

CONFORMATIONAL CONTROL OF STEREOCHEMISTRY IN THE NON-CONCERTED, DEGENERATE REARRANGEMENT OF A VINYL-CYCLOPROPANE

(-)- Δ^3 -THUJENE*†‡

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Abstract—The stereochemistry of the degenerate, thermal vinylcyclopropane rearrangement of (-)-2,2,3-trideuterio- Δ^3 -thujene has been elucidated. Determination of partitioning among the three products of enantiomerization and rearrangement to (+) and (-) 5,5,6-trideuterio- Δ^3 -thujene reveals that the major path is forbidden by orbital symmetry and is therefore non-concerted, while the minor paths are equally divided between a forbidden and an allowed path. The high degree of stereoselectivity of this non-concerted rearrangement is explained by a small barrier to conformational equilibration. The rate of the racemization is given by the expression $\log k (\text{sec}^{-1}) = 14.33 - 43.4/2.303 \text{ RT}$.

VINYLCYCLOPROPANES have been discovered to rearrange to cyclopentenes on heating. The first recorded example is the skeletal rearrangement involved in the thermal reorganization of 1,1-dichloro-2-vinylcyclopropane to a mixture of chlorocyclopentadienes.^{1,2} It is followed by the prototypical example, reported independently by Vogel *et al.*³ and by Overberger and Borchert.⁴ The hypothesis that rearrangement of excited vinylcyclopropane accounts for the production of cyclopentene in the gas-phase addition of methylene to butadiene⁵ was confirmed by Lassila⁶ and Frey.⁷

Energies of activation for several rearrangements of this type have been determined: vinylcyclopropane: $E_a = 49.6$ kcal/mole, $\log A = 13.5$;⁸ 49.7, 13.6;⁹ *trans*-2-methylvinylcyclopropane: 48.6, 13.7;¹⁰ 45.7, 12.5;¹¹ 1-cyclopropylbut-1-ene: 50.0, 13.8;¹² 2-cyclopropylpropene: 50.9, 13.9;¹³ 1-methyl-1-vinylcyclopropane: 49.4, 14.1;¹⁴ 2-(1-methylcyclopropyl)propene: 50.5, 14.1;¹⁵ 1-cyclopropyl-2-methylpropene: 54.6,

* In this paper the (-)- α -thujene of common usage is called (-)- Δ^3 -thujene and the proper name of the subject derivative is (-) (1S, 5S)-2-methyl-3,4,4-trideuterio-5-isopropylbicyclo[3.1.0]hex-2-ene according to the amended formulation of multiple bonds in the sequence rules: R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem. intern. ed.* **5**, 385 (1966)

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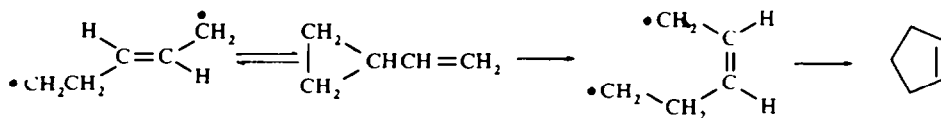
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14.0;¹⁶ 1,1-dicyclopropylethylene: 51.1, 14.3;¹⁷⁻¹⁹ 1-cyclopropylcyclopentene: 51.3, 14.0.¹⁷⁻¹⁹

The rearrangement proceeds unperturbed by carbalkoxy groups,^{20, 21} chlorine atoms,^{2, 17} a second cyclopropyl ring invitingly placed^{17, 18, 22, 23} or by a second double bond situated to offer the opportunity of forming a 7-membered ring (the butadienylcyclopropane rearrangement).²² The rearrangement seems unaffected by incorporation of the normally acyclic vinyl group into a ring.^{17, 18, 24}



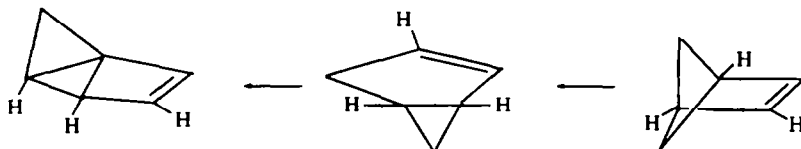
When an H atom is situated on an sp^3 C atom at position 2 which is *cis* to the vinyl group at position 1 the infelicitously named "retro-ene" reaction or 1,5-homodienyl hydrogen shift may intervene. The activation energy of this reaction being considerably lower than that of the vinylcyclopropane rearrangement,^{10, 11, 25-31} this change often appears in bicyclic systems in which the 3-membered ring is fused to a second ring: bicyclo[5.1.0]oct-2-ene,^{32, 33} bicyclo[6.1.0]non-2-ene,^{32, 34, 35} and bicyclo[7.1.0]dec-2-ene.³⁴ Its reversibility is responsible for such changes as the conversion of *cis*-hexa-1,4-diene to 4-methylcyclopentene,³⁶ cyclonona-1,4,7-triene to bicyclo[6.1.0]nona-2,4-diene,^{30, 35, 37, 38} and cycloocta-1,4-diene to bicyclo[5.1.0]oct-2-ene.³³ In other instances, the cyclopropane-propene transformation may appear: 1-cyclopropyl-2-methylpropene,¹⁶ 1-(2-methyl-1-cyclohexenyl)-2-carbomethoxycyclopropane,³⁹ 7-carbomethoxybicyclo[4.1.0]hept-2-ene,⁴⁰ and bicyclo[3.1.0]hex-2-ene.⁴⁰ In bicyclic systems where the 1,5-homodienyl shift is sterically excluded, normal rearrangement of the vinylcyclopropane type is observed: bicyclo[5.1.0]octa-2,5-diene,⁴² bicyclo[6.1.0]nona-2,4,6-triene,^{43, 44} heptacyclo[9.3.2.0^{2,14}.0^{3,10}.0^{4,9}.0^{5,13}.0^{8,12}]-hexadeca-6,15-diene,⁴⁵ and 9-carbomethoxy-,⁴³ 9-carbomethoxy-,⁴⁶ and 9-hydroxymethyl-⁴⁷ bicyclo[6.1.0]nona-2,4,6-triene and related derivatives.⁴⁸

The vinylcyclopropane rearrangement can be blocked by construction of a system (1-vinyltricyclo[2.2.1.0^{2,6}]heptane) which leads to a product in violation of Bredt's rule.⁴⁹

The establishment that *cis*, *trans* interconversion by cleavage and recyclization competes with the rearrangement is presented as evidence for a diradical intermediate lying very close in energy to the transition state of the rearrangement.⁵⁰ A similar conclusion is reached in the extensive investigation of Ketley *et al.* of the behavior of *cis* and *trans* 1-(*para*-substituted phenyl)-1-cyclopropylprop-1-enes.⁵¹ Despite almost identical energies of activation, the *trans* isomers rearrange smoothly, whereas the *cis* isomers lead mainly to polymers. For steric reasons the *cis* isomers are discouraged from opening to the *cis* allylic radical required to produce a cyclopentene ring and instead open to the *trans* allylic radical which can polymerize. Although combined experimental experience does not allow definitive distinction between a non-concerted mechanism involving a singlet intermediate diradical and a concerted mechanism, theoretical arguments can be raised against a concerted migration.⁵²

Since the vinylcyclopropane rearrangement is thermodynamically exothermic by

about 25 kcal/mole, the reverse rearrangement of cyclopentene to vinylcyclopropane is normally not observed. However, if the heat of formation of the cyclopentene product can be raised at least as high as that of the starting vinylcyclopropane by the introduction of strain energy, the reverse rearrangement becomes accessible. In bicyclo[2.1.1]hex-2-ene, the strain of the 4-membered ring is sufficient to reverse the usual thermodynamic preference for the cyclopentene, so that rearrangement to the corresponding vinylcyclopropane, bicyclo[3.1.0]hex-2-ene, occurs.⁵³



Similarly, when a 3-membered ring is fused to the cyclopentene ring, fully degenerate examples of the vinylcyclopropane rearrangement can be observed. Two examples are the racemization of Δ^3 -thujene⁵⁴ and the scrambling of the deuterium label in 6,6-dideuteriobicyclo[3.1.0]hex-2-ene.^{32, 41} Non-degenerate examples, in which small changes in steric and conjugative interactions furnish additional thermodynamic biases, are found in the rearrangements of 1,5-diphenylbicyclo[3.1.0]hex-2-ene⁵⁵ and 1,5-dicarbalkoxybicyclo[3.1.0]hex-2-ene.⁵⁶

The present work is concerned with the behavior of this more restricted bicyclo[3.1.0]hex-2-enyl system. In this system the allylic component of the hypothetical intermediate is not free to choose between a *cisoid* or *transoid* conformation while the second radical component is completely prevented from undergoing a 180° rotation. Despite these restrictions a number of stereomechanistic choices remain. These choices, distinction among which was promised in the earlier paper,⁵⁴ are illustrated in the specific example of Δ^3 -thujene. Optical activity is used to follow the stereochemical changes and deuterium labelling is used to measure the extent of the vinylcyclopropane rearrangement.

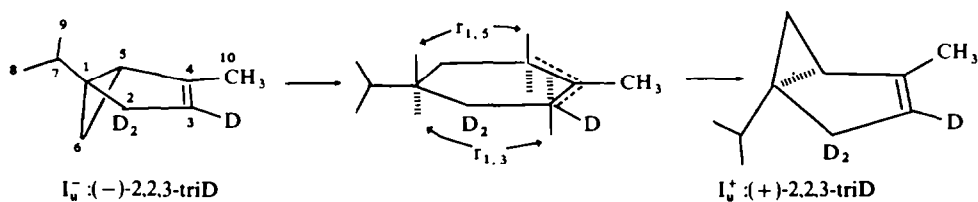


FIG 1. Rearrangement by the concerted and symmetry allowed path A

Path A (Fig 1) represents a potentially concerted mechanism able to benefit from continuous bonding. In this path, C atom 5, the end of the allylic component which was originally bonded to the tertiary C atom 1, remains bonded to that C atom throughout the rearrangement by means of a parallel 2p-2p bond.* The result is enantiomerization of the starting (-)- Δ^3 -thujene [I_u^- : (-)-2,3,3-triD] to (+)- Δ^3 -

* Estimation of the energetic significance of such a bond was one of the purposes of the investigation of the *exo-endo* equilibration of 2-methylbicyclo[2.1.0]pentane.⁵⁷

thujene [I_u^+ : (+)-2,2,3-triD].* The symmetry of the π_2 orbital of the allylic radical (represented by the convention of the solid and crossed lines at the α (C_5) and γ (C_3) C atoms and by no mark at the nodal β (C_4) C atom) permits a parallel 2p orbital to be bonded at one end only, but not simultaneously at both ends. In this hypothetical transition state, two situations should be distinguished: the first in which the distance between C atoms 1 and 5 ($r_{1,5}$) remains smaller than the distance between C atoms 1 and 3 ($r_{1,3}$) and bonding between atoms 1 and 5 is thus greater in magnitude than antibonding between atoms 1 and 3; and the second in which $r_{1,5}$ and $r_{1,3}$ become equal and the net result is zero bonding; that is, no bonding regardless of the actual distance separating C_1 and the two ends of the allyl radical. The first situation corresponds to the concerted path A (the second to non-concerted paths C or D). The consequence of path A is racemization without rearrangement of the deuterium label and is known, from the work of Doering and Lambert,⁵⁴ not to be the exclusive path.

There is no discernible theoretical basis for Path B (Fig 2). It represents a stereospecific vinylcyclopropane rearrangement with retention of the original chirality. This path in which I_u^- is converted to I_r^- [(–)-5,6,6-triD] likewise cannot be the exclusive path since some racemization is observed.⁵⁴

A third path, C (Fig 2), may be described as the stereospecific production of I_r^+ [(+)-5,5,6-triD] from I_u^- by enantiomerization and vinylcyclopropane rearrangement. Having no justification in terms of continuous bonding, which is forbidden by the symmetry of the orbitals, this path can be rationalized in terms of the preservation of conformation. If the rupture of the ring transmutes the conformational features of (–)- Δ^3 -thujene into a nonplanar, hexagonal, intermediate diradical with the original conformation (represented in figure 3 as the "isoconformational" intermediate) and is

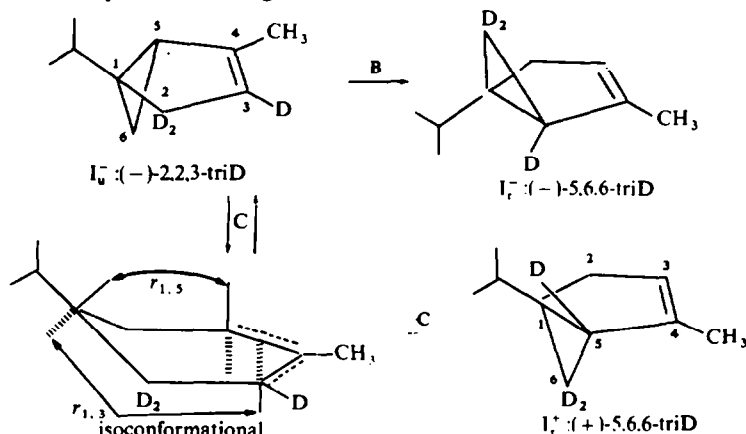


FIG 2. Rearrangement by non-concerted, hypothetically stereospecific paths B and C

followed by reclosure of the ring without prior passage to an intermediate of the inverted, anti-conformation, the products will be regenerated starting material, I_u^- , and rearranged enantiomer, I_r^+ : [(+)-5,6,6-triD]. Under the operation of this

* In the conventional numbering system of terpene chemistry used here, (–)- Δ^3 -thujene of Fig 1 is (–)-2,2,3-trideuterio- Δ^3 -thujene. It is abbreviated as (–)-2,2,3-triD or I_u^- ; i.e., compound I, laevorotatory (–) and unrearranged (u). Its name in the rational system for bicyclic compounds appears in the title of the paper.

