

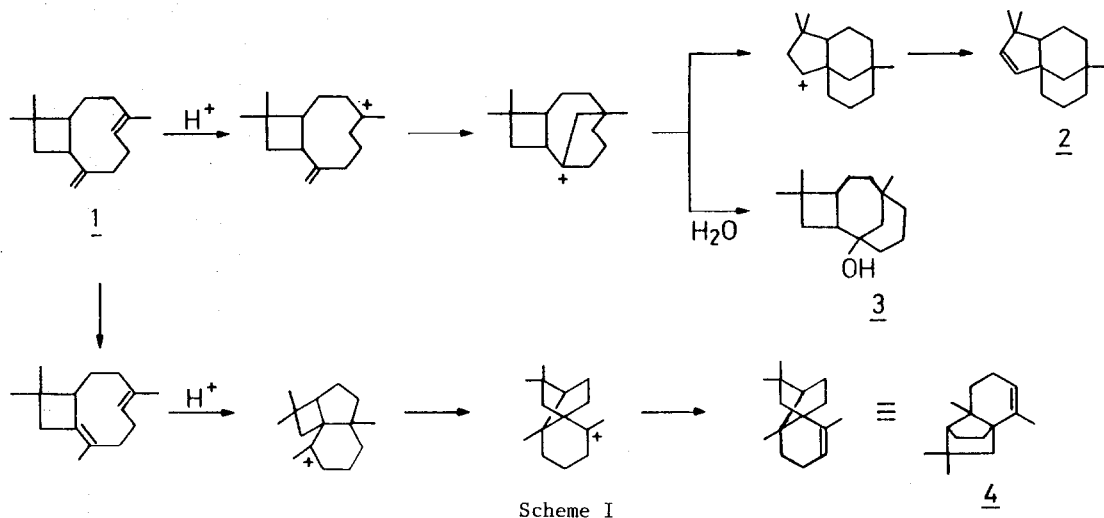
A NOVEL RADICAL INDUCED REARRANGEMENT OF THE
CARYOPHYLLENE SKELETON

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Abstract: The addition of an acetyl radical on caryophyllene leads to formation of the four isomeric ketones 5-8 involving a novel rearrangement of the caryophyllene skeleton.

The acid catalyzed rearrangement of caryophyllene 1 has been studied in detail¹. The final reaction products are clovene 2, caryolan-1-ol 3 and neoclovene 4 (Scheme I). The formation and

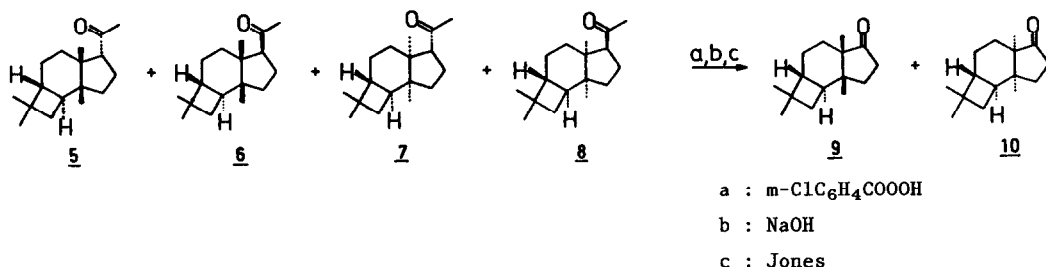


stereochemistry of 2 and 3 have been rationalized by Aebi et al². The mechanism for the formation of 4 was proposed by W. Parker et al³.

As can be seen in Scheme I 1 rearranges depending upon its conformation, to the products 2 or 3. The formation of 4 can be explained by an initial isomerization of the exo-cyclic double bond. In all cases the initial protonation takes place at the highly reactive (E)-double bond. The cation so formed attacks the other double bond in such a way that the most stable cation is formed. For 2 and 3 this reaction leads to formation of a new bridge-atom.

In the course of our current research on new aromachemicals, we were interested in the olfactive properties of the acetaldehyde adduct on caryophyllene⁴. The radical induced addition of acetaldehyde to alkenes is well documented⁵. It proceeds via a Markownikoff directed attack of the acetyl radical at the double bond. The radical thus formed abstracts a hydrogen atom from an acetaldehyde molecule.

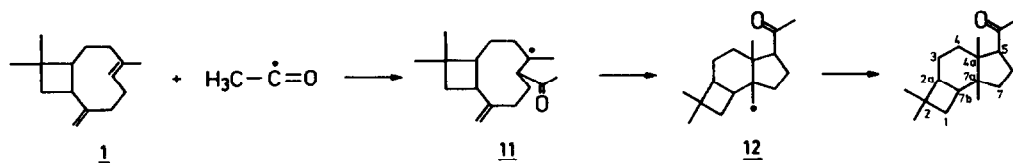
The product mixture obtained after the radical-induced addition of acetaldehyde to caryophyllene⁶ contained four isomeric methyl ketones (Yield 54%). According to the ¹H-NMR-analysis, a base-catalyzed reaction converted two of the isomers into, respectively, the remaining isomers. The four ketones were separated by preparative GLC. In the absence of conclusive evidence as to their structures the ketones were oxidized by *m*-chloroperbenzoic acid to their corresponding acetates⁷. Saponification of the acetates followed by Jones oxidation⁸ gave two isomeric ketones that were purified by GLC. ¹H-NMR-analysis revealed the structures 9 and 10 (Scheme II)⁹. The structure of the degradation products 9 and 10 indicates that the methyl ketones obtained initially have the structures 5-8¹⁰. Upon treatment of the mixture of 5 and



Scheme II

6 with NaOH an equilibrium was obtained in which 6 was the more abundant isomer. In the case of isomers 7 and 8, the latter was the most stable isomer. The isomers initially were present in the following ratio: 5 : 6 : 7 : 8 = 5 : 1 : 2 : 1.

