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THE STEREOCHEMISTRY OF NITRONE CYCLOADDITIONS. dl-ALLOSEDAMINE AND dl-SEDRIDINE.

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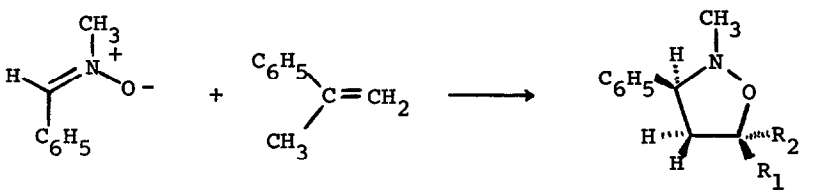
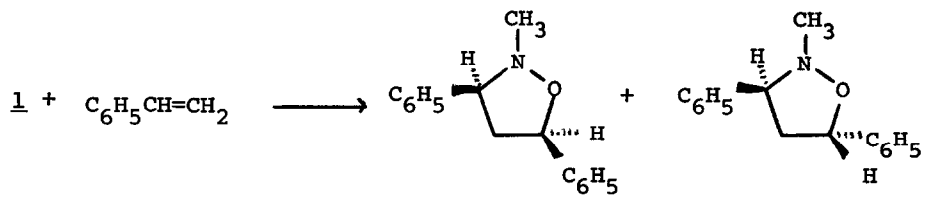
The regiochemical characteristics of the cycloaddition reactions of nitrones with dipolarophiles have been explored in some detail.[1,2] The stereochemistry of these additions has received somewhat less attention although it is clear that an efficient utilization of dipolar cycloadditions in synthesis is in substantial measure dependent on a knowledge of the stereochemical factors involved. The stereochemistry of both intermolecular and intramolecular nitrone-dipolarophile cycloadditions has been examined to some extent. The latter are complicated by constraints introduced by the fixed geometries of the interacting functionalities.[3]

Previously examined nitrone cycloadditions have exhibited a range of stereoselectivities. Thus, C-phenyl-N-methylnitrone (1) reacts with α-methylstyrene to afford a 55:45 ratio of the two possible stereoisomers (2a and 2b)[4], and with styrene to give a 2:1 ratio of 3a and 3b,[5] respectively.



2a, R_1= CH_3, R_2= C_6H_5

2b, R_1= C_6H_5, R_2= CH_3



3a 3b

In addition, 1 has been shown to react with cyclohexene to give a 5:4 ratio of two adducts, presumably the result of cis⇄trans isomerization of the starting nitrone prior to cycloaddition.[6] This occurrence clearly complicates the stereochemical interpretation of the

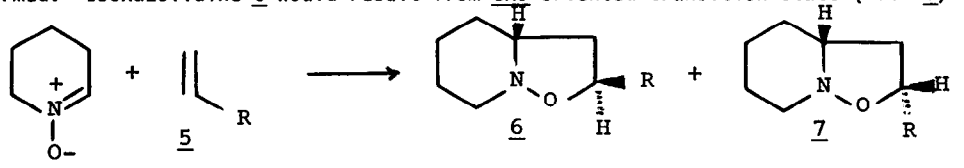
reactions involving acyclic nitrones.

It has been reported[7] that C,N-diphenylnitrone reacts with methyl acrylate to produce a 57:43 ratio of the corresponding diasteromeric adducts while it reacts with acrylonitrile with remarkably high stereoselectivity. More recently, it has been suggested that nitronic esters add to α,β-diactivated alkenes (e.g. dimethyl maleate) with high stereoselectivity to afford endo-adducts, presumably via endo-transition states involving secondary orbital interactions resembling those observed in the Diels-Alder reaction;[8] however, the reaction of conjugated, acyclic nitronic esters with a variety of activated monosubstituted alkenes has been shown[9] to proceed via an exo-transition state (e.g. substituted styrenes), or are completely random (e.g. acrylonitrile). The theoretical possibility of significant secondary orbital interactions in these cycloaddition transition states has been noted.[10]

The attention to stereochemical detail in the dipolar cycloaddition reactions has been limited by the laborious chemical interconversions required to ascertain product configuration, or by the ambiguities inherent in pmr spectral assignments where product configurations are uncertain.

