

SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION V.

TRANSANNULAR REACTIONS OF HEDYCARYOL ISOMERS

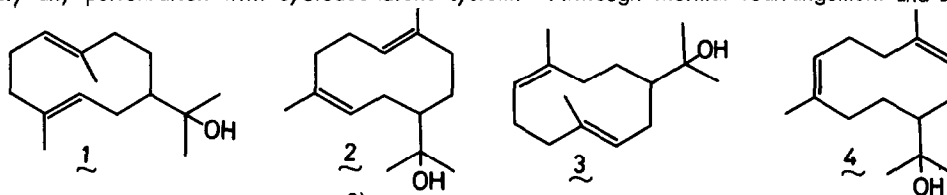
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Thermal rearrangement and acid-catalyzed cyclization of all possible geometrical isomers of hedycaryol were investigated. From the stereochemistry of the products, the reacting conformations were deduced. While three (E,E-, E,Z- and Z,E-) isomers reacted through the crossed conformations, Z,Z-isomer yielded products via parallel conformations. The thermal reaction at higher temperatures revealed the additional pathways involving Cope rearrangement of elemols. All possible stereoisomers of elemol were synthesized. The structure of "epielemol" has to be revised.

Transannular reactions of germacrenes, which create chiral centers regio- and stereospecifically in a single reaction starting from trigonal carbons, have attracted much attention recently in connection with sesquiterpene biogenesis¹⁾. The reactions are also interesting from a mechanistic point of view by the fact that their reacting conformations can be deduced from the configuration of the products. Although the accumulated results permit the generalization that the reactions proceed from the crossed conformations through chair-like transition states, the studies are mostly concerned with natural products and their derivatives with E,E-configuration excepting a few cases. Furthermore, additional functionalities some times cause more complexity^{1b,1c,2)}, thus making systematic studies on stereochemical requirement of these interesting reactions more difficult. Hedycaryols are ideal for such mechanistic studies because the hydroxy propyl group in the molecules is a large enough conformational anchor to fix the proximate geometry and has hardly any perturbation with cyclodecadiene system. Although thermal rearrangement and acid-catalyzed

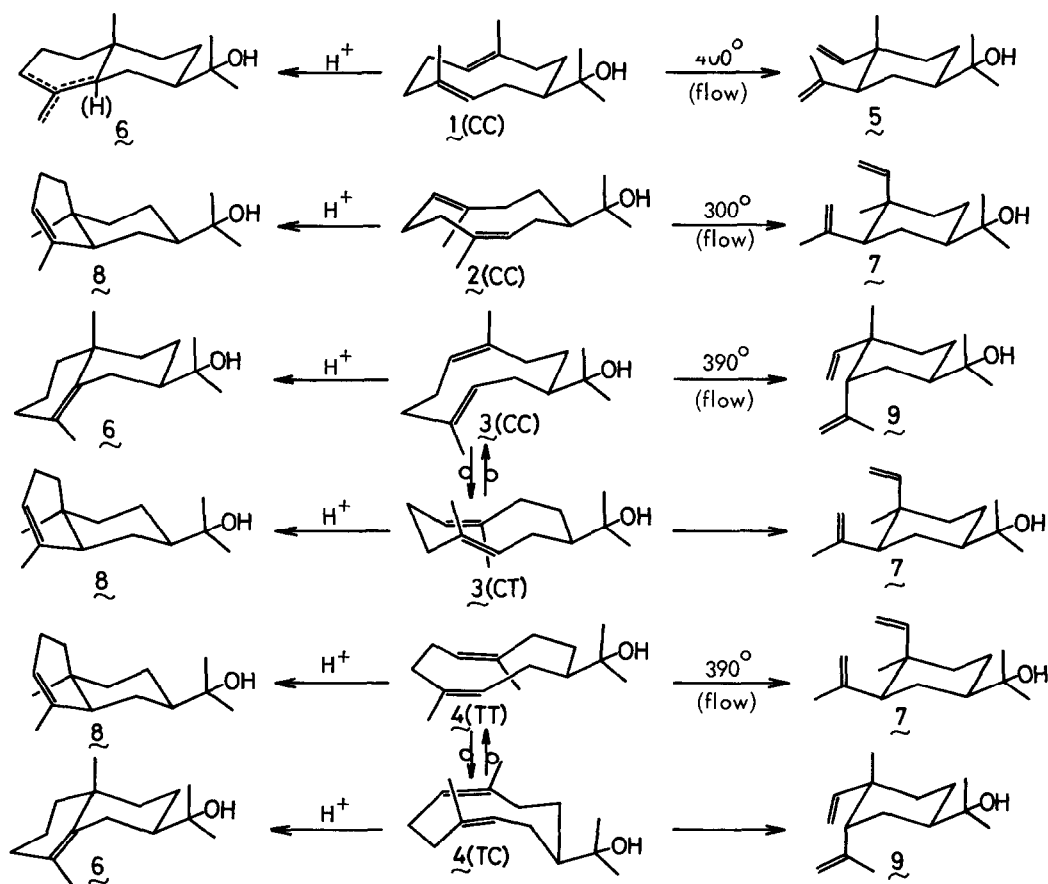


cyclization were reported by Sutherland³⁾ using natural hedycaryol 1, we have investigated the reactions using its geometrical isomers 2, 3 and 4, we have recently synthesized⁴⁾.

