

THE CHEMISTRY OF THUJANE DERIVATIVES

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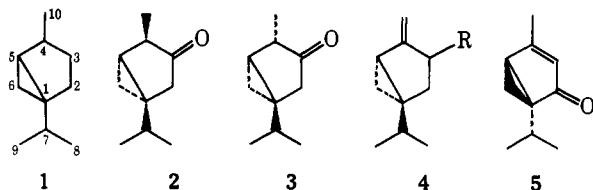
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I. Introduction

Many members of the Compositae, Labiatae, and Cupressaceae, especially *Artemisia*, *Tanacetum*, *Salvia*, *Thuja*, and *Juniperus* species, together with members of certain other plant families, contain large quantities of monoterpenes with the thujane skeleton (1). The most commonly occurring of this class of compounds are (-)-thujone (2), (+)-isothujone (3), (+)-sabinene (4, R = H), and (+)-sabinyl acetate (4, R = α -OAc); (-)-sabinene and (-)-umbellulone (5) are less widely distributed and contain the enantiomorphic ring. These compounds usually occur in high optical purity and the "best" recorded values for 2-5 respectively are:¹⁻³ $[\alpha]^{22D}$ (neat) -20.2, +75.5, +107.2, +80.0, and -39.4°.



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(1) D. V. Banthorpe and H. ff. S. Davies, *J. Chem. Soc. B*, 1356 (1968).
(2) G. Ohloff, G. Uhde, A. F. Thomas, and E. sz. Kováts, *Tetrahedron*, **22**, 309 (1966).
(3) R. H. Eastman and A. Oken, *J. Amer. Chem. Soc.*, **75**, 1029 (1953).

What was known of the chemistry of the thujane series up to 1947 has been reviewed in detail.⁴ Some of this early work is inconclusive or inconsistent as separations were carried out without benefit of chromatographic techniques, and structures, especially of isomers, were assigned largely on the basis of empirical rules. More recently, convenient purification methods⁵ and physical constants for the more important members of the family have been recorded.⁶

This review, which covers the literature up to August 1971, attempts to summarize the major advances in knowledge of the chemistry of thujane derivatives over the last 25 years. Since the structure of the thujane skeleton and the position of the substituents in most derivatives were known at the beginning of this period, and have been adequately reviewed elsewhere,⁴ we have concentrated on the application of spectroscopic techniques to determine conformations, and on reactions of thujane derivatives. We have used throughout the older, well-accepted names of the many well-characterized compounds of the class, following the general practice of recent publications, even though this nomenclature is unsystematic, and a more rational scheme has been recently proposed.⁷

II. Structure

The nature of the thujane skeleton was elucidated by classical techniques at the turn of the century.⁴ The absolute configurations have since been assigned in several ways. 1,4-Addition of hydrogen over palladized charcoal to (+)-sabinene, (+)-sabinyl acetate, and (+)-sabinol (4, R = α -OH) yielded cyclopentane derivatives that could be degraded to substituted glutaric or succinic acids of known absolute configuration (eq 1); the absolute configurations of the other naturally occurring thujane derivative followed from known chemical and optical correlations.^{8,9}

In another study² the configurations at C(4) of the parent hydrocarbons (+)-*cis*-thujane and (-)-*trans*-thujane formed

(4) J. L. Simonson and L. N. Owen, "The Terpenes," Vol. II, 2nd ed, Cambridge University Press, London, 1949, p 5.