Our synthetic plans in alkaloid synthesis demanded that we have some knowledge of the stereochemical nature of the cycloadditions of simple, cyclic nitrones with monosubstituted alkenes. Indeed, we were especially interested in the stereochemical outcome of the additions of cyclic nitrones with non-activated, monosubstituted alkenes (e.g. propylene). A concentration on cyclic nitrones avoids the difficulties associated with the possible cis⇄trans isomerization (vide supra) of their acyclic counterparts. Moreover, we decided to monitor the stereochemical outcome of these cycloadditions by conversion of the resulting isoxazolidines into natural products of known configuration.

In this report, we discuss the stereochemical outcome of the 1,3-dipolar cycloadditions of 2,3,4,5-tetrahydropyridine-1-oxide (4) with a range of monosubstituted olefins (i.e. styrene, propylene, allyl alcohol, and methyl acrylate). These reactions can, in principle, afford two stereoisomers of the sole regioisomer (i.e the 5-substituted isoxazolidine) formed. Isoxazolidine 6 would result from exo-oriented transition state (i.e. 8) while the



4 5 6 7

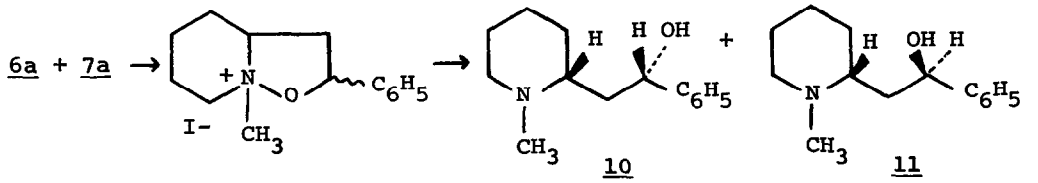
a, R = C_6H_5 c, R = CH_2OH

b, R = CH_3 d, R = CO_2CH_3

stereoisomeric isoxazolidine 7 would result from the endo-orientation depicted in 9.

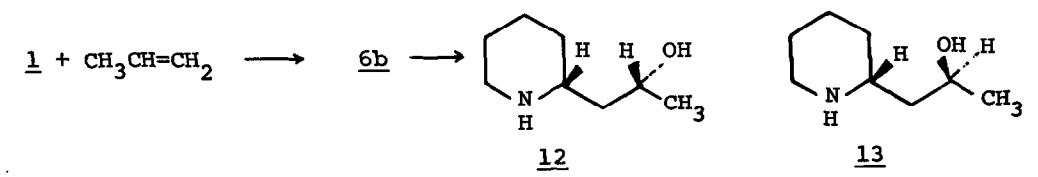
8 9

When nitrone 4 reacts with styrene in refluxing toluene, a nonseparable adduct mixture (6a and 7a, 91%) is formed. This mixture was methylated (methyl iodide, room temperature, ether) to give a quantitative yield of a mixture of stereoisomeric quaternary salts (mp 131°, dec.) which could be converted to a mixture of dl-allosedamine (10, 78%) and dl-sedamine (11, 22%) by treatment with lithium aluminum hydride[11] in refluxing THF for 24 hrs. These alkaloids were compared spectrally with authentic samples[12-14]. The pmr spectrum

