4. SUMMARY

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Several isoxazolines (fifty five numbers) have been synthesised and their spectral characteristics analysed in the present investigation.

4.1 PROTON NMR SPECTRA OF ISOXAZOLINES

The isoxazoline ring is found to possess a rigid conformation when the substituent at C-5 is aryl, n-butyl, (methylthio)methyl or cyclohexyl group. This is inferred from the AMX splitting pattern observed in the proton nmr spectra of these isoxazolines. The $J_{cis} > J_{trans}$ in these systems is in line with an envelope conformation observed in the closely related pyrazolines. The J_{gem} values are found to be around 18 Hz. The H-4 methylene protons are found to be magnetically non-equivalent and it is explained due to the shielding of one of the protons by the C-N double bond as a consequence of the sustaining of envelope conformation. However, when the substituent at C-5 is changed to methoxycarbonyl group, we find a dramatic change in the proton nmr spectra of these isoxazolines. The clear AMX pattern observed in the case of 5-phenyl- or 5-cyclohexyl- or 5-[(methylthio)methyl]-isoxazolines is found to be absent in the proton nmr spectra of these isoxazolines. The H-4 methylene protons appear as a doublet while the H-5 methine proton appears as a quartet in 5-methoxy-

carbonylisoxazolines. It is explained due to the difference in the nature of anisotropic effects caused by methoxycarbonyl and other groups on the H-4 methylene protons on account of adopting a puckered conformation. It has been reported in the literature that there occur ring reversals in the case of pyrazolines. It is not known whether a similar kind of interconversion of one envelope form of isoxazoline ring into another occurs in the case of 5-methoxycarbonylisoxazolines too.

The cis fusion in the bicyclic isoxazolines and the exo fusion in the tricyclic isoxazolines have been very well ascertained with the aid of proton nmr spectral data. The $J_{endo-endo}$ is found to be 8 Hz in the case of tricyclic isoxazolines. The non-observation of coupling between these endo protons and the adjacent bridgehead protons, has been confirmed with the help of 2D COSY spectra of these compounds. These results confirm the exo nature of the fusion in these isoxazolines obtained by the addition of the nitrile oxide to norbornene.

Effect of geminal methyl substitution at C-5 carbon of the isoxazolines has been used to get the β methyl substituent parameter for isoxazolines. The chemical shift values of the β protons (H-4) are shifted to upfield to about 0.05 δ.

In the case of 5-cyclohexylisoxazolines, it is found that the axial and equatorial protons of the cyclohexane ring appear separately along with the AMX splitting pattern for the H-4 and H-5 protons of the isoxazoline ring. It is also inferred that a trans isomer with the cyclohexane ring possessing the isoxazoline ring in the equatorial position is formed.

4.2 CARBON-13 NMR SPECTRA OF ISOXAZOLINES

Chemical shifts of the isoxazoline ring carbons C-3, C-4 and C-5 have been compared with change in the nature of the substituent at C-3 as well as at C-5 carbons. The chemical shift value of the oximino carbon is found to be around 160 ppm and this value is shifted to downfield upon changing the substituent at C-3 from methyl to ethyl. This observation is similar to the shift of oximino carbon of ketoximes to down field compared to those of the corresponding aldoximes. Conjugation of the C-N double bond with a phenyl group is found to shield the oximino carbon and the chemical shift values are shifted to low δ. However, the effect of changing the substituent at C-3 to electron-withdrawing groups such as 4-chlorophenyl or 3-nitrophenyl is not significant. The oximino carbons are found to be shielded when the substituent at C-5 is changed from alkyl to aryl group to a magnitude of about

0.2 ppm. Deshielding of the isoxazoline ring carbons C-4 and C-5 has been observed when the substituent at C-5 is changed from n-butyl to aryl group, the magnitude of change in chemical shifts of C-4 and C-5 carbons being 3.0 ppm and 6.5 ppm, respectively.