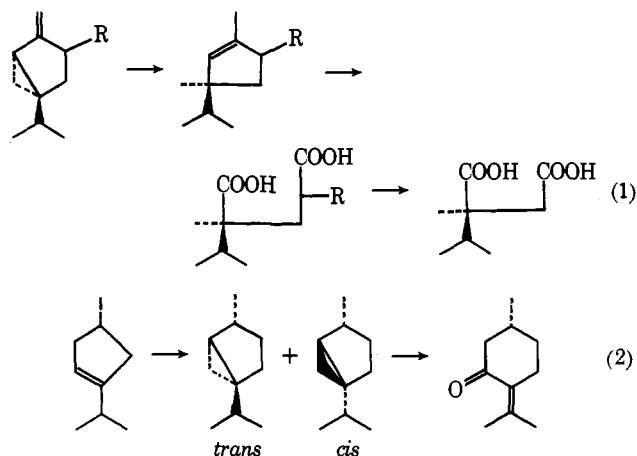
(5) V. Hach, R. W. Lockhart, E. C. McDonald, and D. M. Cartledge, *Can. J. Chem.*, **49**, 1762 (1971).

(6) A. Pelter in Rodd's "Chemistry of Carbon Compounds," Vol. IIc, S. Coffey, Ed., Elsevier, Amsterdam, 1969, p 136.

(7) S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, **34**, 3015 (1969).

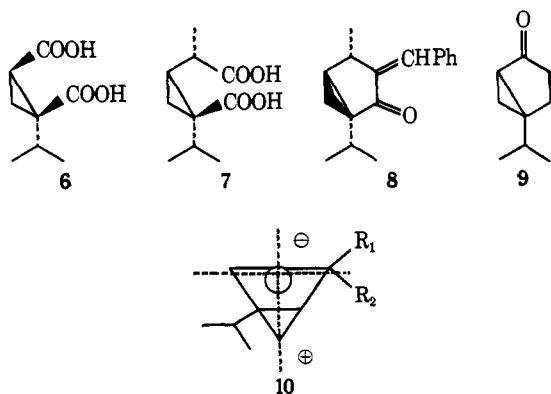
(8) T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962).

(9) H. E. Smith and A. W. Gordon, *J. Amer. Chem. Soc.*, **84**, 2840 (1962).



by addition of methylene to (+)-pulegone were correlated with the corresponding position in (+)-pulegone (eq 2). A third assignment followed the conversion of (-)-umbellulone into umbellularic acid (6) and thence into a substituted succinic acid of known configuration.^{9,10} This conclusion was confirmed by the formation of (+)-homothujadicarboxylic acid (7) from the benzylidene derivative of dihydroumbellulone (8), whereas the corresponding derivative of (-)-thujane gave¹¹ the enantiomer of 7.

Assignments of the configurations of other stereoisomers of the series are dependent on those of the thujones; the latter were deduced to be as in 2 and 3 on the basis of the stereochemistry of reduction of each isomer by lithium aluminum hydride and by catalytic hydrogenation of sabinyll compounds.¹² These configurations were in accord with conclusions derived from calculations of molecular refraction¹³ but differed from those deduced from the Auwers-Skita rule and from certain chemical evidence.^{14,15} However the newer conclusions are consistent with the weight of nmr data on the ketones and their derived alcohols and amines^{12,16,17} and with ORD measurements.¹² In the latter situation, the cyclopropyl ring is symmetrically situated with respect to the chromophore and has little influence on the Cotton effect associated with the $n \rightarrow \pi^*$ transition of the ketone; a different situation occurred



(10) E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966).

(11) H. M. Walborsky, T. Sugita, M. Ohno, and Y. Inouye, *J. Amer. Chem. Soc.*, **82**, 5255 (1960).

(12) T. Norin and M. S. Bergquist, *Arkiv Kemi*, **22**, 137 (1964).

(13) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5491 (1959).

(14) R. H. Eastman and A. V. Winn, *ibid.*, **82**, 5908 (1960).

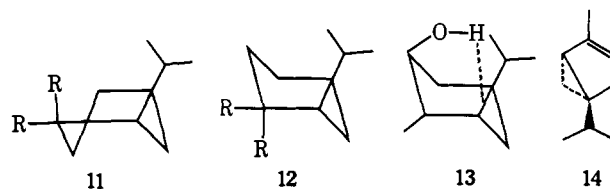
(15) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).