In order to avoid concomitant dehydration, thermal reaction was conducted in a flow system (hexane solution, N₂), while acid cyclization was carried out with either p-toluenesulfonic acid in refluxing ether

or with aqueous 85% formic acid at room temperature. Under these conditions, E, E-isomer 1 afforded elemol 5 as a single product in thermal reaction up to 400°, in accord with Sutherland's result³⁾. Thermal reaction of Z, E-hedycaryol 2 at 300°⁵⁾ afforded cis-isoelemol 7⁶⁾, whereas p-toluenesulfonic acid yielded dihydrooccidentalol 8⁷⁾. Thermal isomerization of E, Z-isomer 3 requires somewhat higher temperatures, and at 390° 7 and a new compound, cis-elemol 9⁸⁾, were formed in the ratio of 2:3 (by NMR). Likewise, acid cyclization (formic acid)⁹⁾ afforded a mixture of 6 and 8 in a similar ratio (28:19). From the product analysis, the reacting conformations of hedycaryols were deduced as shown in the chart below for all reactions¹⁰⁾. Excellent parallelism in reacting conformations between thermal rearrangement and acid cyclization was observed for all three isomers, suggesting that the stereochemical course of the reactions is controlled by the attractive interactions between two double bonds in the former reaction and between a carbonium ion and a double bond in the latter. The crossed forms (CC or CT conformation^{1a)}) appear from inspection of molecular models to have more effective interactions, supporting the experimental results.

The reactions of the fourth (Z, Z) isomer 4 demonstrated again the parallelism¹⁰⁾. Acid cyclization (formic acid) yielded 8 (56% yield) and 6 (trace). Thermal reaction proceeded even more slowly than in 3 and the conversion rate at 390° was very low, affording only 7. However, by the separate experiment



using a pot system, the formation of 2 was detected. The reacting conformations in this case, however, are the parallel (TT and TC) forms. Inspection of molecular model revealed that, in the crossed forms of 4, p-orbitals of the double bonds are kept distant from each other and not suited for the π - π interaction. Thus, the compound appears to be obliged to react slowly through the parallel conformations.

When the thermal reaction is conducted at higher temperatures, new elemol starts forming in addition to the products described above. For example, 2 afforded at 400° a 4:1 mixture of 2 and 2. The result of the reactions at 500° with all the isomers is shown in Table¹¹⁾. The table reveals that (i) new

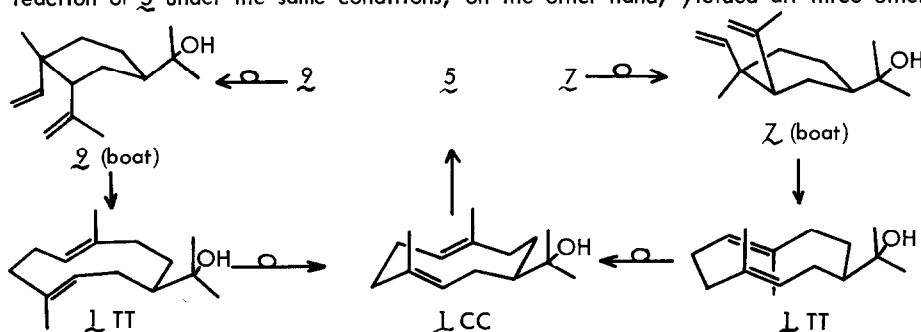
Table Product ratios in thermal reaction at 500° in flow system of hedycaryol isomers¹²⁾
(Figures with underline denote the products at lower temperatures)

product	<u>5</u>	<u>2</u>	<u>10</u> ¹¹⁾	<u>2</u>
E, E-(1)	<u>67</u>	trace	10	23
Z, E-(2)	26	18	0	<u>56</u>
E, Z-(3)	14	<u>46</u>	0	<u>40</u>
Z, Z-(4)	15	<u>27</u>	0	<u>58</u>

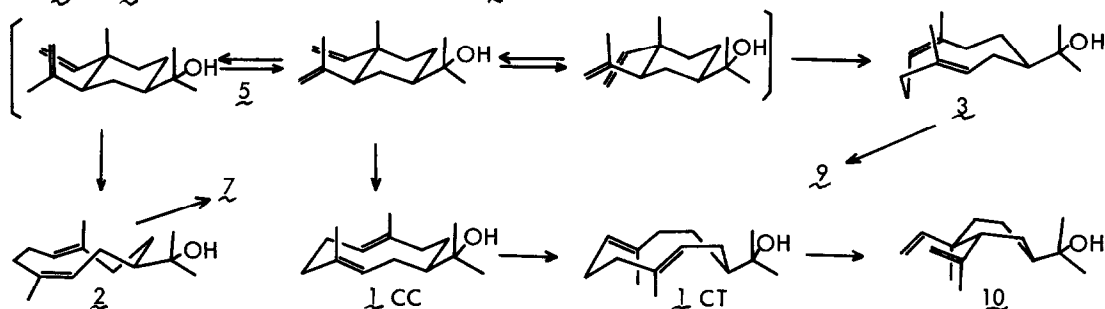
elemols were formed from all four isomers, (ii) only three elemols, 5, 2 and 2, were formed from 2, 3 and 4, and (iii) all four elemols were identified in the reaction of 1. Although these products can be explained as being formed from respective conformation of hedycaryols, a few features against the explanation are noted. First, in the reaction of 2 and 3, TC conformation appears to be involved (formation of 2) but TT conformation which would have a similar energy barrier (to give 10) is not. Secondly, in the reaction of 4, while CT conformation (to 10) is not involved, CC conformation (to 5) which is unlikely to be involved (vide supra) has to be considered.