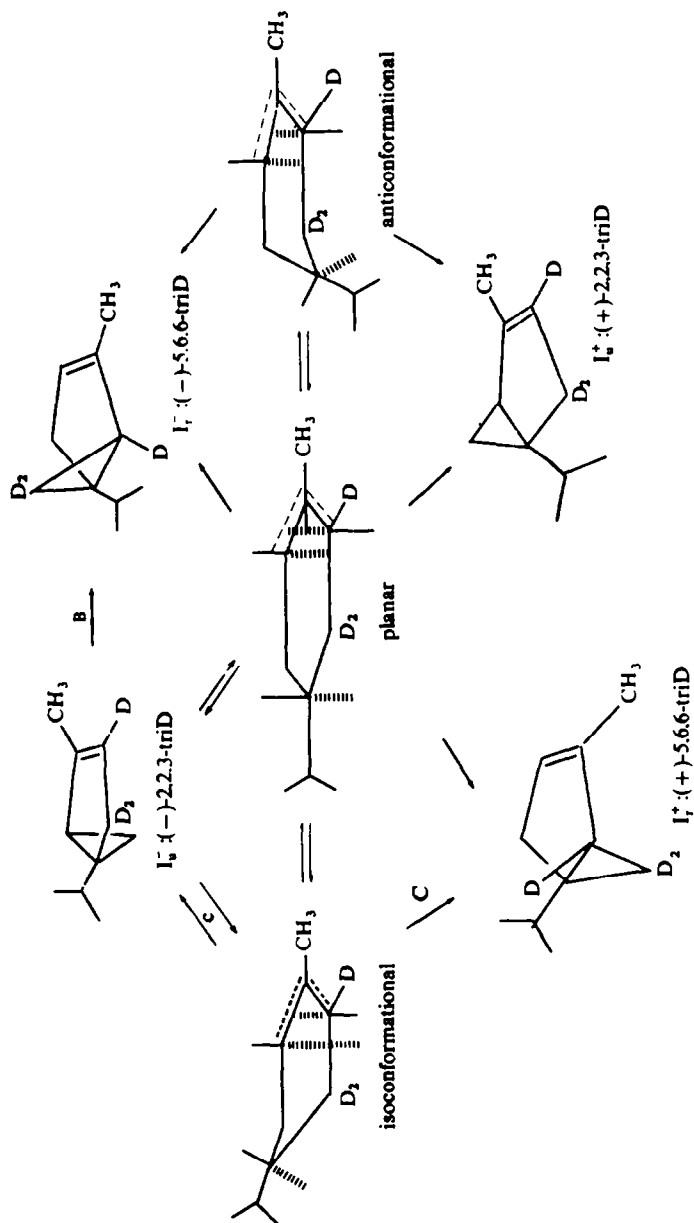


FIG. 3. Rearrangement through planar intermediate or its equivalent, path *D*

mechanism, the rate of racemization is expected to be twice the rate of transmutation of deuterium atoms of the 2,2,3 type to those of the 5,6,6 type.

Path D, illustrated in Fig 3, involves rupture of the ring to a planar intermediate or its equivalent, and is characterized by interconversion of the isoconformational and anticonformational intermediates at a more rapid rate than their reclosure to products. The symmetry of the intermediates leads to equalization of distances C_1-C_5 and C_1-C_3 and precludes bonding between the allylic moiety and the tertiary radical at C_1 (regardless of the planarity or non-planarity of the intermediate). The planar intermediate or its equivalent can be expected to yield all four thujenes, I_u^- , I_r^- , I_u^+ and I_r^+ , in equal amount if the secondary effect of the isotopes be neglected. In path D, the rate of racemization is theoretically twice the rate of transmutation of deuterium.

Since it is true of both paths C and D that the rate of racemization is twice the rate of transmutation of deuterium (vinylcyclopropane rearrangement), these paths cannot be differentiated by an examination of these two rates. Obviously, path A, for which the rate of racemization is zero, and path B, for which the rate of transmutation of deuterium is zero, are easily distinguishable from each other and from paths C and D.

Mutatio interrupta introduces a sufficiently sharpened view into the reaction to permit distinction among these four mechanistic paths. Interruption of the reaction short of complete racemization offers the opportunity to isolate enantiomeric molecules which in principle, have suffered only one inversion of configuration (in reality some will have suffered more than one inversion to a degree determined by the extent of reaction before interruption). The extent of rearrangement in the enantiomeric molecules will be reflected in the transmutation of deuterium, for the detection of which a suitable method must be presupposed. In respect of the rate of enantiomerization and the rate of transmutation of deuterium within enantiomerized molecules, paths C and D now become distinguishable, while paths A and B remain as easily distinguishable as before. Under the operation of path C the rate of enantiomerization should equal the rate of transmutation of deuterium, whereas under the operation of path D enantiomerization should be twice as fast as transmutation of deuterium (within enantiomerized molecules).

Translated into the experimental terms of this investigation in which (-)-2,2,3-trideuterio- Δ^3 -thujene [I_u^- :(-)-2,2,3-triD] serves as the subject, path C would lead to the (+) enantiomer of Δ^3 -thujene in which all molecules were 5,6,6-trideuterio, whereas path D would lead to (+) which consisted half of 5,6,6-trideuterio and half of 2,2,3-trideuterio. Path A in this experiment would lead to (+)- Δ^3 -thujene consisting entirely of 2,2,3-trideuterio species, whereas path B would lead to no (+) enantiomer whatsoever.

Description of the experimental elements involved in the elaboration of the distinction among the four mechanistic hypotheses falls naturally into four parts; (a) the transformation of naturally occurring isothujone to (-)- Δ^3 -thujene and of (-)- Δ^3 -thujene to isothujyl hydrogen phthalate; (b) the preparation of *rac*- Δ^3 -thujene, conversion to *rac*-isothujyl hydrogen phthalate and its resolution, as an indirect means of separating the enantiomeric Δ^3 -thujenes; (c) the preparation of (-)-trideuterio- Δ^3 -thujene and trideuterio-isothujyl hydrogen phthalate, and the identification in the NMR spectrum of the various types of hydrogen atoms germane

to the quantitative assessment of the occurrence of the vinylcyclopropane rearrangement; and (d) analysis of the products of the thermoreaction in the liquid phase and the gas phase of (–)-trideuterio- Δ^3 -thujene.

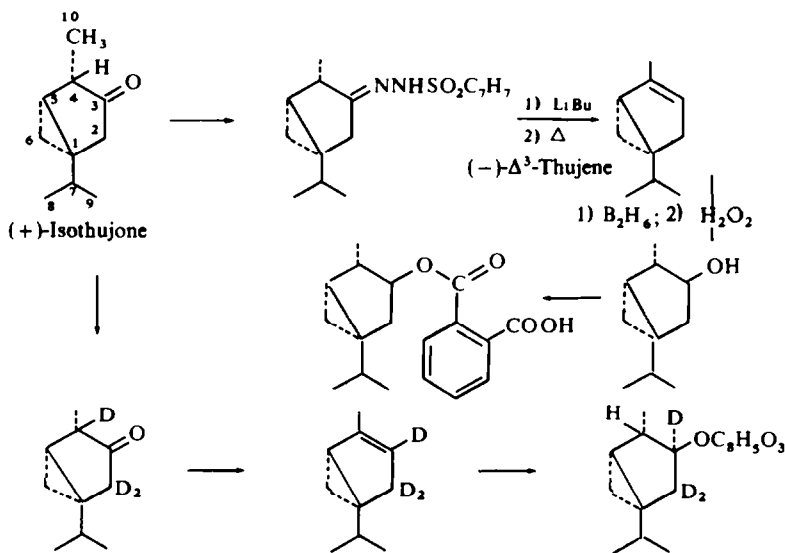


FIG 4. Conversion of (+)-isothujone to (–)- Δ^3 -2,2,3-trideuteriothujene

The starting material is a mixture of (–)-thujone and its C_4 -epimer, (+)-isothujone, obtained from oil of tansy (*Tanacetum vulgare L.*) by fractional distillation. The absolute configuration, though not essential to this work, is based on the relationship of (–)-thujone to (–)-homothujadicarboxylic acid, of (–)-umbellulone to (+)-homothujadicarboxylic acid, and on the transformation of (–)-umbellulone to (+)-2-isopropyl-2-methylsuccinic acid, the absolute configuration of which is now established by crystallographic analysis.⁵⁸ The relationship of the C_1 isopropyl group to the C_4 Me group is based on the interpretation of coupling constants between the C_5 cyclopropane H atom and the C_4 tertiary H atom.^{59, 60, 61} Those derivatives in which the coupling is close to zero have a dihedral angle close to 90° and therefore have the C_1 isopropyl and C_4 Me groups *cis*. (+)-Isothujone is thus taken to be (1*S*)-isopropyl-4(*S*)-methylbicyclo[3.1.0]heptan-3-one.

For the conversion of the thujones to Δ^3 -thujene, the method of thermal decomposition *in vacuo* of the dried lithium salt of the *p*-tosylsulfonylhydrazone is employed.^{62, 63} Although the pure *p*-tosylsulfonylhydrazone of (+) isothujone can be obtained by fractional crystallization, the mixture of hydrazones is satisfactory for conversion to a mixture consisting of (–)- Δ^3 -thujene (85%) and the two Δ^2 -thujenes (15%). The separation, characterization, structural assignment and analysis of the thermoreaction of the Δ^2 -thujenes has been accomplished, but will not be described in this paper. Pure Δ^3 -thujene can be obtained either by VPC or by fractional distillation in a micro spinning band column. The specific rotation is somewhat higher than any previously recorded value.^{54, 60} The temperature required for

decomposition of the lithium salts (160°) is so much lower than the 200°-temperature required for slow racemization (or deuterium migration)⁵⁴ that the Δ^3 -thujene may be safely assumed to be uncontaminated by products of thermoreaction. As a method of preparation of (-)- Δ^3 -thujene, the present sequence is superior to the method of Tschugaev and Fomin,^{54, 64, 65} in being less tedious and affording yields of 65% of theory instead of 8%.

The present investigation requires that partially racemized thujene or a suitable derivative be resolvable in order to permit estimation of the extent of transmutation of deuterium in enantiomerized Δ^3 -thujene. Although any one of the four thujyl alcohols⁵⁹ would have served, it had to be obtainable from Δ^3 -thujene by a procedure which would not jeopardize either optical purity or the integrity of carbon-hydrogen bonds. Such a method is the hydroboration-oxidation of Brown.^{66, 67} It has been

TABLE 1. NMR SPECTRA OF (+)-ISOTHUJYL AND (+)-2,2,3-TRIDEUTERIOISOTHUJYL HYDROGEN PHTHALATE

| Type | Quality | δ (ppm) | J (Hz) | Relative areas | | |
|-------------------------|-------------------------|----------------|--|--------------------|------------------------|------------------------|
| | | | | (+)-Tri H | (+)-Tri D ^a | (+)-Tri D ^b |
| COOH | singlet | 12.56 | — | 1.0 | | |
| Arom. | multiplet | 8.0-7.25 | — | 4.0 | | |
| H ₃ | quartet | 4.63 | 8.1 ^c | 1.0 | 0.28 ₀ | 0.06 ₂ |
| H ₄ | unres | 2.40 | 10-CH ₃ : 6.7 ^d H ₃ : 8.0 ^f | (1.0) ^e | (1.10) ^g | (1.04) ^g |
| 10-CH ₃ | doublet | 1.12 | H ₄ : 6.7 ^d | (3.0) ^h | " | " |
| H ₂ α | pr doublet | 2.42 | H ₃ : 7.5 ^f H ₂ β : 12.5 | (1.0) ^e | (1.10) ^g | (1.04) ^g |
| H ₂ β | pr doublet ^h | 1.75 | H ₃ : 8.0 | 1.0 | 0.21 ₃ | 0.16 ₈ |
| H ₆ β | | | | | | |
| H ₆ α | multiplet | 0.41-0.08 | H ₂ β : 1.0 ^h | 2.0 | 2.0 | 2.0 |
| 8-CH ₃ | triplet ⁱ | 0.82 | H ₇ : 6.9 | " | " | " |
| 9-CH ₃ | | | H ₇ : 6.9 | | | |
| H ₇ | heptet ^j | 1.32 | 8-CH ₃ : 7.0 9-CH ₃ : 7.0 | " | " | " |
| H ₅ | | | | " | " | " |

^a Refers to the sample derived from the sample of Δ^3 -thujene used in the gas-phase thermoreaction.