(16) K. Tori, *Chem. Pharm. Bull.*, **12**, 1439 (1964).

(17) H. E. Smith, J. C. D. Brand, E. H. Massey, and L. J. Durham, *J. Org. Chem.*, **31**, 690 (1966).

in sabina ketone 9 where the asymmetrically disposed ring evoked a large effect.^{18,19} Consequently the Cotton effects of the thujones reflect the configurations at C(4). (-)-Thujone, with a negative effect, must have the group in a negative octant, whereas (+)-isothujone, with the opposite effect, must have the epimeric configuration (10, $R_1, R_2 = \text{Me, H}$). As the absolute configurations of the other asymmetric centers were known, the relative configurations may be deduced. Despite some doubts^{16,20} as to the interpretation of the nmr spectra of bicyclo[*n*.1.0] compounds, the newer configurations appear to have been firmly established.

A unique correlation between the nmr spectra in a variety of aprotic solvents and the relative configurations which have been assigned on nmr and chemical evidence can be made for the thujones and their derived alcohols and amines only if the preferred conformation of the ring is in most cases boat-like.^{12,16,17} The ORD spectra of certain ketones derived from umbellulone were also consistent with this interpretation,²¹ and the nmr spectrum of *trans*-thujane reveals a preferred boat shape, although that of the *cis* isomer is consistent with a half-chair with a flattened C_5 ring.²² The situation can be rationalized by considering the thujane skeleton as a flexible system which adopts the conformation best to minimize interactions between groups at C(3) or C(5) and the methylene bridge of the cyclopropane ring, which is usually the boat form, though in some cases a half-chair or chair may be better; *cf.* 11 and 12. This explanation accommodates the unusual stabilities of thujanes with C(3) substituents *cis* to the cyclopropane ring⁷ and the observation that equilibration of the thujones with base in ethanol gave thujone in predominance by a factor of 2.¹ If both isomers adopted boat forms, the unlikely situation would occur that the isomer corresponding to 11, with R pseudo-axial, would be more stable than that with R pseudo-equatorial; consequently, thujone may be distorted toward a chair form such as 12 where the methyl substituent in the ring could approach an equatorial orientation. In addition, studies of the reductions of these isomers with a variety of reagents¹ were best interpreted if thujone existed in a pseudo-chair and isothujone in a pseudo-boat in the transition state for reduction.



In protic solvents, the situation may be different. Recently, evidence from ir spectra has been presented²³ that hydrogen bonding between *trans*-oriented hydroxy groups and the cyclopropane ring of isomers of thujols can hold the molecules in chair forms; *cf.* 13. This effect only occurred at high dilutions and is consistent with the picture of the thujane skeleton as a highly flexible system in which the conformation may vary between the extremes of boat and chair best to accommodate differing substituents. A change from inter- to intramolecular

(18) T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).

(19) A. I. Scott and W. D. Wrixon, *Tetrahedron*, **26**, 3695 (1970).

(20) P. J. Kropp, *J. Amer. Chem. Soc.*, **88**, 4926 (1966).

(21) R. T. Gray and H. E. Smith, *Tetrahedron*, **23**, 4229 (1967).

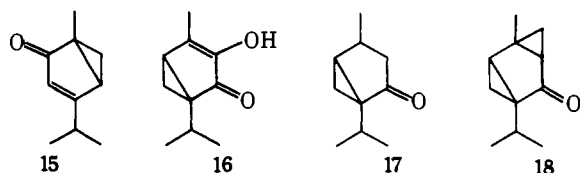
(22) A. Dieffenbacher and W. von Philipsborn, *Helv. Chim. Acta*, **49**, 897 (1966).

(23) V. Hach, R. F. Raimondo, D. M. Cartledge, and E. C. McDonald, *Tetrahedron Lett.*, 3175 (1970).

hydrogen bonding with increasing dilution could then switch the conformation from boat to chair.