Methyl substituent parameters for geminal substitution at C-5 carbon have been evaluated. The α and β carbons are deshielded. Similar deshielding of the isoxazoline ring carbons upon substitution of a methyl group in the C-5 phenyl group has been observed.

The chemical shift value of the methyl carbon in 3-methyl-isoxazolines is found to be around 13 ppm and this value is lower when compared to the axial methyl in cyclohexane. In the ^{13}C nmr spectra of 5-cyclohexylisoxazolines, signals for the diastereomeric cyclohexane ring carbons appear separately.

The ^{13}C nmr chemical shift values of the carbons in bicyclic isoxazoline have been compared with the corresponding alkene to get the effects of incorporation of heteroatoms on the chemical shifts of the ring carbons . The C-1 and C-5 carbons are shifted to upfield whereas the C-6 carbon is shifted to

downfield, upon incorporation of heteroatoms in the ring.

The C-1 and C-2 carbons are deshielded while the C-8, C-9 and C-10 carbons are shielded by the annelation of the isoxazoline ring on to norbornane.

The effect of changing one of the hydrogens in dimethyl sulphide and 1-butane by isoxazoline ring has been evaluated. The α carbon is deshielded to about 10 ppm in 1-butane while the magnitude in dimethyl sulphide is 19 ppm. This discrepancy is explained due to the higher polarizability of the S atom in the latter compounds. The effects of substituting one of the hydrogens in 1-butane by phenyl group have been compared with that of substitution with isoxazoline ring. The α effect is less pronounced in the case of substitution with isoxazoline ring than that by phenyl group and is explained due to the difference in the nature (electronic charge, shape, etc.) of the two rings.

4.3 MASS SPECTRA OF ISOXAZOLINES

The abundance of the molecular ion is found to be more when the substituent at C-3 and C-5 carbons of the isoxazoline ring are aryl groups. In addition, for the 5-arylisoxazolines, the major fragmentation path is retrocycloaddition leading to the formation of nitrile oxide and styrene radical cation. In these compounds, the styrene radical is found to be more abundant.

When the substituent at C-5 carbon of the isoxazoline is CH_2SCH_3, n-butyl or $COOCH_3$, a-cleavage is found to be an important fragmentation path for the molecular ion. For instance, in the case of 5-[(methylthio)methyl]isoxazolines, CH_2SCH_3 ion occurs as the base peak.

Isoxazolines with 2-methylphenyl substituent at C-5 carbon undergo McLafferty rearrangement to afford the $(M-CH_3)^+$ ions which are found to be more abundant.

Bicyclic isoxazolines give rise to cyclopentenyl radical cation by retrocycloaddition. In the case of tricyclic isoxazolines, ring cleavage to form isoxazole and cyclopentenyl radical cation are observed. It is also found that a molecule of ethylene is removed from the molecular ion in the latter compounds.

Cleavage of the C(5)-alkyl bond in the case of 5-methyl-5-phenylisoxazolines is observed while in 5-methoxycarbonyl-5-methylisoxazolines, the C(5)-$COOCH_3$ bond is cleaved. This discrepancy is explained due to the reason that loss of methyl radical from 5-methyl-5-phenylisoxazolines gives rise to isoxazolyl cation with a phenyl group at C-5 carbon and the cation will be stabilized by the presence of phenyl group. On the other

hand, loss of phenyl group will produce isoxazolyl cation with a methyl group at C-5 carbon. The stability of the phenyl bearing isoxazolyl cation will be more than that of the corresponding ion with methyl group. Hence the loss of methyl radical is preferred over the loss of phenyl group. However, in the case of 5-methoxycarbonyl-5-methylisoxazolines, loss of COOMe is observed instead of the loss of methyl radical.

4.4 BIOLOGICAL ACTIVITY OF ISOXAZOLINES

Some of the isoxazolines have been tested for antiviral and antitumor activity. The isoxazolines are not found to possess any antiviral activity. However, certain subpanels of cancer cells are found to show specificity against certain isoxazolines.