^b Refers to the sample derived from the sample of Δ^3 -thujene used in the liquid-phase thermoreaction

^c Coupling constants of H₃ to H₂ α , H₂ β and H₄ are all about equal (possible only for boat conformation⁵⁹)

^d Saturation at 498 upfield from benzene (at $\delta = 2.37$ ppm) converts the H₁₀ doublet ($J = 6.7$ c/s) to a singlet. This behavior identifies the three H₁₀ and assigns H₄ to the region 2.62-2.29 ppm

^e The relative areas of H₂ α and H₄ are measured together

^f The same saturation converts the H₃ quartet to a doublet by removal of coupling with two hydrogen atoms, H₄ and H₂ α . These atoms must have had about the same coupling constants with H₃ as H₂ β which remains coupled ($J = 8.0$ c/s). Irradiation at 1.75 ppm converts the H₃ quartet to a broad triplet ($J \sim 8.0$ c/s)

^g H₃ lies under the 8, 9 and 10-Me groups; the area of these groups and H₇ are measured together (combined area = 11)

^h The pair of doublets at 1.75 ppm is broader than the pair of doublets at 2.42. This type of long-range coupling is characteristic of interaction through a "W-conformation" in rigid bicyclic systems,^{59, 70} and constitutes one basis for assigning the absorption at 1.75 ppm to H₂ β (coupled to H₆ β).^{59, 61} The same difference in chemical shift between H₂ α and H₂ β (+0.67 ppm) parallels that shown in isothujyl alcohol (0.46),⁵⁹ (+)-benzoylisothujyl amine (0.66),⁷¹ and *trans*-bicyclo-[3.1.0]hexan-3-ol (0.44)⁷²

ⁱ These diastereoscopic methyl groups present a fortuitous triplet since they would present a pair of doublets (centered at $\delta = 0.785$ and 0.855 ppm) were it not that coupling constants with H₇ were both 6.9 c/s

^j H₇ is a potential heptet, of which six arms are visible ($J = 7.0$ c/s)

applied to $(-)\Delta^3$ -thujene by Ohloff *et al.*⁶⁰ and independently by us to yield $(+)\text{-isothujyl}$ alcohol essentially free of the other three alcohols. On the assumption that steric interference between the entering diborane and the methylene group of the cyclopropane ring controls the choice of addition (and the further assumption that addition is *cis* and oxidation proceeds with retention of configuration),⁶⁸ Ohloff *et al.*⁶⁰ have considered this result to confirm the stereochemistry assigned to $(+)\text{-isothujyl}$ alcohol by Bergqvist and Norin.⁵⁹

Conversion of $(+)\text{-isothujyl}$ alcohol to $(+)\text{-isothujyl}$ hydrogen phthalate involved reaction with one equivalent of *n*-butyllithium and treatment with phthalic anhydride. The half ester was obtained in good yield and, when recrystallized to constant properties, had $[\alpha]_D^{21} + 86.1 \pm 0.8^\circ$ and mp 117° .

Racemic Δ^3 -thujene was obtained by the thermoracemization of $(-)\Delta^3$ -thujene as uncovered by Doering and Lambert.⁵⁴ The procedure was adapted to a preparatively more convenient form by changing to a continuous flow system at 500° . For resolution, this material was converted to *rac*- isothujyl hydrogen phthalate by the three-step procedure outline above.

The resolution of racemic hydrogen phthalate is effected in two stages. The dextrorotatory isomer (isoconfigurational with $(-)\Delta^3$ -thujene) is separated by fractional crystallization of the cinchonine salt from ethanol. After five crystallizations, $(+)\text{-isothujyl}$ hydrogen phthalate within 97% of optical purity may be recovered. This material can be further enhanced by crystallization from chloroform-carbon tetrachloride. The levorotatory isomer is obtained by fractional crystallization of the strychnine salt. After three recrystallizations, regenerated $(-)\text{-isothujyl}$ hydrogen phthalate is 82% of optical purity and can be brought to purity by direct crystallization.

Deuteriated $(-)\Delta^3$ -thujene is prepared from the equilibrium mixture of 2,2,4-trideuteriated $(+)\text{-isothujone}$ (2 pts) and $(-)\text{-thujone}$ (1 pt) obtained by base-catalyzed exchange from thujone. It is assumed, although without experimental confirmation, that all three positions, 2α , 2β , 4β (in *isothujone*) and 4α (in *thujone*) are deuteriated to the same degree. In the ultimate analysis of the extent of rearrangement in enantiomerized material, the labelling is treated as the sum of deuterium atoms in the three positions and the validity of the mechanistic interpretation does not depend on deviations in deuterium content between individual C atoms.

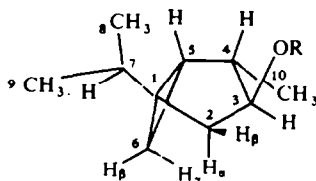
Quantitative analysis of the distribution of deuterium in samples of deuteriated Δ^3 -thujene is not made directly, but in samples of the corresponding *isothujyl* hydrogen phthalate. It is implicitly assumed that one of the steps in this conversion jeopardizes deuterium located at positions 2 and 3 or at positions 5 and 6.

Inspection of the NMR spectra of $(+)\text{-isothujyl}$ hydrogen phthalate and $(+)\text{-2,2,3-trideuterio-isothujyl}$ hydrogen phthalate allows the identification of most of the hydrogen atoms. The analysis of the spectra is given in abbreviated form in Table 1 and the actual spectra are reproduced in the experimental section.

For purposes of quantitative analysis, the NMR spectrum of undeuteriated *isothujyl* hydrogen phthalate reveals five easily distinguishable sets of hydrogen atoms (the aromatic hydrogen atoms being ignored). H_3 is centered at 4.65 ppm (identified as 3 in Table 2) and is assigned the range 4.89 to 4.41 ppm for the purposes of quantitative integration of area. H_4 and $H_{2\alpha}$ are found together at 2.4 ppm ($4 + 2\alpha$, from 2.62 to 2.14 ppm). The H atom β at C_2 (2β) is centered at 1.75 ppm

(1.91 to 1.57 ppm). For the purposes of integration, the eleven protons, H_5 , H_7 , $3H_8$, $3H_9$ and $3H_{10}$, are lumped together (Σ) and are assigned to the range 1.57 to 0.42 ppm. Finally, two hydrogen atoms, $H_{6\alpha}$ and $H_{6\beta}$ ($6\alpha + 6\beta$) are found between 0.42 and 0.04 ppm. From repeated integrations, it is clear that the relative areas do not have precisely integral ratios. These deviations are acknowledged in the form of correction factors and are applied later in the analyses of deuteriated specimens.

Thermoreaction of (-)-2,2,3-trideuterio- Δ^3 -thujene (I_{10}^- :(-)-2,2,3-triD) was effected in tetraglyme at 240° for 196 min and in a flow system at 485°, and resulted



in recovery of partially racemized samples of Δ^3 -thujene. These samples were converted to hydrogen phthalate and resolved into optically pure samples corresponding in sign of rotation to starting material and enantiomer. Analysis of the NMR traces of hydrogen phthalate of isothujyl alcohol for distribution of deuterium was effected by two independent operators.* The results are shown in Tables 3 and 4.

The relative areas of the five easily identifiable types of hydrogen were first corrected for deviations from the theoretical ratio by the correction factors revealed in the quantitative analysis of a sample containing no deuterium (Table 2). The relative areas of protons of types Σ and $6\alpha + 6\beta$ were combined and equated to 13.000 on the assumption that no deuterium had been introduced into these positions in the

TABLE 2. RELATIVE AREAS OF PROTONS IN THE NMR SPECTRUM OF UNDEUTERIATED ISOTHUJYL HYDROGEN PHTHALATE

| H | Sum | Average | σ^a | Fraction | No. of Protons ^b | Corr. Factor | σ^c |
|------------------------|---------------------|------------------------|------------|----------|-----------------------------|--------------|------------|
| 3 | 1138 ^c | 81.28 | 3.3 | 0.0528 | 0.898 | 1.113 | 0.047 |
| 4 + 2 α | 3376 ^d | 171.64 | 6.8 | 0.1116 | 1.897 | 1.054 | 0.049 |
| 2 β | 1911 ^d | 86.86 | 6.1 | 0.0565 | 0.960 | 1.042 | 0.074 |
| Σ^e | 22,359 ^e | 1016.32 | 9.2 | 0.6607 | 11.232 | 0.979 | 0.014 |
| 6 α + 6 β | 4007 ^d | 182.14 | 11.8 | 0.1184 | 2.013 | 0.994 | 0.065 |
| | | (1538.24) ^f | (17.7) | (1.0000) | (17.000) | | |

^a Standard deviation

^b Normalized to 17 hydrogen atoms. Aromatic hydrogen atoms are omitted from this analysis

^c The sum in arbitrary units of one set of six and one set of eight measurements of relative intensity

^d The sum in arbitrary units of one set of six and two sets of eight measurements of relative intensity

^e Σ is a combined measure of the areas of the three methyl groups (8, 9 and 10), H_3 and H_7 (combined relative area = 11)

^f Area for one proton: $1538.24/17 = 90.484 \pm 1.03$

* Our deep appreciation is expressed to Professor M. R. Willcott III, University of Houston, for his invaluable assistance in obtaining measurements of relative area of high precision.

TABLE 3. REORGANIZATION OF (-)-2,2,3-TRIDEUTERIO- Δ^3 -THUJENE IN TETRAGLYME AT 240° FOR 196 MIN

| Type of H | Relative area | Corrected rel. area | No. of H atoms | Sums of H atoms |
|---|---------------|----------------------|---------------------|-----------------|
| Part 1. Distribution of Deuterium in Original Stereoisomer | | | | |
| 3 | 0.50 ± 0.26 | 0.557 | 0.026 ^a | 1.274 |
| 4 + 2 α | 8.90 ± 0.36 | 9.384 | 1.044 ^a | |
| 2 β | 1.45 ± 0.30 | 1.510 | 0.168 ^a | |
| Σ | 99.97 ± 0.30 | 97.906 | 10.888 | 13.000 |
| 6 α + 6 β | 19.11 ± 0.23 | 18.988 | 2.112 | |
| | | 128.345 | | 14.274 |
| Part 2. Distribution of Deuterium in Recovered (-) Enantiomer | | | | |
| 3 | 1.44 ± 0.32 | 1.603 | 0.178 ^b | 1.575 |
| 4 + 2 α | 9.99 ± 0.34 | 10.533 | 0.167 ^b | |
| 2 β | 1.99 ± 0.37 | 2.073 | 0.230 ^b | |
| Σ | 100.00 ± 0.36 | 97.935 | 10.852 ^b | 12.699 |
| 6 α + 6 β | 16.78 ± 0.29 | 16.673 | 1.847 ^b | |
| | | [*] 128.817 | 14.274 | |
| Part 3. Distribution of Deuterium in (+) Enantiomer | | | | |
| 3 | 6.03 ± 0.29 | 6.713 | 0.746 | 3.282 |
| 4 + 2 α | 14.90 ± 0.51 | 15.710 | 1.747 | |
| 2 β | 6.81 ± 0.32 | 7.094 | 0.789 | |
| Σ | 94.07 ± 0.65 | 92.128 | 10.243 | 10.992 |
| 6 α + 6 β | 6.78 ± 0.26 | 6.737 | 0.749 | |
| | | 128.382 | 14.274 | |

^a Corrected relative area divided by 8.992, the area for one proton (116.89/13)

^b The product of the corrected relative area and the total number of H atoms (14.274) divided by the sum of corrected relative areas over all H atoms

preparation of the samples of starting material. The number of protons in positions 3, 4 + 2 α and 2 β was then calculated (Tables 3 and 4). The difference between 17.000 and the sum of all protons in each sample of the starting original stereoisomer represents the amount of deuterium distributed among positions 3, 4 + 2 α and 2 β and the maximum number of deuterium atoms that can be transmuted to positions Σ and 6 α + 6 β during racemization.