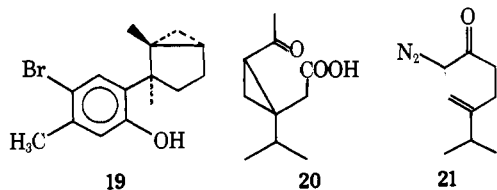
The only other conformational information available is a nmr study of (-)- α -thujene (14), which was proved to exist in an L-shaped conformation with the cyclopentene ring planar.²⁴

Electronic interactions involving the cyclopropyl ring were revealed by the absorption in the uv. The spectrum of umbellulone was so unlike that expected for an α,β -unsaturated ketone that an isomer, 15, was synthesized, but this was found to have an identical spectrum.²⁵ The spectra have since been shown to be consistent with conjugation involving the cyclopropyl ring,^{26,27} and the wavelength of maximum absorption was close to that predicted using the Woodward rules for an α,β - γ,δ -conjugated ketone. To preserve this conjugation, α -hydroxyumbellulone (16) exists in the enol form rather than as a diketone and exhibits an acidity akin to that of a phenol.²⁸ Dihydroumbellulone (17) and its homolog 18 had similar uv spectra which were indicative of much less conjugation than occurred in umbellulone, and thujone exists in only a few per cent in the enol form.²⁸ Clearly, a chain of conjugation incorporating both cyclopropyl rings does not occur in 18, and each ring is separately in conjugation with the carbonyl group.



This situation is predictable from the relative orientations of the "banana" orbitals of the rings.

The existence of a ring current in the cyclopropyl system, coupled with the uncertainties already referred to in the application of the Karplus equation to these strained structures, makes attempts to calculate the dihedral angle between the three- and five-membered rings by the usual nmr methods a procedure subject to considerable uncertainty. The only accurate data in this field have been obtained from a crystallographic study of the naturally occurring substance laurinterol (19); this revealed²⁹ that the bicyclo[3.1.0]hexane moiety existed as a boat with a dihedral angle of 114°.



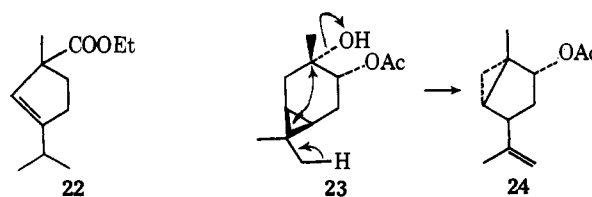
The mass spectra of the thujanes are consistent with the general pattern of monoterpene fragmentation,³⁰⁻³² and the ir spectra of many thujane derivatives have been published.³³

- (24) D. Whittaker and M. A. Cooper, unpublished results.
 (25) H. E. Smith and R. H. Eastman, *J. Amer. Chem. Soc.*, **79**, 5500 (1957).
 (26) R. H. Eastman, *ibid.*, **76**, 4115 (1954).
 (27) R. N. Moore and G. S. Fischer, *ibid.*, **78**, 4362 (1956).
 (28) R. H. Eastman and J. C. Selover, *ibid.*, **76**, 4118 (1954).
 (29) A. F. Cameron, G. Ferguson, and J. M. Robertson, *J. Chem. Soc. B*, 692 (1969).
 (30) E. Von Sydow and R. Ryhage, *Acta Chem. Scand.*, **17**, 2025 (1963).
 (31) A. F. Thomas and B. Willhalm, *Helv. Chim. Acta*, **47**, 475 (1964).
 (32) H. C. Hill, R. I. Reed, and M. T. Robert-Lopes, *J. Chem. Soc. C*, 93 (1968).
 (33) B. M. Mitzner, E. T. Theimer, and S. K. Freeman, *Appl. Spectrosc.*, **19**, 169 (1965).

