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STEREOCHEMISTRY OF "NO-MECHANISM" REACTIONS. II.[1]

ASYMMETRIC INDUCTION IN THE CLAISEN REARRANGEMENT.

Richard K. Hill[2] and Anthony G. Edwards

Frick Chemical Laboratory, Princeton University, Princeton, N.J.

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Probably the best-known of a now widely recognized group of thermally initiated rearrangements, nearly insensitive to acid and base catalysis, is the Claisen rearrangement. All of the evidence which has been accumulated about the mechanism is consistent with an electron reorganization via a concerted, cyclic process:[3]

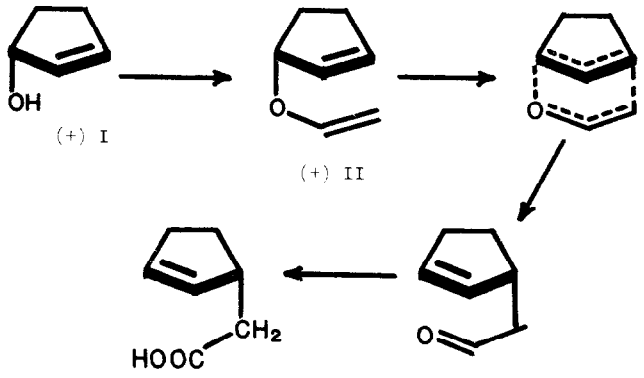
It would be anticipated that a reaction with such a highly ordered transition state would have an appreciable degree of stereospecificity, but this is a conclusion which has been generally accepted on the basis of little experimental evidence. Although a number of investigators have studied changes in geometry of the allylic double bond[3], only one previous investigation has been directed specifically at the possibility of asymmetric induction, i.e., the simultaneous destruction of asymmetry at center a and creation of a new asymmetric center b in a stereospecific direction. Alexander and Kluiber[4] were able to show that some optical activity was retained in the rearrangement of (-) 4-phenoxypentene-2, but attempts to

determine the direction and degree of selectivity were thwarted by low optical rotations and lack of knowledge of absolute configurations of the reactant and product.

In order to attack this problem with compounds of easily measurable rotation and known absolute configuration, we chose to work with the vinyl ether of a cyclic allylic alcohol, of the type studied by Burgstahler and Nordin.[5] The results provide a clear demonstration of asymmetric induction and stereochemical evidence for a cyclic transition state.

Cyclopenten-3-ol[6] (I) was converted to the acid succinate[7] and partially resolved with (+) α-(1-naphthyl)-ethylamine.[8] The succinate regenerated after eight crystallizations of the salt from acetonitrile had $[\alpha]_D^{21}$ +[illegible]° (c= 5 in $CHCl_3$) and gave, on lithium aluminum hydride reduction, alcohol with $[\alpha]_D^{21}$ +22.8° (c= 5 in CCl_4). The alcohol was converted to the vinyl ether (II), b.p. 31-33° (18 mm.), $[\alpha]_D^{21}$ +[illegible]° (c= 4 in CCl_4), by the trans-vinylation procedure of Watanabe and Conlon[9].

Rearrangement of (+) II at 180-185° in a sealed tube under nitrogen yielded (-) cyclopentene-3-acetaldehyde (III), b.p. 51-52° (19 mm.), $[\alpha]_D^{}$ -14.0° (c= 4 in CCl_4), in 81 % yield. The aldehyde function was identified by characteristic infrared bands at 3.67 and 5.76 μ and the n.m.r. signal (triplet) at 0.33 τ, and was converted to a yellow 2,4-dinitrophenylhydrazone, m.p. 101-103° (Found: C, 54.1; H, 4.96. $C_{13}H_{14}N_4O_4$ requires C, [illegible]; H, 4.86). Oxidation of III with alkaline silver oxide afforded (-) cyclopentene-3-acetic acid (IV), b.p. 76-79° (0.75 mm.), $[\alpha]_D^{21}$ -[illegible]° (c= 4 in $CHCl_3$), identified by comparison of infrared spectra of both the acid and the derived iodolactone with those of authentic samples.

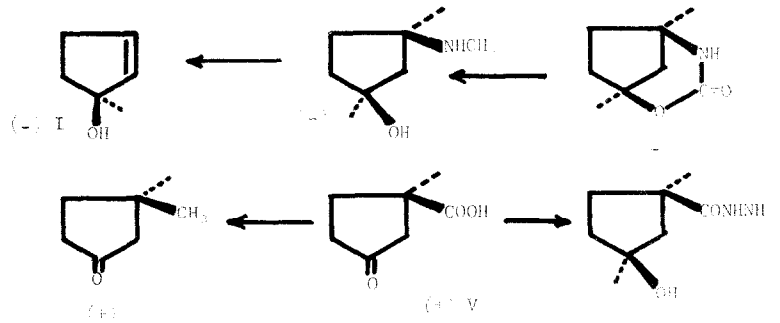


(+) I (+) II (-) IV (-) III

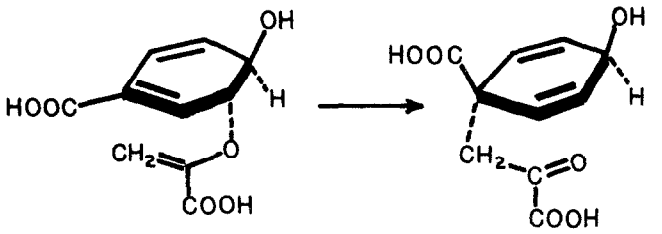
Absolute Configurations. (-) I has been related to (+) 3-ketocyclopentane carboxylic acid (V) by the sequence of reactions[7] outlined in Chart I; (+) V was subsequently converted to R-(+)-3-methylcyclopentanone.[10] The R configuration of (-) IV was established by Mislow and Steinberg[11] in the course of their work on the configuration of chaulmoogric acid. The conversion of the R-(+) vinyl ether II to the R-(-) aldehyde III thus demonstrates that the new carbon-carbon bond formed in the rearrangement is cis to the carbon-oxygen bond being broken, a conclusion certainly consistent with the accepted cyclic mechanism but never, until now, specifically proved. The conversion of a C-O bond at one asymmetric center to a C-C bond at a new asymmetric center, in a definable steric direction, provides a valuable method of correlating configurations.

It may also be noted that the rearrangement of II to III reported here serves as an excellent stereochemical model for the enzymatic conversion of chorismic acid[12] (VI) to prephenic acid (VII). Although this reaction was

Chart I. Absolute Configuration of (-) Cyclopenten-3-ol.



described as "presumably a stereospecific S'n$_i$ reaction", it has the appearance of a straightforward Claisen rearrangement. It will be of particular interest to discover by what mechanism the enzyme is able to circumvent the usual necessity for thermal initiation of such a rearrangement.



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