The distribution of hydrogen and hence of deuterium in the samples of recovered stereoisomer of original configuration and of enantiomer recovered from partial racemization is calculated from the corrected relative areas by multiplying the fraction of hydrogen in each position by the total number of hydrogen atoms present in the starting material (Tables 3 and 4). The assumption underlying this operation is validated by the observation that no change in mass spectral pattern results from heating a mixture of non-deuteriated and trideuteriated Δ^3 -thujene. The extent of rearrangement is given by the ratio of the number of hydrogen atoms migrated into positions 2 and 3 (3, 4 + 2 α , and 2 β and the maximum number that could have

TABLE 4. REORGANIZATION OF (-)-2,2,3-TRIDEUTERIO- Δ^3 -THUJENE IN A GAS-PHASE FLOW SYSTEM AT 485°

| Type of H | Relative area | Corrected rel. area | No. of H atoms | Sums of H atoms |
|--|---------------|---------------------|---------------------|-----------------|
| Part 1. Distribution of Deuterium in Original Stereoisomer | | | | |
| 3 | 2.22 ± 0.29 | 2.471 | 0.282 ^a | 1.595 |
| 4 + 2 α | 9.12 ± 0.28 | 9.616 | 1.098 ^a | |
| 2 β | 1.80 ± 0.36 | 1.875 | 0.214 ^a | |
| Σ | 97.10 ± 0.55 | 95.095 | 10.861 | 13.000 |
| 6 α + 6 β | 18.85 ± 0.36 | 18.730 | 2.139 | |
| | | 126.787 | | 14.595 |
| Part 2. Distribution of Deuterium in Recovered Stereoisomer | | | | |
| 3 | 3.26 ± 0.24 | 3.629 | 0.409 ^b | 1.933 |
| 4 + 2 α | 10.64 ± 0.32 | 11.219 | 1.264 ^b | |
| 2 β | 2.21 ± 0.36 | 2.302 | 0.259 ^b | |
| Σ | 97.40 ± 0.92 | 95.389 | 10.751 ^b | 12.662 |
| 6 α + 6 β | 17.06 ± 0.64 | 16.951 | 1.911 ^b | |
| | | 129.490 | 14.595 | |
| Part 3. Distribution of Deuterium in Enantiomer | | | | |
| 3 | 6.05 ± 0.42 | 6.735 | 0.759 ^b | 3.049 |
| 4 + 2 α | 13.84 ± 0.28 | 14.593 | 1.645 ^b | |
| 2 β | 5.48 ± 0.30 | 5.708 | 0.644 ^b | |
| Σ | 93.90 ± 1.08 | 91.961 | 10.370 ^b | 11.546 |
| 6 α + 6 β | 10.50 ± 0.57 | 10.433 | 1.177 ^b | |
| | | 129.430 | 14.595 | |

^a Corrected relative area divided by 8.756 the relative area for one proton (113.825/13)

^b The corrected relative area divided by the sum of the corrected relative areas multiplied by the total number of hydrogen atoms in the sample (14.595)

rearranged into these positions. The results are given in Table 5 and, for the reaction in the liquid phase, also in Fig 5.

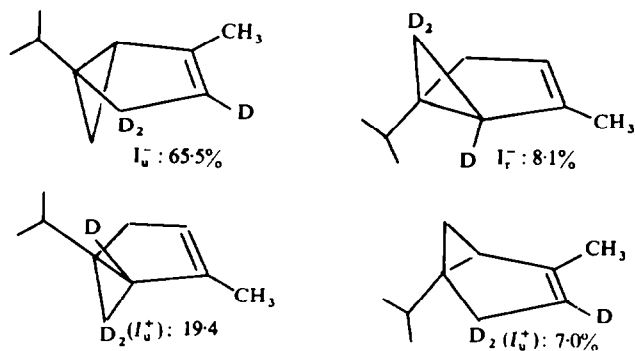


FIG 5. Composition of the four optically and isotopically distinguishable thujenes after rearrangement of I_w^- for 196 min at 240°

TABLE 5. DISTRIBUTION OF OPTICAL ACTIVITY AND DEUTERIUM IN THERMALLY PARTIALLY REORGANIZED (-)-2,2,3-TRIDEUTERIO- Δ^3 -THUJENE

| | I_u^- | I_r^- | I_r^+ | I_u^+ |
|---|-------------|--------------------|-------------|--------------------|
| Part 1. From Solution (Tetraglyme) at 240° for 196 min ($\alpha_{\text{obs}}/\alpha_0 = 0.473$) | | | | |
| Opt. Activity ^a | | 0.736 ₅ | | 0.263 ₅ |
| Rearr. H ^b | | 0.301 | | 2.008 |
| Fraction ^c | 0.890 | 0.110 | 0.737 | 0.263 |
| Composition ^d | 65.48 ± 3.1 | 8.12 ± 1.3 | 19.44 ± 3.1 | 6.96 ± 1.3 |
| Part 2. From Gas-Phase Flow System at 485° ($\alpha_{\text{obs}}/\alpha_0 = 0.252$) | | | | |
| Opt. Activity ^a | | 0.626 | | 0.374 |
| Rearr. H ^b | | 0.338 | | 1.454 |
| Fraction ^c | 0.859 | 0.141 | 0.604 | 0.396 |
| Composition ^d | 53.80 ± 3.2 | 8.80 ± 2.0 | 22.61 ± 3.2 | 14.79 ± 2.0 |

^a Fraction of original (-) enantiomer [$0.5(1 + \alpha_{\text{obs}}/\alpha_0)$] and (+) enantiomer [$0.5(1 - \alpha_{\text{obs}}/\alpha_0)$]

^b The difference between the sum of the hydrogen atoms in positions 3, 4 + 2 α and 2 β in the starting material (Tables 3 and 4, Parts 1) and the similar sum in the recovered (-) stereoisomer (Tables 3 and 4, Parts 2) and the (+) enantiomer (Tables 3 and 4, Parts 3), obtained by resolution of the hydrogen phthalates of the derived isothujyl alcohol.

^c The fraction of rearranged materials, I_r^- and I_r^+ , is given by dividing the preceding quantity, the extent of rearrangement, by the maximum possible amount of rearrangement, which is given by subtracting the sum of the hydrogen atoms in positions 3, 4 + 2 α , and 2 β in the starting material (Tables 3 and 4, Parts 1) from 4.0000. The fraction of unrearranged materials is then given by $I_u^- = 1 - I_r^-$ and $I_u^+ = 1 - I_r^+$

^d The composition of the recovered Δ^3 -thujene is given in percent as the product of the fraction of each enantiomer (Opt. Activity) and the fraction of rearranged product in each enantiomer (Fraction)

Three of the possible mechanisms considered in the introduction can be rejected quickly. Path A (Fig 1) is the only mechanism which is allowed to be concerted according to analysis of the symmetry of orbitals.⁷³ The product expected from the operation of this mechanism, I_u^+ , is the least favoured and is formed in approximately the same amount as the non-allowed product, I_r^- , and in far smaller amount than the likewise non-allowed product, I_r^+ . It is concluded that the rearrangement of Δ^3 -thujene is not controlled by the operation of orbital symmetry and is not concerted.

The failure of the concerted mechanism A to operate is explained by the assumption that the two distances $r_{1,5}$ and $r_{1,3}$ (Fig 1) become equal. When this equality is achieved there is precisely zero-bonding between the allylic radical and the electron on C₁, control by orbital symmetry vanishes and concert is excluded as a factor in the reaction. In the intramolecular vinylcyclopropane rearrangement of Δ^3 -thujene, the free energy of a zero-bonded symmetrical intermediate (distances $r_{1,3} = r_{1,5}$ in Fig 1) is lower than the free energy of any of the unsymmetrical transition states in which $r_{1,5}$ would remain smaller than $r_{1,3}$ and the favored product would be I_u^+ . Apparently the rate at which bonding increases as the 1,5-distance is shortened never outweighs the strain energy with which the shortening must be purchased.

Path B would have led to the production of I_r^- (Fig 2), had no theoretical foundation

and is as little preferred in fact as is the orbitally symmetrically allowed path A. Experimentally the products of these two paths are formed in essentially equal and minor amounts.

The third path, C (Fig 2), is limited to a non-planar state; forbidden by the symmetry of the orbitals from showing the effects of concert; chiral in regard of the three deuterium atoms; achiral in disregard of them; isoconformational with the starting material I_u^- ; able to reproduce I_u^- or to produce I_r^+ ; and unable to generate the anticonformational isomers I_r^- and I_u^+ . In the event, I_r^+ , the product anticipated of path C, is favored but not to the exclusion of I_r^- and I_u^+ .

Path D required the production of I_u^+ and I_r^+ (and I_u^- and I_r^-) in equal amount. Inspection of Table 5 reveals that I_r^+ , the product of enantiomerization with rearrangement, is favored by a factor of three over I_u^+ . Thus, path D also fails to provide a satisfactory mechanistic description of the thermoreaction of Δ^3 -thujene.

Path D can be more closely related to path C than might first appear, if there is imagined an infinite set of mechanisms constituting the combination of two processes in varying proportion. One process is identical with path C and involves an isoconformational intermediate having an equal chance of returning invisibly to starting material, I_u^- , or by proceeding visibly to I_r^+ . The other involves an anticonformational intermediate having an equal chance of producing I_r^- or I_u^+ . Path D can then be described as the situation in which the rates or Gibbs free energies of activation of each of these two processes are equal. It can be described equally well in terms of the direct formation of a planar intermediate or in terms of the initial formation of the isoconformational intermediate (path C) which passes over a planar transition state to the anticonformational intermediate significantly faster than it closes to I_u^- , and I_r^+ .

Between the extremes of paths C and D, intermediate situations can be visualized in which the rate of closure of the isoconformational intermediate to I_u^- and I_r^+ is comparable to the rate of passage to the anticonformational intermediate from which I_r^- and I_u^+ are obtainable. Experimentally these intermediate situations would be characterized by formation of I_r^- and I_u^+ in equal amount and of I_r^+ in a ratio* to $I_r^- + I_u^+$ which could vary from infinity (Path C) when the ratio of closure to conformational inversion is very high to 1 (Path D) when the ratio of closure to conformational inversion is very low.†

The experimental results, particularly those from the rearrangement in the liquid phase at lower temperature, can be accommodated in terms of such an intermediate picture. The opening of the ring in I_u^- should be more easily effected with retention of conformation and would give rise to the isoconformational intermediate, which could close to I_r^+ and, in equal amount, to I_u^- somewhat faster than it underwent conformational inversion to the anticonformational intermediate, which, for its part, could close to I_r^- and I_u^+ in equal amount. In this picture conformational remembrance is the factor controlling the stereochemistry of the rearrangement.

In order better to approximate the true ratio of products isoconformational with

* In this mechanism, the isoconformational intermediate is hypothesized to give equal amounts of I_r^+ and the unobservable I_u^- .

† In the modification in which I_u^- proceeds by two distinct transition states to the isoconformational and anticonformational intermediates a new result is imaginable. If the rate of formation of the latter were much greater than the former, I_r^- and I_u^+ would be the products unaccompanied by I_r^+ ; i.e., the ratio of $2 I_r^+$ to $I_r^- + I_u^+$ would be zero.

the starting material (I_u^-) to anticonformational products (I_r^- and I_u^+), a correction can be made on the basis of the hypothesis that each product reacts with the same rate constant and according to the same pattern as did the starting material.

The first order rate constant of reaction is given the relative value, $k + 2$, where k is the relative rate constant for formation of the favored isoconformational congener and 1 is the relative rate constant for the formation of either of the anticonformational congeners. In the first round of the reaction, I_u^- produces I_r^+ , I_r^- and I_u^+ in the ratio $k:1:1$; in the second round of reaction, molecules which have already reacted once react a second time according to the same pattern and in amount proportional to the relative rate at which they had been formed in the first round. In this way, a table of the relative amounts of molecules which have reacted once, twice, and three times can be constructed (Table 6).

