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THE CYCLIZATION OF EPOXYOLEFINS (1). IV. BICYCLIC ETHERS FROM A CITRONELLAL DERIVATIVE.

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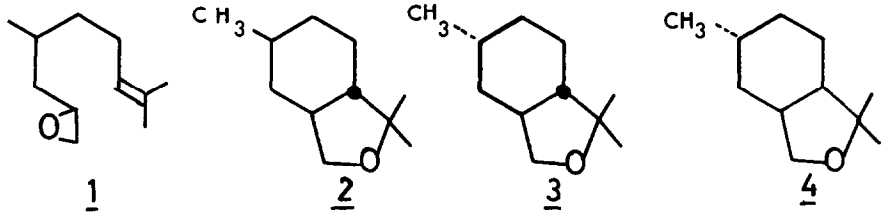
We first reported (3) the cyclization of an epoxyolefin as a model for lanosterol and cholesterol biosynthesis, a process now shown (4) to be the probable pathway for the *in vivo* formation of these compounds. In this and the following communication we report the cyclization of two unsaturated oxirane systems which appear to be promising synthetic entries into the diterpene series of natural products.

Treatment of citronellal with dimethyloxosulfonium methylide (5) gave the diastereoisomeric epoxides 1 (6) * in 51% yield. The latter reacted readily with stannic chloride in benzene solution to yield, after distillation, 65% of a mixture of five compounds. Two of these, unreacted starting material and an aldehydic substance, amounted to 5% of the total. The major portion of the product consisted of three substances, 2, 3, and 4 in relative yields of 56%, 14%, and 25% respectively. The mass spectra of these three substances are identical and are consistent with the gross structural assignment of an α,α-dimethyltetrahydrofuran system. Prominent peaks in the mass spectrum appear at m/e 153 and m/e 110 for the loss of a methyl radical and the elements of acetone respectively from the molecular ion (m/e 168).

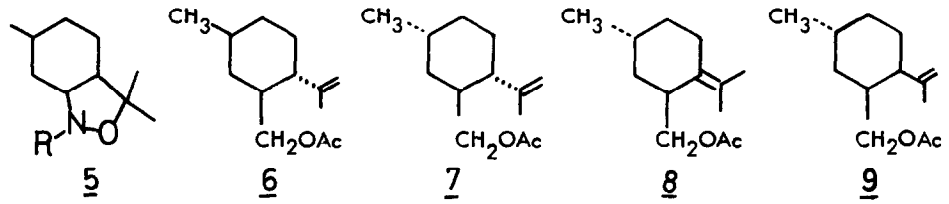
* It is assumed that 1 is at 1:1 mixture of diastereoisomers. Although no separation could be effected it is unlikely that the epoxide formation reaction should be subject to asymmetric induction by the distant asymmetric center of citronellal.



1 2 3 4

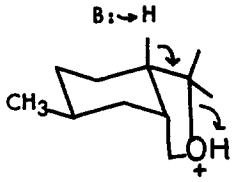
The assignment of the ring junction stereochemistry of 2, 3, and 4 is based on NMR spectral evidence, and on the structure of products obtained by cleavage of the tetrahydrofuran rings. The NMR spectrum (7) of 4 shows a six proton singlet for the gem-dimethyl group at 1.12 p.p.m. and a three proton doublet at 0.86 p.p.m. for the cyclohexyl methyl group. In contrast, both trans compounds 2 and 3 show three separate methyl resonances, a doublet at 0.98 p.p.m., and two singlets at 0.95 p.p.m. and 1.16 p.p.m. respectively. This marked upfield shift of one of the gem-dimethyl group line positions has been found by LeBel (8) for the trans - fused isomers of the isoxazolidine system 5 (9) and our results for both the cis- and trans-tetrahydrofuran isomers reported here are in accord with his.

Chemical support for these stereochemical assignments is supplied by the results of cleavage reactions of the ether rings of 2, 3, and 4 with pyridine hydrochloride in acetic anhydride (10). Both 2 and 3 yield acetates (6 and 7 respectively) which contain a terminal double bond only. In contrast, the cis-fused compound 4 affords a mixture of the tetrasubstituted and terminal olefinic materials 8 and 9.

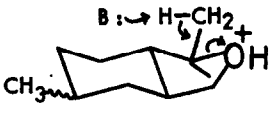


5 6 7 8 9

This latter finding is in accord with the cis assignment (11) for 4 since only in the elimination reaction of this isomer is the ring junction hydrogen trans-coplanar with the departing oxygen; pathway a, below. With the trans isomers 2 and 3 only the methyl group hydrogens may enter into a "concerted" trans elimination; pathway b.

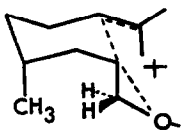


a

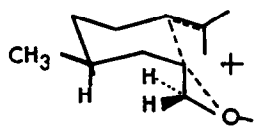


b

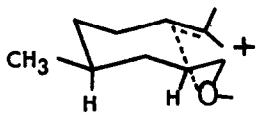
Finally, the assignment of the stereochemistry of the carbocyclic ring methyl group is based on a conformational argument. Assuming "chair" geometry for these cyclizations it may be noted that of the diastereoisomeric transition states, c and d, leading to possible cis products, c clearly involves the equivalent of a 1,3-dimethyl diaxial interaction. Contrastingly, the transition states, e and f, leading to trans products appear to differ in energy by an amount related to the conformational energy of a single methyl group only. Thus the single cis isomer obtained in this cyclization ought to arise solely from d and have the relative stereochemistry depicted in 4. Correspondingly, the minor trans isomer 3 must be derived from the same diastereoisomeric epoxide as 4 through transition state f, and the major product 2 from the other diastereoisomer of 1 through transition state e.



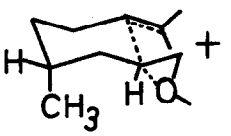
c



d



e



f

References

1. This work was generously supported by a grant from the Public Health Service, GM-11728.
2. NASA Predoctoral Research Fellow.
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5. E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 87, 1353 (1965).
6. Satisfactory elemental analyses were obtained for all new compounds reported.
7. The NMR spectra were obtained with a Varian Associates A-60 spectrometer and the chemical shifts are given relative to tetramethylsilane as internal reference.
8. Private communication from N. A. LeBel, Wayne State University.
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11. For an alternative explanation for these stereochemical conclusions see; F. Johnson and S. K. Malhotra, J. Am. Chem. Soc., 87, 5492 (1965).