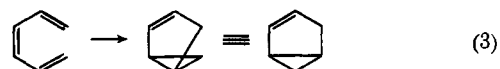
III. Synthesis of Thujanes

Most thujane derivatives are prepared from the naturally occurring and readily available thujones,⁴ but several routes for the construction of the thujane skeleton have been developed. An early claim³⁴ to have prepared thujane by treatment of 2,4-dibromomenthone with zinc followed by Clemmensen reduction was disproved; reinvestigation with modern techniques demonstrated the formation of only menthane derivatives.^{35,36} However, the contemporaneously reported³⁷ synthesis of a thujaketonic acid (20) and the conversion of the latter into thujone did constitute a total synthesis of the bicyclic skeleton.

A route to sabina ketone is by intramolecular insertion when the diazo compound 21 is decomposed in the presence of copper;^{38,39} addition of methylene to 22 followed by conventional functionalization also led to thujane⁴⁰ or to sabina ketone.⁴¹ An unusual synthesis of a thujane analog, 24, resulted from treatment of 23 with phosphorus oxychloride in pyridine,^{20,42} and a similar interconversion occurred on refluxing β -3,4-epoxycarane with acetic anhydride.⁴³ A remarkable claim⁴⁴ to have prepared thujones by base-catalyzed condensation of acetone (*sic*) could not be repeated.¹



Concerted photochemically induced bicyclizations of *cis*-hexatrienes are allowed by orbital symmetry⁴⁵ and have been demonstrated⁴⁶ in several examples (eq 3), but this approach has not been applied to the synthesis of any particular thujane derivative.



IV. Reactions

A. REDUCTION

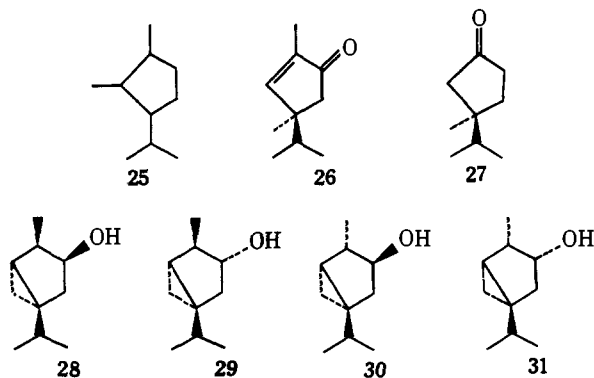
As α -thujene has an L-shaped conformation, the double bond would be expected to undergo attack from the side remote from the methylene group of the cyclopropyl ring; this is observed. Catalytic hydrogenation over platinum at low temperatures gave⁷ *trans*- and *cis*-thujanes in the proportions 85:15 (*cf.* eq 2 for nomenclature), and addition of borane and

- (34) P. C. Guha and B. Nath, *Ber.*, **70**, 931 (1937).
 (35) A. K. Bose and M. S. Tibbetts, *Tetrahedron*, **23**, 3887 (1967).
 (36) W. E. Dauben, A. C. Albrecht, E. Hoerger, and H. Takimoto, *J. Org. Chem.*, **23**, 457 (1958).
 (37) M. S. Muthanna and P. C. Guha, *Ber.*, **71**, 2671 (1938).
 (38) O. P. Vig, M. S. Bhatia, K. C. Gupta, and K. L. Matta, *J. Indian Chem. Soc.*, **46**, 991 (1969).
 (39) K. Mori, M. Ohki, and M. Matsui, *Tetrahedron*, **26**, 2821 (1970).
 (40) P. C. Guha and S. Krishnamurthy, *Ber.*, **70**, 2112 (1937).
 (41) W. I. Fanta and W. F. Erman, *J. Org. Chem.*, **33**, 1656 (1968).
 (42) P. J. Kropp, U. S. Patent, 3,510,510; *Chem. Abstr.*, **73**, 15039 (1970).
 (43) G. Z. Isaeva, V. I. Shaithudinor, and B. A. Arbuзов, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1154 (1968).
 (44) B. T. Zubakhin, *Zh. Obshch. Khim.*, **24**, 1164 (1954).
 (45) K. Fukui, *Accounts Chem. Res.*, **4**, 60 (1971).
 (46) J. Meinwald and P. H. Mazzocchi, *J. Amer. Chem. Soc.*, **88**, 2850 (1966).