TABLE 6. STATISTICAL DISTRIBUTION OF THUJENES AS A FUNCTION OF THE NUMBER OF REARRANGEMENTS

| Isomer | Number of Rearrangements | | | |
|---------|--------------------------|-----------|-------------|-------------|
| | 0 | 1 | 2 | 3 |
| I_u^- | A_0 | 0 | $k^2 + 2$ | $6k$ |
| I_r^+ | 0 | k | 2 | $k^3 + 6k$ |
| I_r^- | 0 | 1 | $2k$ | $3k^2 + 4$ |
| I_u^+ | 0 | 1 | $2k$ | $3k^2 + 4$ |
| Sums | A_0 | $(k + 2)$ | $(k + 2)^2$ | $(k + 2)^3$ |

Since the reaction can be considered as a sequence of simple first order reactions of the type, $X_0 \xrightarrow{r} X_1 \xrightarrow{r} X_2 \xrightarrow{r} X_3 \xrightarrow{r} X_4 \xrightarrow{r} \dots$, with the specific rate constant r being applicable to all species (if the secondary effect of the deuterium isotopes is ignored), the instantaneous concentration of species which have reacted $i = 1, 2, 3 \dots$ times is given by $X_i(t) = (rt)^i (e^{-rt}) / (i!)$ and the relative concentrations at time t by $X_0(t)/X_0(t) = 1$; $X_1(t)/X_0(t) = (rt)$; $X_2(t)/X_0(t) = (rt)^2 / (2!)$; and $X_3(t)/X_0(t) = (rt)^3 / (3!)$.⁷⁴ The combination of the statistical distribution in Table 6 and these equations allows the calculation of the distribution and total amounts of I_u^- , I_r^+ , I_r^- and I_u^+ for any value of k and (rt) , provided rt , the extent of reaction, is small enough to tolerate neglect of species which have reacted more than three times.*

It was decided to solve for k and (rt) from two equations representing the fraction of enantiomeric material produced ($I_r^+ + I_u^+$) and the ratio of isoconformational products ($2 I_r^+$) to anticonformational products ($I_r^- + I_u^+$). Other mixes of the experimental data could have been selected. For each equation, a set of solutions was determined by numerical calculation and plotted. The intersection of the two sets occurred at a large angle and fixed k and (rt) . The refinements were carried to give arithmetic reliability to the third decimal.

$$I_r^+ + I_u^+ = (1 - \alpha)/2 = (k + 1) e^{-rt} [(rt)/(k + 2) + (rt)^2/(k + 2)^2 + (k^2 + 2k + 4)(rt)^3/3!(k + 2)^3] \text{ and}$$

$$0 = (k - c)(k + 2)^2 (rt) + 2(k + 2)(1 - kc)(rt)^2/2! + (k^3 - 3ck^2 + 6k - 4c)(rt)^3/3! \\ \text{where } c = 2I_r^+ / (I_r^- + I_u^+).$$

* The two experiments in this work were interrupted early enough so that 99.9% of the species in the liquid phase reaction have reacted three times or fewer and 98.8% in the gas-phase reaction.

The results of the correction for molecules reacting more than once are shown in Table 7. The magnitude of the correction is less for the reaction in the liquid phase, which had not proceeded as far before interruption as had the gas phase reaction. Compare the fraction of enantiomeric molecules [(+) column of Table 7] or the extent of reaction, *rt*. In both liquid and gas phase, the ratio of products which retain the conformation of the starting material to those in which the conformation has been inverted, is about 3 (column *k* of Table 7).

In view of the sizeable experimental error in both reactions, but particularly in the gas-phase reaction (compare the found and calculated concentrations of I_u^- , I_r^- , I_r^+ and I_u^+ in Table 7), little quantitative significance can be attributed to the calculated difference in activation energy, $\Delta\Delta E_a = 0.5$ kcal/mole, between the iso- and anti-conformational processes (C_{iso}/C_{anti} of Table 7). The calculated difference in the Gibbs free energy of activation of the two processes in the liquid phase reaction ($\Delta\Delta G_a = 1.2$ kcal/mole) is appropriate to the hypothesized conformational change which involves the planar hexagonal geometry as transition state. The increase of 22° [$2(120^\circ - 109^\circ)$] of angle is not large when spread over six bond angles, and its effect may be attenuated in part by the removal of eclipsing between the two pairs of pseudoequatorial H atoms and the adjacent H atoms of the allylic radical (Fig 3).

TABLE 7. CALCULATED AND OBSERVED VALUES OF CONFORMATIONAL INVERSION IN THE THERMOREACTION OF (-)-2,2,3-TRIDEUTERIO- Δ^3 -THUJENE (I_u^-)

| | | (+) ^a | C_{iso}/C_{anti} ^b | I_u^- | I_r^- | I_r^+ | I_u^+ | <i>k</i> | (<i>rt</i>) |
|------------------------|--------------|------------------|---------------------------------|---------|---------|---------|---------|----------|---------------|
| Liquid Phase 513° K | <i>Found</i> | 0.2635 | 2.579 | 0.6548 | 0.0812 | 0.1944 | 0.0696 | 3.282 | 0.464 |
| | <i>Calc.</i> | 0.2633 | 2.595 | 0.6634 | 0.0732 | 0.1902 | 0.0732 | | |
| Gas Phase 758° K | <i>Found</i> | 0.374 | 1.917 | 0.5380 | 0.0880 | 0.2261 | 0.1479 | 2.817 | 0.897 |
| | <i>Calc.</i> | 0.373 | 1.916 | 0.4988 | 0.1280 | 0.2452 | 0.1280 | | |

^a The fraction of (+) enantiomeric molecules (I_r^+ and I_u^+).

^b The ratio C_{iso}/C_{anti} is a measure of the ratio of products (2 I_r^+) having the same conformation as starting material (I_u^-) to products having the inverted conformation ($I_r^- + I_u^+$).

For the hypothetical Benson activation energy of 8.2 kcal/mole for the closure of trimethylene to cyclopropane⁷⁵ to operate in the ring closure of the intermediate, the activation energy of conformational interconversion would have to be 1.2 + 8.2 kcal/mole. Unrealistically high in our opinion for such a simple conformational change, this value is further increased by any reasonable estimation of the effect of the allylic resonance energy in the intermediate.

As a bicyclic vinylcyclopropane, Δ^3 -thujene is denied by structural restriction access to two other symmetry-allowed concerted pathways which are available to the more commonly encountered monocyclic vinylcyclopropanes. These are the suprafacial 1,3 shift with inversion of configuration of the migrating group and the antara-

facial shift with retention of configuration. Consequently, monocyclic vinylcyclopropanes might react by a concerted mechanism even though this bicyclic vinylcyclopropane does not. Such a difference might be expected to manifest itself as a lower activation energy of rearrangement of the monocyclic congeners.

The activation parameters of racemization of Δ^3 -thujene have been determined in the gas-phase in the pressure range of 1–3 mm:

$$\log k(\text{sec}^{-1}) = 14.33 \pm 0.24 - (43.41 \pm 0.54)/2.303RT$$

$$\text{whence } \Delta H^\ddagger = 42.40 \pm 0.54 \text{ kcal/mole and } \Delta S_{226}^\ddagger + 3.02 \pm 1.09 \text{ kcal/deg mole}$$

These values may be compared with the results of the numerous studies mentioned in the introduction, in which E_a ranges between 49–51 kcal/mole and $\log A$ from 13.5–14.3. The origin of the higher temperature ($\sim 300^\circ$ and above) required by these monocyclic vinylcyclopropane lies in the enthalpy of activation not in the entropy. It is obvious that the theoretical availability of concert is not exploited by the monocyclic congeners in such a manner as to reveal itself as a lower energy of activation.

Rationalization of the lowering may be found in the higher degree of substitution of the radicals: the unstabilized radical is tertiary instead of primary or secondary as it is in the monocyclic reference compounds; the allylic moiety is no longer secondary-primary but secondary-secondary. Perhaps more important is the partial release of an incremental strain associated with the cyclopentene ring (+6.8 kcal/mole).⁷⁶ Although some of this strain is owing to non-bonded repulsions and must vanish as one pair in each ring is absorbed into the fusion of the two rings,* that which remains can contribute to the lowering of the activation energy, on the reasonable assumption that the opened diradical is essentially unstrained.

Δ^3 -Thujene provides an example of the caution which must be exercised in equating a lowered activation energy with concert. The satisfying of this criterion is necessary but not sufficient for inferring an element of concert in a reaction. The present example also illustrates the usefulness of Woodward–Hoffmann conservation of orbital symmetry as a criterion of concert: failure to follow the stereochemical course associated with conservation of orbital symmetry is a sufficient condition for excluding concert. The converse may not be true: the following of the predicted stereochemical course is a necessary, but not demonstrably sufficient, condition for the existence of a concert in a pathway of reaction.

The mechanism of the thermoreaction of Δ^3 -thujene is concisely expressed as the combination of two processes involving the opening of the three-membered ring to an intermediate consisting of two independent radicals. In the favored process the original conformation is preserved. In the competitive process the transition state includes conformational inversion along with the opening of the ring at the small extra cost of 1.2 kcal/mole. The characteristic of conformational remembrance owes its existence to this small increment in activation energy.

EXPERIMENTAL

IR spectra were taken on Perkin–Elmer spectrophotometers, models 421 and 337 (intensities are indicated by very strong, strong, medium, weak, and shoulder). NMR spectra were recorded on Varian Model

* The strain (33.5 kcal/mole) in bicyclo[3.1.0]hexane is less than the sum of the strain energies of the two rings (35 kcal/mole). This value for ΔH° (liquid), $+1.3 \pm 0.7$ kcal/mole, is to be compared with an earlier value of J. L. Wood, R. J. Lagow and J. L. Margrave, $+0.88 = 0.36$ kcal/mole.⁷⁸ Combined with the value of ΔH_{vap} (298°), ΔH_f° (gas, 298°) becomes $8.9 = 0.5$ kcal/mole.

A-60 and A-60A analytical spectrometers. Decoupling experiments were performed with a Model V-6058A spin decoupler. Chemical shifts are reported on the δ scale in ppm downfield from TMS. Melting points were taken in sealed capillaries with a modified Hershberg m.p. apparatus and are uncorrected. Rotations were measured with a Rudolf Model 200 Photoelectric Polarimeter, with a Bendix Ericsson Automatic Polarimeter and with a Perkin-Elmer 141 Polarimeter. Concentrations are given as grams of solute per ml of soln.

VPC analyses and separations were carried out on Aerograph Fractometers A-90 and Autoprep Model A-700 with the following columns:

Column A: 6m \times 1/4" 5% Carbowax 20 M on 60/80 mesh firebrick.

Column B: 6m \times 1/4" 20% 1,2,3-tris (2-cyanoethoxy)propane on 60/80 mesh Chromosorb P.

Column C: 5m \times 1/4" 5% diethyleneglycol succinate on 50/60 mesh ABS Super Support.

Column D: 4m \times 1/4" 15% Dow Silicon Fluid 710 on 60/80 mesh Chromosorb P.

Column E: 4m \times 1/4" 10% Carbowax 20M on 60/70 mesh Anakrom.

Mass spectral analyses were made with an AEI Model MS 9 double focussing mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(+)-*Isotujone* and (-)-*Thujone*. Tansy oil, obtained from Magnus, Mabee and Reynard, Inc., was distilled in a 40-cm, vacuum-jacketed Vigreux column at 29 mm. From 10 lbs tansy oil, there was obtained 1200 ml, bp $< 97^\circ$, 3090 ml of mixed thujones, bp $98-110^\circ$, and a 500-ml residue. Analysis of the major fraction by VPC on Column E at 105° indicated (-)-thujone (rel. ret. time 1.00) and (+)-isotujone (rel. ret. time 1.14) in a ratio of about 1:2. Both ketones were identified by comparison of NMR spectra with those reported by Bergvist and Norin.⁵⁹ (-)-Thujone showed $[\alpha]_D^{22} - 16.3^\circ$ (c, 0.00683; abs EtOH) [reported $(\alpha)_D - 19.94^\circ$ (neat),⁷⁹ $[\alpha]_D^{17.5} - 20.25^\circ$ neat,⁸⁰ $[\alpha]_D^{15} - 17.52^\circ$ (c, 1.1, EtOH),⁸⁰ $[\alpha]_D^{20} - 19.57^\circ$ (neat)⁵⁴ and $[\alpha]_D - 18.5^\circ$ (c, 1.3, CHCl₃)⁵⁹]. (+)-Isotujone showed $[\alpha]_D^{22} + 77.3^\circ$ (c, 0.01643, EtOH) [reported $[\alpha]_D^{15} + 72.46^\circ$ (neat),⁷⁹ $[\alpha]_D^{21} + 80.93^\circ$ (neat),⁸⁰ $[\alpha]_D + 86^\circ$ (c, 1.9, CHCl₃)⁵⁹ and $[\alpha]_D^{20} + 73.4^\circ$ (neat)⁶⁰].

At equilibrium, which has been established from both ketones, the ratio of (-)-thujone and (+)-isotujone is 1:2.^{79, 80} In our experience, a similar result is obtained when a sample of (-)-thujone is heated at 110° with 5 ml D₂O containing 0.5 g KOH. At various times, the ratio of (-)-thujone to (+)-isotujone is indicated: 0 hr - 8:1; 12 hr - 1:1; 19 hr - 2:3.