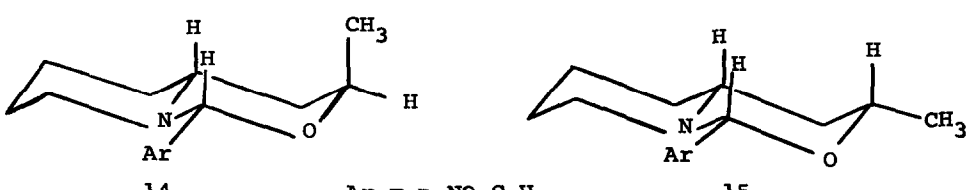


of the crude reaction product exhibits two well-defined patterns attributable to the benzylic protons of the alkaloids. The signal for the benzylic protons of dl-allosedamine appears as a doublet of doublets centered at δ 5.04 ppm (J = 4, 10 Hz) while the corresponding signal for dl-sedamine occurs at δ 4.84 ppm (J = 2.5, 9.5 Hz). The integrations of these signals were used to obtain the product composition. These figures were confirmed by glpc analysis on carbowax 20M.

The reaction of nitrone 4 with propylene was carried out at 110° in toluene and led to the formation of an adduct (i.e. 6b), bp 52°/4mm, in 53% yield. This isoxazolidine, 6b, whose pmr spectrum ($CDCl_3$) exhibits a clean doublet at δ 1.2 ppm (J = 7Hz), was reduced with lithium aluminum hydride in reluxing THF for 24 hours to give the naturally occurring alkaloid dl-sedridine (12) in quantitative yield. The crude product was recrystallized from



pentane to afford the alkaloid[12], mp 74-74.5°. There was no indication, even in the pmr spectrum of the crude product, of the stereoisomeric alkaloid dl-allosedridine (13), which would be derived from isoxazolidine 7b. Spectral examinations of authentic samples of both alkaloids indicate that they can be distinguished by differences in the chemical shifts of the methyl signals (i.e. δ 1.16 ppm for dl-sedridine and δ 1.13 ppm for allosedridine). The lack of dl-allosedridine was confirmed by reaction of the crude product with p-nitrobenzaldehyde in chlorobenzene to give only one of the two possible oxazines (i.e. 14). The two



Ar = $p\text{-}NO_2C_6H_5$

oxazines can be readily distinguished by pmr spectral investigation[15] and no evidence could be discerned to support the presence of any dl-allosedridine. This suggests that the nitrone-propylene cycloaddition is highly stereoselective.

Nitrone 4 was treated with allyl alcohol in chloroform to afford an isoxazolidine 6c, bp 80°/0.2 mm, in 92% yield. This cycloadduct was converted into the corresponding methanesulfonate, then reduced with Super-Hydride[16], to give isoxazolidine 6b in 86% yield. This compound has identical spectral properties with that obtained from the cycloaddition of nitrone 4 and propylene (vide supra). Moreover, 6b was reduced with lithium aluminum hydride, and the resulting amino alcohol was converted into the corresponding oxazine 14. An nmr investigation suggested that the formation of the stereoisomeric oxazine 15 occurred in less than 5% yield.

Finally, the cycloadduct (i.e. a mixture of 6d and 7d) derived from 4 and methyl acrylate was reduced with lithium aluminum hydride in ether to give a 97% yield of a mixture of amino alcohols (i.e. 6c and 7c) which were converted into a mixture of dl-sedridine and dl-allosedridine by the method described above. The corresponding oxazines (i.e. 14 and 15) were prepared from p-nitrobenzaldehyde, and the mixture analyzed by integration of the benzylic proton singlets at δ 4.81 ppm (for 14) and δ 4.55 ppm (for 15). The analysis indicated the formation of 82% of dl-sedridine and 18% of dl-allosedridine.

We conclude that those activated, monosubstituted alkenes (i.e. styrene and methyl acrylate) which are capable of secondary orbital interactions give a mixture of endo- and exo-addition with nitrone 1. Exo-addition predominates in these cases (~80:~20). The unactivated, monosubstituted alkenes give exo-addition overwhelmingly with this nitrone. This exo-preference can be largely attributed to steric interactions between ring hydrogens and the substituent R in the disfavored endo-mode of addition (i.e. 9).

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12. We are indebted to Professors H. C. Beyerman and L. Maat (Delft University of Technology, the Netherland) for providing us with samples of dl-sedamine, dl-allosedamine, dl-sedridine, and dl-allosedridine.
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