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REVERSIBILITY IN THE INTRAMOLECULAR NITRONE-OLEFIN ADDITION

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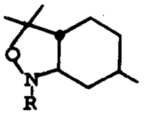
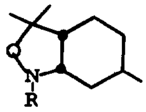
Intra- and intermolecular additions of nitrones to olefins represent reactions of potential synthetic utility in the formation of new carbon-carbon bonds. We report herein a thermal interconversion of configurational isomers of fused, bicyclic isoxazolidines obtained from the intramolecular reaction of ϵ,ζ-unsaturated nitrones.

Earlier work (1) had established that the absolute configuration of the major product in the mixture of two isoxazolidines produced from reaction of R-(+)-citronellal and N-methylhydroxylamine may be represented as (-)-I. The ratio of compound I to the minor isomer (+)-II was found to be dependent upon the temperature of cyclization; values ranging from 97:3 at 25° to 87:13 at 138° were observed (2). These isomers were separable by elution chromatography on acid-washed alumina, and the purified bases were shown to be homogeneous by gas and thin-layer chromatography. Each compound could be recovered unchanged after reflux in xylene and in benzene containing slightly more than one equivalent of p-toluenesulfonic acid.

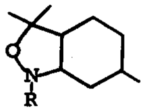
Pyrolysis of pure (-)-I at 230-300°, either neat or in solution (33% w/w in tridecane), resulted in the formation of two additional isomers, (+)-II and (-)-III (3). Compound II was shown to be identical with the minor product detected in the preparation of I from citronellal. The equilibrium concentrations of I, II, and III at 300° were established by a combination of IR and g. c. analysis and elution chromatography, and were shown to be in the



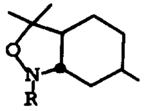
I, R=CH_3



II, R=CH_3



III, R=CH_3



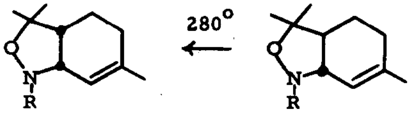
IV, R=CH_3

approximate ratio 50:34:16, respectively. This same composition was noted when samples of both II and III were pyrolyzed under identical conditions. At lower temperatures, the amount of I seemed to increase at equilibrium (ca. 55% at 230°). The presence, albeit in very small amounts, of the remaining diastereomer IV was indicated by the thin-layer chromatograms.

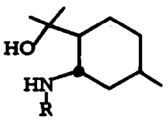
It was possible that isoxazolidines II and III could have had a bridged, bicyclic structure resulting from orientation in the opposite direction in the 1,3-dipolar addition reaction. However, this alternative may be rejected because this pathway would require the oxygen atom of the isoxazolidine to be attached to a carbon atom bearing a hydrogen; the n.m.r. spectra of II and III (and IV as well, vide infra) showed no absorption in the vicinity of δ 4.5 p.p.m., characteristic of -N-O-C-H.

The observation that condensation of citral and N-methylhydroxylamine also afforded fused bicyclic isoxazolidines proved valuable for firm structural assignments of II-IV. In this study, two unsaturated products V and VI were detected in the ratio 3:1. It must be noted that the redistilled citral employed was a mixture of neral (cis) and geranial (trans). Only nitrone from the former can react by an intramolecular pathway, and it did so at a rate slower than that observed with the nitrone from citronellal. In fact, a nitrone could be recovered from the reaction mixture (4).

Thermal isomerization of VI at 280° proceeded smoothly to give only cis-fused isomer V. Apparently the equilibrium at these temperatures for the unsaturated isoxazolidines lies heavily in favor of V; and, as expected, V could be pyrolyzed and none of its isomer VI was seen in the pyrolysate.



V, R=CH$_3$ VI, R=CH$_3$



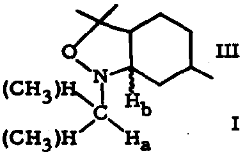
VII, R=CH$_3$
(racemate)

Catalytic hydrogenation of V in the presence of 10% palladium-carbon was stopped after the uptake of 1.2 molar equivalents of hydrogen. From the resulting product mixture, *racemates* of II and III in the ratio 3:2 were isolated in 40% yield by column chromatography and g.c. separation. Identity was established by IR in carbon tetrachloride solution and by comparison of g.c. retention times (5). Because II and III were the *only* saturated isoxazolidines detected from this reduction, and since I has been verified to have a *trans*, *trans*-configuration, this data confirms a *cis* ring fusion for compounds II, III and V. Attempted hydrogenation of the *trans*-unsaturated isoxazolidine VI led to the rapid uptake of *two* molar equivalents of hydrogen to afford a crystalline, racemic amino-alcohol (VII) whose IR spectrum (CCl_4) indicated that it was a diastereomer of the aminoalcohols from hydrogenolysis of I, II and III. Thus VII must be related to the heretofore unknown *trans*, *cis*-isoxazolidine IV (isomenthyl series). Examination of a molecular model of VI indicates that hydrogenation of the double bond should occur preferentially from the side opposite that to which the isopropyl moiety is attached encouraging the prediction that IV would be formed and suffered facile -N-O- bond cleavage to VIII. Partial hydrogenation of VI in the presence of a small amount of catalyst allowed the isolation and characterization of *racemic* IV: no d, l-I was detected.

The one remaining stereochemical question is that of the relative configurations of the *cis*-fused isomers II and III. The assignments are based upon the well documented observations that an equatorial hydrogen attached to a cyclohexane is less shielded and absorbs at lower field in the n.m.r. than does its axial counterpart (6). There are listed in Table I the pertinent chemical shift data for the isoxazolidines I-IV.