(+)-*Isotujone p-toluenesulfonylhydrazine*. Tosylhydrazine⁶² (198 g, 1.06 mole) and mixed thujones (230 ml) in 300 ml dry THF were refluxed for 2 hr. After being cooled to room temp, the yellowish soln was stirred with 25 g anhydrous MgSO₄ overnight. After filtration, the soln was warmed to 50° , and light petroleum (bp $35-58^\circ$) was added with stirring till the mixture became cloudy. Standing in the refrigerator overnight caused part of the hydrazone to crystallize. Further crops could be obtained from the concentrated mother liquor. Purification of this crude material by precipitation from its soln in THF gave 210 g of the tosylhydrazone of the mixed thujones pure enough for further experiments: m.p. $125-126^\circ$ (dec.).

Three recrystallizations of a small sample from EtOH gave pure (+)-isotujone tosylhydrazone as colorless needles: m.p. 136° (dec.); $[\alpha]_D^{19} + 166^\circ$ c, 0.043, MeOH); (Found: C, 63.6; H, 7.6; N, 8.9; S, 10.2. C₁₇H₂₄N₂O₂S requires: C, 63.7; H, 7.6; N, 8.7; S, 10.0%); ν_{\max}^{KBr} 3220 (vs. NH), 3015 (w) and 3050 (w) (arom CH), 2860-2980, 1665 (m, C=N), 1600 (m, C=C) cm⁻¹; NMR (CH₂Cl₂) δ 7.39 (2, d, $J = 9$ Hz) and 7.90 (2, d, $J = 9$ Hz) (aromatic); 2.50 (3, s, p-CH₃); 2.23 (2, AB system, $J = 20$ Hz, C₂-CH₂); 2.97 (1, quin, assigned to H₄ since spin decoupling (5.1 mG, $\Delta = -110$ Hz) causes collapse of C₁₀CH₃ [1.10 (3, d, $J = 6.5$ Hz)] to a singlet; -0.17 (1, pr of d, $J_{6a, 6\beta} = 5$ Hz, $J_{6a, 5\beta} = 4.5$ Hz; assigned H₆ α because *trans* coupling in cyclopropanes ($J = 2.6-5.6$ Hz) is less than *cis* ($J = 6.9-9.3$ Hz)⁶¹; 0.45 (1, pr of d, $J_{6\beta, 5\beta} = 8.2$ Hz; doublets, broadened by long-range coupling to H₂ β ^{59, 61} are sharpened in a sample of (+)-isotujone tosylhydrazone 90% deuteriated at C₂; assigned to H₆ β).

Dry lithium salt of thujone tosylhydrazone. The reaction was carried out in a 1-l., 3-necked flask equipped with reflux condenser and CaCl₂ tube, stirrer, and a straight vacuum take-off, the side arm of which was used as inlet for N₂ while its top was closed with a serum stopper. Mixed tosylhydrazones (159 g, 0.488 mole) were dissolved in 250 ml dry THF and introduced into the apparatus, through which a slow stream of N₂ was passed. One equivalent of 1.6 N n-BuLi in hexane was added through the serum cap, using a 50-ml syringe. The temp in the flask rose to boiling, n-butane was evolved, and by the end of the addition, which required about 40 min. part of the salt had precipitated necessitating vigorous stirring. Removal of solvent, first at water-aspirator vacuum and then by applying oil-pump vacuum, left a yellow-white solid which was pulverized under N₂ in the same flask but it did not seem to be hygroscopic and was handled in air for short periods. Stored under N₂ at room temp it was stable for weeks.

Δ^3 - and Δ^2 -Thujenes. A 1-l, 2-necked flask immersed in an oil bath (160°) was connected to a Dry-Ice cooled, 250-ml receiver-flask by a Claisen-type adapter with a vacuum outlet to the water aspirator. The second joint was connected to the 3-necked flask of the experiment above by a 150°-bent glass tubing having two male joints. The whole apparatus, which now contained the pulverized salt, was swept with N_2 (inlet at the 3-necked flask) and evacuated to 20 mm. A small portion (about 3 g) of the salt was transferred into the pyrolysis-flask by rotating elbow-tube and storage-flask appropriately. The pressure in the system rose to 40–50 mm during the decomposition and returned to its initial value when all salt had been pyrolysed. At this point the next portion was added. The mixture of thujenes distilled directly into the receiver flask during the pyrolysis which took about 4 hr. The collected liquid was filtered and distilled *in vacuo* through a 10-cm Vigreux column to give thujenes (bp 54–57°/25 mm) in 80–85% theoretical yield. VPC analysis showed the ratio of α -thujene to β -thujenes to be about 85:15. Only traces of higher and lower boiling impurities could be detected. Separation by distillation with a micro spinning band column gave 2.3 g of almost pure Δ^2 -thujenes (bp 146–147°/760 mm), 4.7 g of a mixture of the two Δ^2 -thujenes and Δ^3 -thujene (bp 148–152°/760 mm), 21.5 g of Δ^3 -thujene (bp 152–152.5°/760 mm) (99% of purity by VPC), and 4.0 g of higher-boiling compounds, including some *p*-cymene which had formed during the day-long refluxing. After further purification on column A (column temp: 70°, flow rate: 60 ml helium/min), Δ^3 -thujene had IR and NMR spectra⁵⁴ and mass spectrum⁸² identical with those reported. The specific rotation, $[\alpha]_D^{26} - 51.8^\circ$ (neat, $d_4^{26} 0.829$) was essentially the same as that reported for Δ^3 -thujene prepared by vacuum pyrolysis of the methylxanthate ester of thujylalcohols from LAH-reduction of oil of *thuja occidentalis* and purified by VPC: $[\alpha]_D^{26} - 45.7^\circ$ and, by Ohloff *et al.*,⁶⁰ $[\alpha]_D^{20} - 49.3^\circ$.

Hydroboration of (-)- Δ^3 -thujene. The procedure described for the hydroboration of norbornene⁶⁸ was followed and has recently been applied to Δ^3 -thujene.⁶⁰ A large excess (3–4 times) of diborane was generated externally and bubbled through a stirred soln of (-)- Δ^3 -thujene in THF at 0°. The reaction required 6 to 9 hr for completion. After oxidation with NaOH/H₂O₂ and distillation under reduced pressure (bp 92°/10 mm) nearly pure (~96% by VPC, column C) (+)-isothujyl alcohol was obtained in 80–85% of theory. Comparison of its NMR spectrum with that of Bergvist and Norin⁵⁹ and observation of the same retention times on several different columns as those shown by an authentic sample prepared from sodium-ethanol reduction of thujone⁵⁹ served to identify the alcohol: $[\alpha]_D^{21} + 110.8^\circ$ (neat, $d_4^{21} 0.917_4$, $n_D^{22} 1.4616$).

(+)-*Isothujone from (-)- Δ^3 -thujene.* The hydroboration-oxidation procedure described by Brown for the conversion of 1-methylcyclohexene to α -methylcyclohexanone, was applied to Δ^3 -thujene.^{66, 67} Diborane was generated initially from NaBH₄ and BF₃-etherate in ethyl ether at room temp. After oxidation, considerable amounts of thujene were recovered along with (+)-isothujone in 40% of th. yield. No (-)-thujone could be detected by VPC. (+)-Isothujone, purified by VPC on column A, was identified by comparison of retention times on different columns with authentic material and identity of its NMR spectrum with the published spectrum:⁵⁹ $[\alpha]_D^{20} + 74.0^\circ$ (neat, $n_D^{19} 1.4525$).

Preparation of (+)-Isothujyl hydrogen phthalate. A 3-necked, 100-ml flask was fitted with reflux condenser (protected by a CaCl₂ tube), magnetic stirring bar and inlet for N₂. The third neck was closed with a serum cap. After the apparatus had been swept with dry N₂, 4.7 g (28 mmole) of (+)-isothujyl alcohol in 15 ml THF was introduced through the serum cap with a syringe followed by 1.05 equiv (18.5 ml) of a 1.6 N soln of *n*-BuLi in hexane, added dropwise with a syringe. The well-stirred soln reached reflux temp during the addition and evolved *n*-butane. After the soln had been boiled under reflux on the water bath for 30 more min, 1.1 equiv of recrystallized phthalic anhydride was added in small portions under N₂. The immediate, exothermic reaction was completed by a 60-min period of reflux. After standing at room temp for 1 hr the soln was poured into 200 ml of water containing 10g of NaHCO₃, stirred for 1 hr, and extracted with three 15-ml portions ether. VPC analysis of this extract showed the absence of thujyl alcohol and confirmed the completeness of the reaction. The aqueous layer was acidified with dil H₂SO₄ and extracted repeatedly with CHCl₃. A small amount of insoluble phthalic acid was filtered. After being dried with anhyd MgSO₄ and concentrated, the soln afforded a white crystalline mass. Four crystallizations from CCl₄ gave material having $[\alpha]_D^{21} + 86.1^\circ$ (c. 0.164, CHCl₃) m.p. 116.7–117.1° (m.p. 114–115° after second recrystallization; m.p. 116–117° after the third); (Found: C, 71.6; H, 7.5. C₁₈H₂₂O₄ required: C, 71.5; H, 7.3%; NMR (CH₂Cl₂) δ 12.56 (1H, s, COOH); 8.0–7.25 (2H m, aromatic); 4.25–7.75 (1H, C₃) 0.56–0.05 (2H, C₄ cyclopropane) (a more detailed assignment is described in connection with the deuterium labeled sample below; $\nu_{max}^{CCl_4}$ 3400–2500, 1695 (s, COOH), 1728 (s, COOR) cm⁻¹).

Cinchonine salt of (+)-isothujyl hydrogen phthalate. Hydrogen phthalate (1.218 g, 3.97 mmoles) was dissolved in 5 ml of hot abs EtOH, and treated with one equiv (1.17 g) cinchonine. The soln was kept

TABLE 8. NMR SPECTRUM OF (-)- Δ^3 -THUJENE IN CCl_4

| Type ^a | Quality | δ (ppm) | J (Hz) | Rel. area |
|---|----------------------------------|--------------------|---|----------------|
| 8-CH ₃ } 9-CH ₃ } | doublet | 1.055 } 1.105 } | H ₇ :6.2 | 6 ^b |
| H ₇ | doublet | ~1.4 | | |
| 10-CH ₃ | apparent quarter ^d | 1.835 | H ₂ α \approx H ₂ β \approx H ₃ :1.4 | 3 |
| H ₅ | pair of doublets | 1.38 | H ₆ β :7.5; H ₆ α :3.3 ^e | 1 ^c |
| H ₆ α | pr. doub. | 0.113 ^f | H ₆ β :3.3 | 1 |
| H ₆ β | | 0.723 ^f | | 1 ^b |
| H ₂ α } H ₂ β } | multiplet | ~2.34 | | 2 |
| H ₃ | | | | |

^a See formula of (-)- Δ^3 -thujene in Figure 1.

^b Area measured as the sum of 8-CH₃, 9-CH₃ and H₆ β .

^c Area measured as the sum of H₅ and H₇.

^d In (-)- Δ^3 -2,2,3-trideuteriothujene, 10-CH₃ is a sharp singlet.

^e In (-)- Δ^3 -2,2,3-trideuteriothujene, long-range coupling is removed and H₅ appears as a pair of doublets superimposed on H₇ (multiplet or heptet?).

^f Two criteria were used to assign absorptions to H₆ α and H₆ β : the fact that H₆ α should resonate at higher field than H₆ β (because it protrudes beyond the shielding cone of the double bond) and the observation that in all cyclopropanes investigated so far, *trans*-vicinal coupling (H₅, H₆ α) was found to be smaller than *cis*-vicinal coupling (H₅, H₆ β).⁸¹

warm till all alkaloid had dissolved. On standing overnight, most of the salt crystallized. Further crystallization gave $[\alpha]_D^{20} + 147.7^\circ$ (c. 0.07365, CHCl_3), m.p. 175.5–175.6°; and finally, $[\alpha]_D^{20} + 147.4^\circ$ (c. 0.09437, CHCl_3), m.p. 175.8–176.2°. From this salt, 0.472 g of hydrogen phthalate was regenerated and had $[\alpha]_D^{20} + 84.3 \pm 0.1^\circ$ (c. 0.065, abs EtOH). This sample and one prepared directly from (+)-isothujyl alcohol were combined and recrystallized from $\text{CCl}_4 - \text{CHCl}_3$ (6:1) two times; $[\alpha]_D^{21} + 86.2^\circ$ (c. 0.00650, CHCl_3), $[\alpha]_D^{21} + 85.4^\circ$ (c. 0.002495, CHCl_3). Further recrystallizations from the same solvent gave the following results: (a) third recrystallization: $[\alpha]_D^{21} + 85.2^\circ$ (c. 0.02875, CHCl_3) (b) fourth: $[\alpha]_D^{21} + 87.2^\circ$ (c. 0.0692, CHCl_3); and (c) fifth: $[\alpha]_D^{21} + 86.5^\circ$ (c. 0.07010, CHCl_3).

rac- Δ^3 -Thujene by thermoreaction in a flow system. A Pyrex tube (30-cm long, 1-cm i.d.) was filled with glass beads and heated in a tubular furnace where temp, measured with a thermocouple, could be varied between 200 and 700°. A 50-ml, 2-necked flask containing 5–10 ml of (-)- Δ^3 -thujene had an inlet for N₂. The other end of the heated tube was connected to a spiral condenser in a bath of Dry-Ice in acetone. The condenser outlet was attached to the oil pump. After having been swept with N₂, the apparatus was slowly evacuated to 0.07 to 0.03 mm. Δ^3 -Thujene was transferred through the hot zone at a rate of about 1 ml/hr, completely condensed in the receiver, and shown by VPC to be essentially free of side products (typically 5 g Δ^3 -thujene gave racemic material in 97%th yield). The NMR spectrum was identical with that of starting material. Heating at 403, 471, 476 and 501° gave Δ^3 -thujene with 76, 9.6, 1.4 and 0.0% optical activity.