oxidation gave almost exclusively a thujol with the hydroxyl group trans to the methylene bridge. In contrast, sabinene (which presumably has a similar conformation) could be similarly hydrogenated to give 86% *cis*-thujane although hydroboration-oxidation gave a mixture of thujan-10-ols in which the opposite configuration predominated.⁷ It has been suggested that sabinene has the cyclopropyl ring and the double bond better aligned for conjugation than has α -thujene, and the partially conjugated system of the former is attached *en bloc* onto the catalytic surface whereas attachment by only the double bond occurs for α -thujene. The latter molecule may align itself with the cyclopropane ring away from the catalyst in order to reduce steric hindrance.

The hydroboration-reduction procedure is the most convenient method for preparing thujanes⁴⁷ and has superseded Wolff-Kishner or Clemmensen reduction of thujones.⁴ Mild acidolysis of the trithujylborane derived from sabinene gave an excellent yield of thujanes, whereas the conventional conditions for acid cleavage resulted in no thujanes but up to ten isomeric cyclopentane and menthane derivatives.⁴⁸

Catalytic reduction of thujyl compounds over metals under forcing conditions sometimes gave products of ring fission, although this mode could be completely eliminated by using borohydride-reduced catalysts.⁴⁹ Early reports claimed that catalytic reduction of thujanes, thujones, or sabinyl acetate led to derivatives with the skeleton **25**, but recent studies on the last compound⁶⁰ showed the main product to be **26** in which cleavage of the cyclopropane ring had occurred at the *least* hindered bond. Highly stereoselective cleavage of the ring in the analogous position occurred on reduction of sabinone



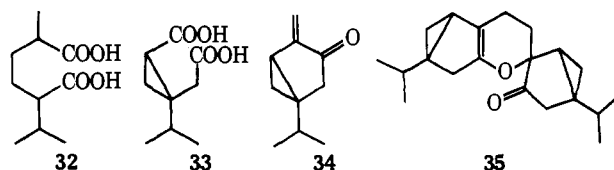
with lithium in ammonia to give **27**; apparently the bond that is cleaved is that possessing maximum overlap with the π orbital of the carbonyl group.⁶¹

Reduction of the thujones by metal hydrides or aluminum alkoxides or over metal catalysts gave four isomeric thujols in which the relative orientations of hydroxyl and methyl groups have been rationalized on the basis of the favored directions of approach for the reagents of differing bulk^{1,11,52} and also by interpretation of the nmr spectra.¹¹ These alcohols are thujol (**28**), neothujol (**29**), isothujol (**30**), and neoisothujol (**31**). The expected isomeric alcohols resulted from reduction of umbellulone with lithium aluminum hydride, but reduction

with sodium borohydride or lithium alkoxyhydrides led⁵⁸ to **17** together with the corresponding alcohols in 30–80% yield. Such behavior is atypical for metal hydride reductions, and presumably steric hindrance to approach of the bulky reducing agent leads to 1,4 addition to form first the enol of **17**.