These facts led us to consider the retro-Cope Rearrangements of the first-formed elemols. The thermal reaction of 2 and 2, under the same conditions in fact afforded 5 in 10-18% yield. These thermal changes are only explicable by the routes shown below. The result being taken into consideration, the reaction from 2 and 3 to 5 should involve the same sequence.

Thermal reaction of 5 under the same conditions, on the other hand, yielded all three other elemols.



While the formation of **10** involves **5** (CT form), that of **7** and **8** would require **2** and **3** as shown. It is quite reasonable that **10** can not be formed directly from other hedycaryols because the reacting conformation of **2** and **3** to it has to be TT and that of **4** be CT form.



Thus, transannular reactions of all hedycaryol stereoisomers are well understood by considering CC or CT form even at higher temperatures except for the Z,Z-isomer which takes TC and TT conformations.

"Epielemol" isolated by Babkin *et al.*¹³⁾ from *Pinus sibirica* was found to have the identical PMR spectrum with our *cis*-isoelemol and its structure therefore has to be revised.

References and Notes

- 1) *Inter al.*, a) J.K. Sutherland, *et al.*, *Tetrahedron*, **30**, 1651 (1974), *J. Chem. Soc. Perkin I*, 2326 (1975). b) K. Takeda, *et al.*, *Tetrahedron*, **30**, 1525 (1974), *J. Chem. Soc. Perkin I*, 870 (1975). c) S. Yamamura, *et al.*, *Bull. Chem. Soc. Japan*, **49**, 3137, 3148 (1976).
- 2) a) K. Takeda, I. Horibe and H. Minato, *J. Chem. Soc. Chem. Commun.*, 88 (1971). b) K. Tori, I. Horibe, H. Minato and K. Takeda, *Tetrahedron Letters*, 4355 (1971).
- 3) R.V.H. Jones and M.D. Sutherland, *J. Chem. Soc. Chem. Commun.*, 1229 (1968).
- 4) a) M. Kodama, Y. Matsuki and S. Itô, *Tetrahedron Letters*, 1121 (1976). b) M. Kodama, S. Yokoo, H. Yamada and S. Itô, *ibid.*, 3121 (1978).
- 5) The same reaction occurs by heating benzene solution of **2** at 200° (autoclave) for 20 min. (ref. 4a).
- 6) *Cis*-elemol in our previous paper (ref. 4a) is now renamed as *cis*-isoelemol, prefix *cis* denoting the 1,2-*cis* relationship between two vinyl groups and *iso* referring to the 1,4-*cis* relationship between the hydroxypropyl and vinyl groups.
- 7) T. Nakatsuka and Y. Hirose, *Bull. Agr. Chem. Soc., Japan*, **20**, 215 (1956). A.G. Hortmann and J.B. de Rood, *J. Org. Chem.*, **34**, 736 (1969).
- 8) Colorless oil, *m*/*e* 222 (*M*⁺), 161 (b.p.), 59. *v* 3375, 915, 890 *cm*⁻¹. *δ* 1.08 (1 Me), 1.13 (2 Me), 1.71 (1 Me), 4.68-4.95 (4H, m), 5.70-6.00 (1H, ABX). The structure was established by its dehydration (SOCl₂/Py) to give *cis*-*γ*-elemene (ref. 2a).
- 9) *p*-Toluenesulfonic acid causes concomitant dehydration and conjugation of the resulted double bonds.
- 10) Conformations leading to **6** from **3** and **4** have some ambiguity caused by the elimination of the crucial hydrogen, and are deduced by analogy with other reactions.
- 11) The structure of isoelemol **10**, the fourth isomer, was secured by its spectra [*m*/*e* 204 (*M*⁺-18), 59, *v* 3410, 1635, 910, 895 *cm*⁻¹. *δ* 0.94 (1 Me, s), 1.09 (2 Me, s), 1.81 (1 Me, m), 4.7-5.1 (4H, m), 5.79 (1H, dd, *J*=18.0, 10.0)] and its dehydration (SOCl₂/Py) to *γ*-elemene.
- 12) The ratio of **5**, **7**+**8** and **10** was determined by GC, while the value **7**:**8** was determined by PMR.
- 13) V.A. Babkin, Z.V. Dubovenko, V.V. Babkin and V.A. Pentegova, *Izv. Sib. Otd. Akad. Nauk, SSSR, Ser. Khim. Nauk*, 76 (1971).

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