Preparation and resolution of (\pm)-isothujyl hydrogen phthalate. The procedure described above for the preparation of (+)-isothujyl hydrogen phthalate was followed (NMR spectrum identical with that of the optically active compound). The rotation of the crude product was $[\alpha]_D^{20} \pm 0.0^\circ$ (c. 0.134, abs EtOH). Recrystallization from CCl_4 gave colorless crystals, m.p. 124°.

Crude, brownish racemic hydrogen phthalate (6.2 g, 20.6 mmoles) in 10 ml of hot abs EtOH was treated with cinchonine (1 equiv, 6.02 g). After all alkaloid had dissolved, the soln was cooled to room temp and seeded with the cinchonine salt of (+)-isothujyl hydrogen phthalate. The salt was recrystallized from

EtOH; only head fractions were characterized: (a) first crystallization: $[\alpha]_D^{20} + 125.5^\circ$ (c, 0.1653, CHCl_3), m.p. 171.5–172.5°; (b) first recrystallization: $[\alpha]_D^{20} + 132.5^\circ$ (c, 0.1772, CHCl_3), m.p. 171.7–171.8°; (c) second: $[\alpha]_D^{20} + 90.9 \pm 0.9$ (c, 0.011684, CHCl_3), m.p. 174.6–175.2°; (d) third: $[\alpha]_D^{20} + 92.6 \pm 0.9$ (c, 0.008244, CHCl_3); and (e) fifth: $[\alpha]_D^{20} + 141.8^\circ$ (c, 0.06919, CHCl_3), m.p. 175.8–176.3°. The acid phthalate regenerated (0.346 g) from this last salt had $[\alpha]_D^{20} + 83.5^\circ$ (c, 0.03604, abs EtOH).

Racemic acid phthalate (11.37 g, 37.6 mmoles) and strychnine (12.5 g, 37.6 mmoles) were dissolved in 20 ml of hot n-propyl alcohol. After 12 hr at room temp, the crystals were filtered from the very viscous mother liquor (positive pressure filtration) to give 13.8 g of brownish salt. Recrystallization from n-propyl alcohol gave 7.8 g of air-dried salt. Regenerated hydrogen phthalate showed $[\alpha]_D^{19} - 51.4^\circ$ (c, 0.1298, CHCl_3). Three more crystallizations of the strychnine salt gave hydrogen phthalate of $[\alpha]_D^{19} - 70.0^\circ$ (c, 0.05894, CHCl_3) which, on recrystallization from CCl_4 -light petroleum (5:1), gave 0.367 g $[\alpha]_D^{19} - 79.0^\circ$ (0.07337, CHCl_3).

2,2,4-Trideuterio-thujone and isothujone. When the mixture of thujones (150 ml) 30 ml D_2O , and 1 g NaOD were refluxed under N_2 (oil bath at 120°), small samples were withdrawn from time to time, dried over anhyd Na_2SO_4 and analyzed by VPC and NMR spectroscopy. No change in composition of the tansy oil could be detected and exchange of hydrogens at C_2 and C_4 could be followed easily. After 30 hr when no further exchange seemed to be taking place, the alkaline D_2O soln was replaced by 30 ml of fresh D_2O containing 2g of NaOD. After four days' reflux, 90–95% exchange had been effected at C_2 and C_4 . NMR integration revealed a mixture of (+)-isothujone and (–)-thujone in a ratio of 2:1.

d_4 -Thujone tosylhydrazone. Following the same procedure as that described above, 119 g of the deuteriated mixture of isothujone and thujone and 115 g of *p*-toluenesulfonic acid d_3 -hydrazide (from two treatments of 118 g tosylhydrazine with 30 ml D_2O in THF for 2 days each) gave 128 g of deuteriated tosylhydrazone, m.p. 125–127° (dec); $[\alpha]_D^{20} + 139^\circ$ (c, 0.03, MeOH).

2,2,3-Trideuterio (–)- Δ^3 -thujene. The deuteriated tosylhydrazone (123 g; 0.375 mole) was converted to its Li salt and heated in a manner described above to yield 27 g of distilled thujenes (53% of th) consisting of the Δ^3 -thujene (80%) and the mixture of Δ^2 -thujenes (20%). After distillation through the spinning band column (bp₇₆₀ 152–153°) and purification by VPC on column B, Δ^3 -thujene had the following physical constants: α_D^{19} (neat) – 43.78°, $[\alpha]_D^{19}$ (neat) – 51.1 ± 0.02°, $d_4^{20.5}$ 0.8557, micropycnometer), $n_D^{23.8}$ 1.4559; NMR spectrum showed reduced absorption at δ 1.95–2.25 (attributed to the α - and β -protons on C_2), at 5.0 (vinyl proton at C_3 , rel. area 0.32), collapse at $\delta = 1.82$ to a singlet (10-Me) and appearance at 1.25–1.70 (H_5 – and H_7) of a quartet superimposed on a broad multiplet; ν_{max} 3060 (reduced intensity) 2478, 2378, 2097 (C–D), 1023 and 1627 (asymmetric stretch of the cyclopropane methylene group, previously 1024, and *cis* C=C, previously 1647) cm^{-1} . Introduction of deuterium into the molecule also had quite distinctive effects on the absorptions in the skeletal-vibration region.

Deuteriated (+)-isothujyl hydrogen phthalate. A 2.13 g (0.0154 mole) sample of partly deuteriated (–)- Δ^3 -thujene was converted by the hydroboration procedure above to 2.1 g (86% of distilled deuteriated (+)-isothujyl alcohol of better than 96% purity by VPC); after purification on column A, $[\alpha]_D^{21} + 110.5 \pm 0.002^\circ$ (neat, d_4^{24} 0.927₄ assumed).

Deuteriated (+)-isothujyl alcohol hydrogen phthalate (2.15 g) was obtained from 2.1 g of alcohol by the procedure described above. After crystallization of its cinchonine salt from EtOH, and subsequent crystallization of the hydrogen phthalate from CCl_4 , the material had $[\alpha]_D^{19} + 85.6 \pm 0.02^\circ$ (c, 0.0586, CHCl_3), m.p. 117.2°. Recrystallization from CHCl_3 – CCl_4 gave hydrogen phthalate with $[\alpha]_D^{19} + 86.0^\circ$ (c, 0.03605, CHCl_3). The NMR spectra of this sample and of undeuteriated (+)-isothujyl hydrogen phthalate are shown in Fig. 6.

Thermoreactions of (–)- Δ^3 -thujene. Following the procedure of Doering and Lambert,⁵⁴ measured amounts of (–)- Δ^3 -thujene were transferred *in vacuo* to 800-ml ampoules and degassed at 0.0005 mm. The ampoules were sealed and placed in a tube furnace. The time of thermoreaction varied from 3 to 20 hr at temp ranging from 200 to 260°. The vapor pressure of Δ^3 -thujene was calculated from the ideal gas law, and the range from 15 to 350 mm was investigated. After reaction, products were condensed (liquid N_2) in the tip of the ampoule; the tip was broken and its content analyzed by VPC and NMR.

In all runs, at least twelve different compounds with retention times longer than Δ^3 -thujene were found. NMR revealed a high percentage of olefinic and aromatic products (mainly *p*-cymene). Especially at high temp, long reaction time, and high pres, little Δ^3 -thujene was left, while at low pressure (15mm) nearly pure Δ^3 -thujene could be recovered. Product distribution was not affected by washing the ampoule with aqueous NH_3 instead of distilled H_2O .

When 400 mg of recrystallized diphenylamine was added, no discoloration of diphenylamine or Δ^3 -thujene

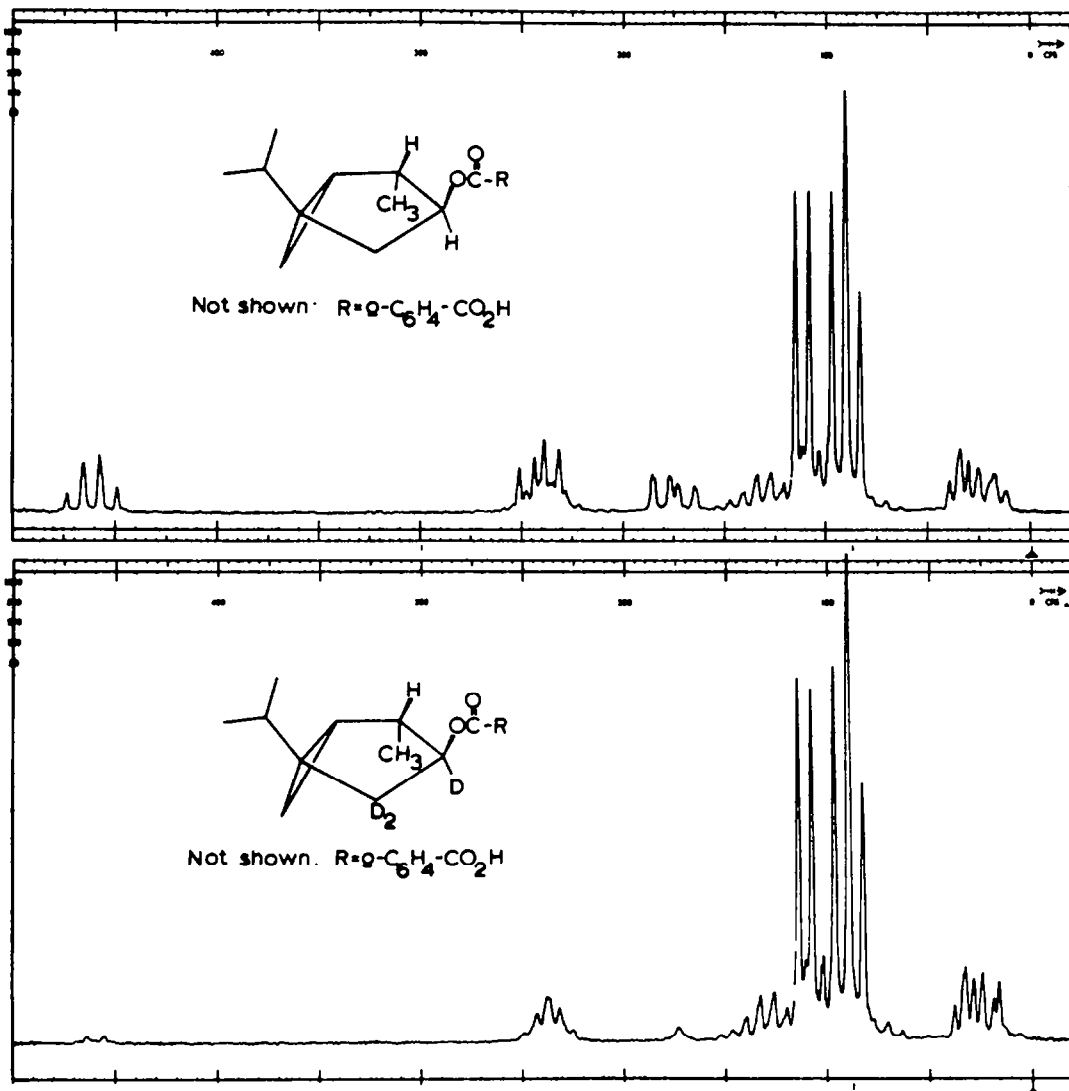


FIG 6. NMR spectra of deuteriated and undeuteriated (+)-isothujyl hydrogen phthalate

was observed and recovery was essentially quantitative. In these experiments only traces of products other than Δ^3 -thujene were detected, even at higher pressure and temp. Thus, 600 mg ($-$)- Δ^3 -thujene and 400 mg diphenylamine in a 700-ml ampoule, heated at 255° for 6 hr, gave 95 to 98% racemic Δ^3 -thujene.