B. OXIDATION

Reaction with potassium permanganate under mild conditions opened the ring of thujane to form **32**, whereas the same treatment of α -thujene or thujone led to **20** or **33** in which oxidation took place at the double bond or carbonyl group.⁴ In contrast, treatment of sabinol with selenium dioxide did not cleave either ring but yielded a ketone which rapidly dimerized. Similar reactions with manganese dioxide gave sabinone (**34**) which formed **35** on heating.⁵⁴ This study



corrected an erroneous structure that had been proposed⁵⁵ for the dimer. Oxidation of α -thujene with selenium dioxide did, however, completely cleave the smaller ring to give **36**; no trace of a cyclopropane derivative could be isolated.⁵⁶ Oxidation of sabinene with peracids gave the expected derivatives of sabinyl glycol^{57,58} together with a menthanetriol formed from terpinen-4-ol, itself produced by a side reaction of the substrate with the acid solvent.⁵⁹

Dehydrogenation of the thujane skeleton to an aromatic residue is promoted by many reagents; thus, α -thujene gave *p*-cymene in good yield when treated with pyridinium bromide perbromide⁶⁰ and thujone reacted with chloranil to give carvacrol.⁶¹

C. CARBONIUM ION FORMATION

Acetolysis of the optically active tosylate of **29** gave the racemic acetate of the same alcohol; similarly, the optically active ester of **31** gave the racemic acetate of the same configuration. In contrast, the tosylates of the two thujols having axial hydroxyl groups yielded a complex mixture of products in a much slower reaction.⁶² These results have been discussed in terms of a scheme in which the esters of the equatorial alcohols (*e.g.*, **37**) are assisted in solvolysis by participation of the cyclopropane ring to form nonclassical trishomocyclopropenyl ions **38** such as have been proposed to occur in the

(47) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

(48) H. Strickler, G. Ohloff, and E. sz Kováts, *Tetrahedron Lett.*, 649 (1964).

(49) C. A. Brown, *J. Amer. Chem. Soc.*, **91**, 5901 (1969).

(50) J. D. Edwards and N. Ichikawa, *J. Org. Chem.*, **29**, 503 (1964).

(51) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

(52) V. Hach, E. C. Fryberg, and E. McDonald, *Tetrahedron Lett.*, 2629 (1971).

(53) J. W. Wheeler and R. H. Chung, *J. Org. Chem.*, **34**, 1149 (1969).

(54) R. E. Clinck, P. de Mayo, and J. C. Stothers, *Chem. Ind. (London)*, 471 (1961).

(55) J. Kovar and F. Petru, *Collect. Czech. Chem. Commun.*, **25**, 604 (1960).

(56) F. Petru and J. Kovar, *ibid.*, **15**, 478 (1950).

(57) G. V. Pigulevskii and A. I. Konototina, *Zh. Obshch. Khim.*, **30**, 3492 (1960).

(58) M. I. Goryaev and G. D. Tolstikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 67 (1962).

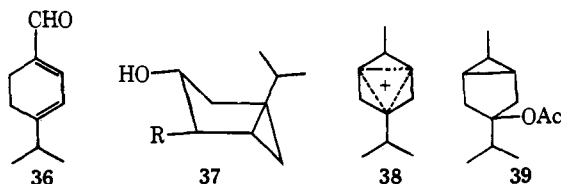
(59) P. Garside, T. G. Halsall, and G. M. Hornby, *J. Chem. Soc. C*, 716 (1969).

(60) K. K. Sugathan and J. Verghese, *Indian J. Chem.*, **2**, 497 (1964).

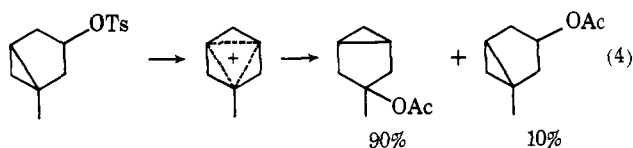
(61) Y. Fujita, *J. Chem. Soc. Jap.*, **63**, 1441 (1942); *Chem. Abstr.*, **41**, 3175 (1947).

