the dipolarophile by yet another methylene group led *via* $\underline{7c}$ to a 3:1 mixture of $\underline{8c}$ and $\underline{9c}$. No interconversion of $\underline{8c}$ and $\underline{9c}$ occurred on heating the isolated regioisomers in boiling toluene for 3h, thus indicating the observed regiochemistry to result from kinetic control.⁶ Opposite regioselectivity was also displayed by the intramolecular additions of the C-*p*-nitrophenyl nitrones $\underline{7d} \rightarrow \underline{9d}$ and $\underline{7e} \rightarrow \underline{8e}$.

In order to understand this apparent kinetically controlled,⁶ bridge length-dependent reversal of regioselectivity⁷ transition state geometries were examined using appropriate models.

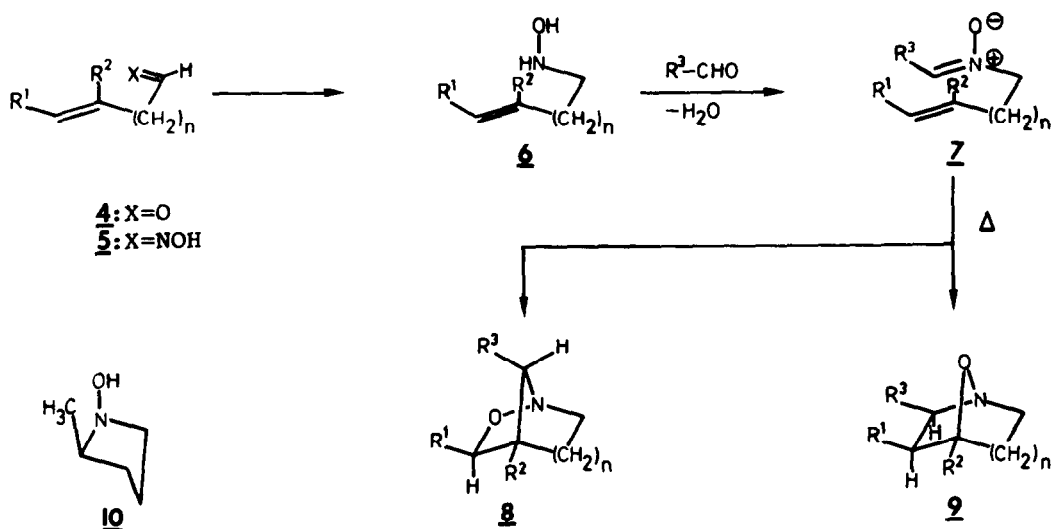
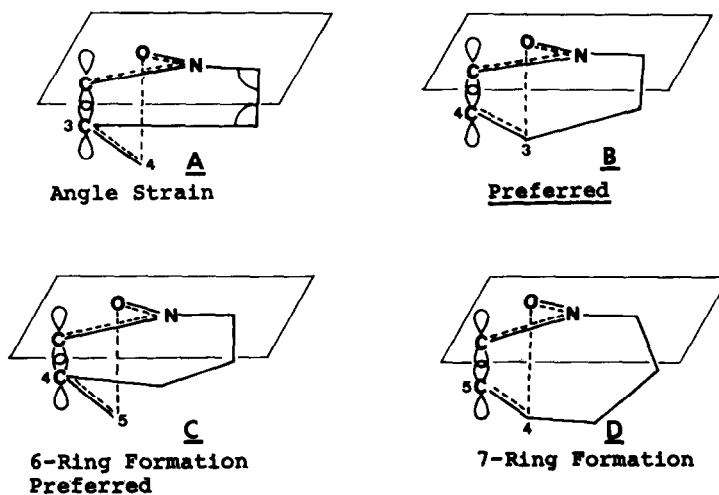


Table 1. Intramolecular Cycloadditions of the N-Alkenyl Nitrones 7 formed *in situ* from 6.^a

Entry	n	R ¹	R ²	R ³	Reaction time/110°	Yield of <u>8</u>	Yield of <u>9</u>	m.p. ^{°C} of <u>8</u> ^b	m.p. ^{°C} of <u>9</u> ^b
a	1	Me	H	H	6h	0%	76%	-	116-118
b	2	Me	H	H	3h	95%	0%	158-160	-
c	3	Me	H	H	3h	68%	23%	104-106	108-111
d	1	Me	H	pNO ₂ Ph	1.5h/180° ^d	0%	85%	-	117-118 ^c
e	2	Me	H	pNO ₂ Ph	18h	69%	0%	110-112 ^c	-
f	1	Ph	H	H	2h	9%	56%	122-123	147-148
g	2	Ph	H	H	3h	87%	0%	74-76 ^c	-
h	2	Ph	H	pNO ₂ Ph	11h	95%	0%	144-146 ^c	-
i	2	H	H	H	3h	47%	23%	127-129	148-151
j	2	H	Me	H	2.5h	10%	77%	oil	127-130
k	2	H	Ph	H	6h	0%	82%	-	73-74 ^c

^aThe hydroxylamines 6 and the products 8 and 9 showed IR, ¹H-NMR, and mass spectra in full agreement with the assigned structures. Mixtures of regioisomers 8 and 9 were analyzed by GC, ¹H-NMR or HPLC and separated either by fractional crystallization of their hydrogenoxalates (c, i), or by chromatography on SiO₂ (f), or by prep. GC (j). ^bm.p. of hydrogenoxalate. ^cm.p. of free base. ^dHeating the dimers of 7d in refluxing *o*-dichlorobenzene.

Considering coplanarity of the nitron unit and the first bridge carbon atom⁸ the observed regiochemistry can only be explained on the assumption that the new C,C bond is more developed than the C,O bond in the corresponding transition state.⁹ Thus, comparing the possible orienta-



tions for N-3-alkenyl nitron additions, C,C bond formation to the nearer olefinic centre C(3) implies a strained transition state A, whereas the exclusively observed C,C(4) bond formation corresponds to the unstrained transition state B.¹⁰ With regard to N-4-alkenyl nitron additions, both orientations C and D do not exhibit strain. However, the observed preference of the transition state C over D may be ascribed to an entropically favoured 6-ring closure as compared with 7-ring formation. An analogous argument (preferred cyclization to a 7- rather than an 8-membered ring) applies to the less selective cyclization of 7d to 8d. We then studied the competition of these intramolecular-derived orientational effects with those of dipolarophile substituents.¹¹ Thus, a phenyl group on the terminal olefinic centre diminishes the predominance of the transition state B over A during the N-3-alkenyl nitron addition 7f → 8f + 9f (1:6), whereas in the higher homologues 7g and 7h both influences cooperate to give exclusively the products 8g and 8h. Similarly, substituents on the nearer olefinic centre C(4) of N-4-alkenyl nitrones may counteract the intramolecular favouring of the transition state C over D. Thus, with no terminal olefinic methyl group the regioselectivity is reduced (7i → 8i + 9i (2:1)) while a methyl group at C(4) leads already to a reversal of regiochemical control (7j → 8j + 9j (1:8)), which becomes complete when replaced by a phenyl substituent (7k → 9k). Intramolecular cycloadditions thus provide a valuable mechanistic tool for the study of orientational substituent effects and in particular the geometry of transition states which are subject to controversy;¹² moreover, the above findings may prove of value in the synthesis of complex alkaloids.^{4,10}

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