Thermoreaction of ($-$)-2,2,3-trideuterio- Δ^3 -thujene in flow system (480°). A sample of ($-$)-2,2,3-trideuterio- Δ^3 -thujene prepared in the manner above (11.45 g, 0.083 mole) was passed through the previously described flow apparatus at $480\text{--}489^\circ$ and 0.05 mm and then was treated with diborane as previously described to yield 10.4 g (0.0642 mole, 78% of th) of partially racemized deuteriated isothujyl alcohol which was purified by VPC on column A: $[\alpha]_D^{21} + 27.84^\circ$ (neat, $d_4^{25} 0.927_4$, [microcycnometer]); 74.2% racemization. This alcohol was then converted to the hydrogen phthalate as previously described.

The hydrogen phthalate (18.33 g, 0.060 mole) and cinchonine (10.93 g, 0.037 mole) were dissolved in 70 ml of hot abs EtOH and allowed to stand overnight. The crystalline salt, 2.67 g, was reconverted to hydrogen phthalate: $[\alpha]_D^{19} + 78.1^\circ$ (c, 0.267, CHCl_3). One crystallization from CCl_4 gave 0.962 g of

colorless needles: $[\alpha]_D^{25} + 85.5^\circ$ (c, 0.12, CHCl_3), m.p. 116.8–117.0°; after one recrystallization from $\text{CCl}_4\text{—CHCl}_3$ (6:1): $[\alpha]_D^{25} + 86.4^\circ$ (c, 0.042, CHCl_3).

The filtrate from the crystallization of the cinchonine salt was evaporated to dryness, treated with an excess of 0.5 N H_2SO_4 and extracted with ether (3 150-ml portions). The combined extracts were washed with saturated NaCl -soln (3 150-ml portions), dried over anhyd MgSO_4 and evaporated to dryness to yield 15.5 g of crystalline material, $[\alpha]_D^{20} + 8^\circ$. To a hot soln of this hydrogen phthalate in EtOH there was added 8.5 g (0.5 equiv.) of strychnine. The crystals which had formed overnight at $\sim 4^\circ$ were collected, washed with a small amount of cold EtOH, and decomposed with 1.5 equiv. of H_2SO_4 in 300 ml H_2O . The aqueous phase was extracted with 150-ml portions of ether; the extracts were combined, washed with 3 20-ml portions of saturated NaCl -soln, dried over anhyd MgSO_4 and evaporated to dryness. The remaining solid was dissolved in a minimum quantity of CCl_4 , filtered through a layer of anhyd MgSO_4 , and evaporated to dryness to yield 3.06 g of hydrogen phthalate: $[\alpha]_D^{19} - 44.2^\circ$ (c, 0.101, CHCl_3). The strychnine salt of this hydrogen phthalate (molar ratio 1:1) was recrystallized 3 times from EtOH. The hydrogen phthalate regenerated from the last fraction showed $[\alpha]_D^{19} - 83.8^\circ$ (c, 0.029 CHCl_3) m.p. 116.8–117.0°; after recrystallization from $\text{CCl}_4\text{—CHCl}_3$ (6:1): $[\alpha]_D^{21} - 83.7^\circ$ (c, 0.041, CHCl_3).

Thermoreaction of (–)-2,2,3-trideuterio- Δ^3 -thujene in solution (240°). Another sample of deuteriated thujone tosylhydrazone was prepared from 143 g deuteriated thujones (*vide infra*) and 186 g deuteriated tosylhydrazine (*vide infra*). These materials were placed in a 1-l 3-necked round-bottom flask equipped with stirrer and reflux condenser with 230 ml dry THF and stirred under N_2 at 25° . After 80 min VPC showed 30–40% of unreacted thujones and after 20 hr with 20 g anhyd MgSO_4 about 10% remained consisting almost entirely of (–)-thujone. Heating at 70° completed the reaction. The soln was treated with an additional 23 g thujones for 12 hr at $60\text{--}65^\circ$. Filtered through Celite and concentrated *in vacuo*, the soln left a semi-solid mass which was leached with 6 50-ml portions of heptane and dried over paraffin chips and P_2O_5 ; 230 g (0.702 mole).

This sample of tosylhydrazone was converted to (–)-2,2,3-trideuterio- Δ^3 -thujene by the procedure described above: $\alpha_D^{23} - 43.41^\circ$; $n_D^{25} 1.4511$; m/e (11 eV) 133 (0.0), 134 (0.0), 135 (2.30), 136 (6.85), 137 (9.93), 138 (50.8), 139 (100), 140 (11.5), 141 (0.6) [undeuteriated (–)- Δ^3 -thujene: 133 (0.1), 134 (9.32), 135 (1.36), 136 (100), 137 (11.5), 138 (0.69), 139 (0.0)]. This sample of (–)-2,2,3-trideuterio- Δ^3 -thujene was converted to the corresponding isothujyl alcohol [$\alpha_D^{21} + 105.5$ (neat)] and hydrogen phthalate by the procedures described above. The cinchonine salt was recrystallized twice from EtOH, hydrogen phthalate was regenerated and crystallized once from $\text{CCl}_4\text{—CHCl}_3$ (6:1) [$\alpha]_D^{21} + 84.6$ (c, 0.050, CHCl_3).

(–)-2,2,3-trideuterio- Δ^3 -thujene (7.2 ml) and dry tetraglyme (30 ml, dist, from LAH) were frozen under N_2 , degassed, and sealed under vacuum into a 60-ml Pyrex ampoule. The ampoule was heated in a tubular furnace for 196 min at 240° (thermocouple). A second sample of 8 ml of thujene was treated exactly the same way, and the combined solns were poured into 400 ml H_2O . The organic layer was separated and the aqueous phase was extracted with ether (3 25-ml portions). The combined extracts were washed with H_2O (three 5-ml portions), dried over anhyd Na_2SO_4 , and concentrated by slow distillation through a 30-cm Vigreux column. This sample of Δ^3 -thujene (12.6 g, 0.091 mole) was converted to isothujyl alcohol: 9.0 g, 0.058 mole; $\alpha_D^{21} + 49.88^\circ$ (neat) after purification on column B; 52.7% racemization. The isothujyl alcohol was then converted in the usual way to hydrogen phthalate which was resolved as the cinchonine salt. Four recrystallizations of the salt from EtOH and two crystallizations of recovered hydrogen phthalate from CCl_4 [$\alpha]_D^{25} + 85.6$ (c, 0.11, abs EtOH), 116.6–116.8° and one from $\text{CCl}_4\text{:CHCl}_3$ (6:1) afforded pure material: $[\alpha]_D^{21} + 86.7^\circ$ (c, 0.040, CHCl_3).

The residual hydrogen phthalate was converted to the strychnine salt which was crystallized six times from EtOH. Crystallizations of regenerated head fraction from CCl_4 [$[\alpha]_D^{24} - 101.9^\circ$ (c, 0.060, CHCl_3), m.p. 116.0–116.3°) and $\text{CCl}_4\text{:CHCl}_3$ (6:1) afforded (–) hydrogen phthalate: $[\alpha]_D^{21} - 85.5^\circ$ (c, 0.045, CHCl_3). Pure (+)-enantiomer has $[\alpha]_D^{25} + 85.6$ (EtOH) and $[\alpha]_D^{24} + 101.4^\circ$ (c, 0.058, CHCl_3).

Distribution of deuterium in samples of isothujyl hydrogen phthalate. Measurements of relative areas were carried out on the Varian HR-100 NMR Spectrometer through the courtesy of Professor M. R. Willcott, III, Department of Chemistry, University of Houston, Texas. We are grateful for his generous, able assistance. Samples of 0.1000 ± 0.0030 g were dissolved in 440 μl HCl_4 containing a small amount of TMS.

Intensities of absorption were measured sweeping upfield and downfield, each three or four times. Heights were taken off the trace between the following points corresponding to the indicated H atoms in isothujyl hydrogen phthalate. These measurements are given in tables which include the integrations in arbitrary numbers and an average with its standard deviation (σ). In the undeuteriated example (Table II), the fraction corresponding to each type of hydrogen is indicated, its multiplication by 17, the total number

of H atoms (the five aromatic hydrogen atoms are not included), and a correction factor defined as the quotient of the theoretical and experimentally-determined number of H atoms.

Kinetics of racemization of (-)- Δ^3 -thujene. The air-thermostat employed is a copy of the Clark design,^{8,3} constructed by Mr. Glenn Beasley and modified by the inclusion of a thermoregulator* and a platinum resistance thermometer as regulator. The reaction vessel is an untreated 12-liter Pyrex flask connected to a vacuum line fitted with Teflon stopcocks to avoid absorption of reactants and products by stopcock grease. Temperature variation from one part of the thermostat to the other was $\pm 0.2^\circ$ and within the reaction vessel $\pm 0.02^\circ$.†

Samples of (-)- Δ^3 -thujene purified by VPC on column B (70–140 ul leading to reaction pressure of 1.5–3.0 mm at 500° K) were degassed, transferred at 10^{-5} mm to a storage finger cooled in liquid N₂ and located at the entrance to the reaction flask outside the thermostat. About 20 sec was required for transfer of the sample (warmed to room temp) into the evacuated reaction vessel.

Recovery of reaction product from the 12-l flask into the storage finger required about 2 min. The end-time was taken after 1 min.

Pure Δ^3 -thujene, usually in better than 90% of the theoretical yield, was recovered by VPC on column B at 60°. The optical rotation was determined in a Perkin-Elmer 141 Polarimeter at 365 nm and 22° in a 10-cm cell holding 1 ml of the soln in CCl₄.

Plots of the logarithms of specific rotations against time gave straight lines (up to 9.5 half-lives at 254° C) from which specific rate constants were calculated by the method of least squares. For one temperature (254° C) the standard deviation was calculated ($\pm 2\%$). Similar uncertainties were assumed for the rates at other temperatures.

Rate constants were determined at six temperatures from 201.6 to 258.6°. Over this range the half-life varied from 3.5 days to 39 min. The relevant data is collected in Table 9.

TABLE 9. FIRST-ORDER RATE CONSTANTS FOR THE RACEMIZATION OF (-)- Δ^3 -THUJENE

| Temperature [°C] | Reciprocal temp [°K ⁻¹] | Rate const [sec ⁻¹] | log (rate const) |
|---------------------|--|------------------------------------|------------------|
| 201.61 | 2.1063×10^{-3} | 2.3164×10^{-6} | $\bar{6}.36482$ |
| 210.80 | 2.0663×10^{-3} | 5.0260×10^{-6} | $\bar{6}.70122$ |
| 211.17 | 2.0647×10^{-3} | 5.0460×10^{-6} | $\bar{6}.70294$ |
| 231.52 | 1.9815×10^{-3} | 3.4580×10^{-5} | $\bar{5}.53882$ |
| 254.15 | 1.8964×10^{-3} | 2.1738×10^{-4} | $\bar{4}.33718$ |
| 258.63 | 1.8804×10^{-3} | 2.9680×10^{-4} | $\bar{4}.47245$ |

TABLE 10. INFLUENCE OF GLASS WOOL ON THE RATE OF SIDE REACTIONS

| Flask* | Time [min.] | Temp. [C] | Rac. [%] | Δ^3 -Thujene [%] | Side products [%] |
|--------|----------------|--------------|-------------|----------------------------|----------------------|
| 12-l | 457 | 254 | 99 | 94 | 6 |
| 12-l | 250 | 232 | 41 | 99.3 | 0.7 |
| 2-l | 9 | 254 | 12 | 97.3 | 3 |
| 2-l | 195 | 254 | 91 | 32 | 68 |
| 2-l | 552 | 232 | 57 | 43 | 57 |
| 2-l | 635 | 232 | 60 | 7.6 | 93 |

* The ratios of surface to volume in the 12- and 2-liter flasks were 0.21 and 12.6 cm⁻¹, respectively.

* "Thermotrol", Model 1053A, Shell Development Design, Hallikainen Instruments, Richmond, California.

† Temperature measured with an iron-constantan thermocouple which was referred to an ice-water junction and was calibrated at 100.0° and 444.6°.

A test for homogeneity was conducted in a 2-l Pyrex flask filled with 8 g Pyrex wool in which the ratio of surface to volume was increased by a factor of 60. At 254.6° the specific rate constant was $2.0406 \times 10^{-4} \text{ sec}^{-1}$; at the same temperature in the 12-l flask, the rate constant was $2.1738 \times 10^{-4} \text{ sec}^{-1}$. Although the specific rate constant for racemization is unaffected by added Pyrex wool, the yield of recovered Δ^3 -thujene was markedly lowered (Table 10).

The activation parameters were calculated from the Arrhenius plot by least squares treatment. Each specific rate constant was given the same weight.

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