TABLE I

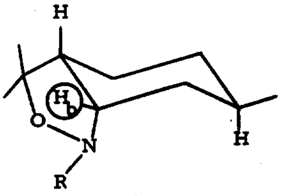
Chemical Shifts for Bicyclic Isoxazolidines



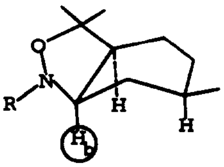
Compound		Configuration	δ, p.p.m.	
			H_a	H_b
II,	$R=CH_3$	*cis*-*trans*	2.46	2.78
	$R=(CH_3)_2CH$		2.99	3.30
III,	$R=CH_3$	*cis*-*cis*	2.48	masked
	$R=(CH_3)_2CH$		2.84	2.05
I,	$R=CH_3$	*trans*-*trans*	2.40	masked
	$R=(CH_3)_2CH$		2.86	2.46
IV,	$R=CH_3$	*trans*-*cis*	2.40	masked

For a starting point in the analysis, one may assume that each of the compounds will adopt that chair conformation for the six-membered ring which will have the fewest number of attached substituents in an *axial* orientation. This leads to the conclusion that only the *cis*-*trans* isomer II will have an *equatorial* H_b (*cf*. VIII). The H_b resonances for II appear at lower field than those for *any* of the remaining isomers, and it is the one compound for which the H_b resonance appears at significantly lower field than the N-methyl singlet (H_a). Furthermore, the splitting pattern for H_b of II corresponds to an unresolved multiplet expected of an *equatorial* hydrogen in the preferred conformation VIII.

In view of the evidence given above, III must, by necessity be assigned a *cis*-*cis* configuration. Its most favorable chair conformation would require the quaternary carbon to be axially oriented, and H_b would also be *axial*. However, H_b in III absorbs at *higher* field than all other hydrogen atoms with the -O-N-C-*H* environment in these isoxazolidines. This abnormally high shielding of H_b in III may be attributed to the adoption of the twist conformation IX as the most stable arrangement for this isoxazolidine. The stereochemical assignments are further supported by the observation of a greater thermodynamic stability for II relative to III, and the fact that II (axial R_3N:) is eluted from alumina before III (*pseudo*-equatorial R_3N:).

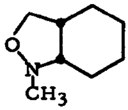


VIII

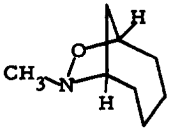


IX

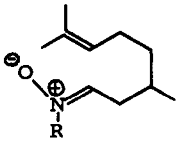
A similar thermal isomerization was observed with the unsubstituted analogs of I and II, prepared from condensation of 6-heptenal and N-methylhydroxylamine (1). With this simple series, the *cis*-fused isomer X dominated at equilibrium. A third compound was also detected in the preparation of X, and its properties were consistent with a bridged structure XI. Pyrolysis of XI also afforded X.



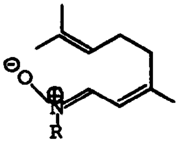
X



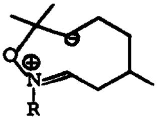
XI



XII



XIII



XIV

The thermal isomerizations presented here are attributed to a *retro*-1,3-dipolar addition in which the unsaturated nitrones XII and XIII are generated from the isoxazolidines. We have not as yet succeeded in trapping these nitrone intermediates with other dipolarophiles; rather they appear to recyclize to equilibrium mixtures of the isoxazolidines. The only reasonable alternative to a *retro* nitrone-olefin addition which can account for the observed configurational isomerizations is a mechanism involving the dipolar intermediate XIV. Kinetic studies in solvents of differing polarity might prove useful; but it does appear that involvement of XIV would require prohibitive activation energy. In any case, an intermediate such as XIV is not sufficient to account for those thermal isomerizations that involve a change in orientation; such as, the reorganization of XI to X, and isomerizations of the adducts from α, β-unsaturated esters and nitrones (8, 9). Rearrangements of the latter type are much more facile because of the activating influence of the carboalkoxy substituent. The present work indicates that even intramolecular additions between simple, aliphatic nitrones and unactivated olefins are readily reversible.

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REFERENCES

(1) N. A. LeBel, M. E. Post and J. J. Whang, J. Am. Chem. Soc., 86, 3759 (1964).

(2) M. E. Post, unpublished observations. The citronellal employed contained approximately 12% of the double bond isomer, which does not lead to isoxazolidine products.

(3) Satisfactory elemental analyses have been obtained for all new compounds reported, as well as for crystalline derivatives. Thin-layer chromatography was carried out with Eastman "Chromatogram Sheets" with ether as solvent and iodine vapor as developer. Gas chromatographic analyses were carried out with columns packed with 15% GE Silicone XE-60 on Chromsorb-P at 158° C.

(4) This material appeared to be a mixture of nitrones of geranial and neral as determined by n. m. r. analysis. Further reflux in xylene afforded additional quantities of V and VI. Conjugate addition provides a convenient way to equilibrate these nitrones.

(5) Further verification was made by employing d, l-citronellal in the preparation of I and II. It was obtained by lithium-ammonia reduction of citral to d, l-citronellol, and oxidation of the latter with lead tetraacetate in pyridine.

(6) For a summary and leading references see L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1959, pp. 115-119.

(7) N. m. r. data were obtained with a Varian Associates DP-60 spectrometer as approximately 20% solutions in carbon tetrachloride. Chemical shifts, measured by the audio-sideband method, are given in p. p. m. from tetramethylsilane.

(8) G. R. Delpierre and M. Lamchen, J. Chem. Soc., 4693 (1963).

(9) F. Paritee, unpublished observations.