The mechanism proposed for the formation of 5-8 is outlined in Scheme III.



Scheme III

As can be seen from schemes I and III, the mode of cyclization of the cation initially formed differs markedly from that of the alkyl radical 11. It is known that intramolecular additions of radicals containing a 5,6-double bond lead to formation of a five membered ring¹¹.

A striking feature of the products 5-8 is that the internal cyclization results in a *cis*-

ring junction between the five and six membered ring. A study of Dreiding models of the intermediate radical 11 revealed that cyclization to products with a cis-ring junction proceeds via a chair conformation of the 6-ring formed. Cyclization leading to a trans-ring junction proceeds via a boat conformation and is prohibited by considerable strain between the methyl group at C_{4a} and the hydrogen atom at C_{2a}.

As the cation attack on caryophyllene results in a different kind of skeletal rearrangement than an acetyl radical attack, caryophyllene may serve as a general indicator system for the nature of the intermediate(s) involved in a reaction viz. a radical or a cation.

Further work is in progress to reveal whether or not different types of radicals lead to the same type of skeletal rearrangements.

Acknowledgement

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References and notes

- 1 D.H.R. Barton and P. de Mayo, *Quart. Rev.* 11, 189 (1957); W. Parker, R.A. Raphael and J.S. Roberts, *Tetrahedron Lett.* 2313 (1965); T.F.W. McKillop, J. Martin, W. Parker and J.S. Roberts, *J. Chem. Soc., Chem. Commun.* 162 (1967); A. Nickon, F.Y. Edamura, T. Iwadare, K. Matsuo, F.J. McGuire and J.S. Roberts, *J. Amer. Chem.Soc.* 90, 4196 (1968).
- 2 A. Aebi, D.H.R. Barton, A.W. Burgstahler and A.S. Lindsey, *J. Chem. Soc.* 4659 (1954).
- 3 W. Parker, R.A. Raphael and J.S. Roberts, *J. Chem. Soc. (C)* 2634 (1969).
- 4 A recent review on caryophyllene based aromachemicals is published: H. Kikuchi, *Koryo* 56, 21 (1981).
- 5 G. Sosnovsky, *Free radical reactions in preparative organic chemistry*, Macmillan, New York, 1964, p. 125-33.
- 6 A mixture of 0.1 mol of caryophyllene, 0.6 mol of acetaldehyde and 0.01 mol of di-t-butylperoxide was heated at 125-130°C for 3 hours in a glass-lined, sealed vessel. After cooling, the reaction mixture was washed with soda water. Having separated the organic layer, it was distilled yielding 15 g of a product mixture (bp = 120-140°C). The same product mixture was obtained upon irradiation of a mixture of caryophyllene, acetaldehyde and benzophenone with $\lambda = 366$ nm.
- 7 H.C. Brown, G.W. Kabalka and M.W. Rathke, *J. Amer. Chem. Soc.* 89, 4530 (1967).
- 8 Houben-Weyl, *7/2a*, 1973, p. 732.
- 9 Characteristic ¹H-NMR-data (CCl₄, 100 MHz) for 9: 0.76 (3H, s); 1.01 (6H, s); 1.03 (3H, s); 2.25 (2H, m). Applying Eu(fod)₃, the protons H₃ (axial), H₄ (equatorial) and H₇ shifted relatively fast.
For 10: 0.8 (3H, s); 0.92 (3H, s); 1.07 (3H, s); 1.11 (3H, s). Applying Eu(fod)₃, the protons H₄ and CH₃-C₄ shifted relatively fast.
- 10 Characteristic ¹H-NMR-data (CCl₄, 100 MHz).
5 : 0.84 (3H, s); 0.99 (3H, s); 1.02 (6H, s); 2.12 (3H, s); 2.6 (1H, m). Applying Eu(fod)₃, the protons H₄ and H_{7b} shifted relatively fast.

6 : 0.60 (3H, s); 0.87 (3H, s); 1.04 (3H, s); 1.08 (3H, s); 2.05 (3H, s); 3.32 (1H, m).

Applying $\text{Eu}(\text{fod})_3$, the protons H_4 (equatorial) and $\text{CH}_3\text{-C}_4$ shifted relatively fast.

7 : 0.76 (3H, s); 0.89 (3H, s); 1.03 (3H, s); 1.06 (3H, s); 2.02 (3H, s); 2.6 (1H, m).

Applying $\text{Eu}(\text{fod})_3$, the protons $\text{CH}_3\text{-C}_{4a}$ shifted relatively fast. The protons H_4 shifted relatively slow.

8 : 0.79 (3H, s); 1.04 (3H, s); 1.08 (3H, s); 1.16 (3H, s); 2.02 (3H, s); 2.83 (1H, m).

Applying $\text{Eu}(\text{fod})_3$ the protons H_4 shifted relatively fast.

- 11 A.L.J. Beckwith and G. Moad, J. Chem. Soc., Chem. Commun. 472 (1974); A.L.J. Beckwith, G.E. Gream and D.L. Struble, Austr. J. Chem. 25 1081 (1972).

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