(62) T. Norin, *Tetrahedron Lett.*, 37 (1964).

solvolyses of certain bicyclo[3.1.0]hexane derivatives^{63,64} or a set of rapidly equilibrating classical or essentially classical ions.⁶⁵ However, this theory does not account for the fact that the observed products did not include any of the tertiary acetate **39** although reaction of neoisothujyl tosylate gave a small



yield (7%) of the acetate of an unidentified alcohol. Possible explanations for the absence of this expected product are that it was unstable and rapidly rearranged to a thujyl acetate or that, because the ion involved in tosylate solvolysis was better represented by **40**, the tertiary acetate never formed. In either event, it is not easy to understand the contrast between the thujyl system and that in eq 4 in which reaction *via*

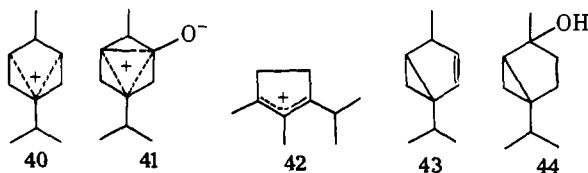


a trishomocyclopropyl cation yields the tertiary acetate in high (90%) yield.⁶⁶

In another example of this type of reaction, racemic neothujyl azide was prepared by treatment of (-)-neothujyl tosylate with azide ion. Once again, the configuration of the reacting center was retained, but again there were no products of attack at the tertiary cationic center.¹⁰

No evidence has been obtained¹ for non-Markovnikov addition to α -thujene to form a species such as **38**, and there is no reason to suspect that thujone can exist to any extent as represented by **41**.

All four epimeric thujyl tosylates gave solutions in concentrated sulfuric acid whose identical nmr and uv spectra could be assigned⁶⁷ to the existence of the ion **42**.



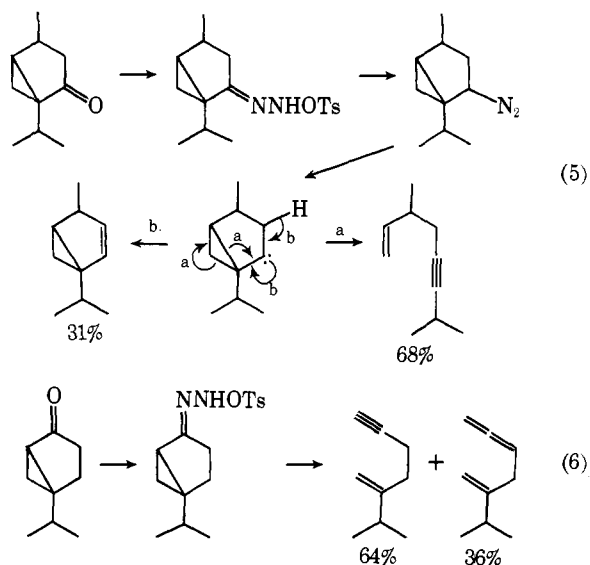
D. ELIMINATION

α -Thujene and the two isomeric forms of β -thujene (**43**) are readily prepared by treatment of the appropriate thujols with phosphorus oxychloride in pyridine, by pyrolysis of amine oxides or xanthate esters, or by Hofmann degradation of the appropriate onium compounds.⁶⁸ The first reaction requires an anti-periplanar orientation of the leaving groups, and the

pyrolyses require a syn-periplanar relationship, so that the relative configurations of the starting materials have been deduced from the nature of products from various thujols. Products of both syn and anti elimination are found from the Hofmann degradations, and tracer studies showed that part of the former process from the isothujyl onium compound involved an α',β mechanism. Other convenient preparations of α -thujene are by reaction of thujone with sodium in liquid ammonia⁶⁹ and (together with sabinene) by pyrolysis⁷⁰ of the xanthate of sabinene hydrate (**44**); this last alcohol has been isolated from peppermint oil.⁷⁰ Pyrolyses of miscellaneous amine oxides and onium compounds derived from various thujylamines have also been reported.^{71,72}

Treatment of either α -thujene or sabinene with potassium *tert*-butoxide in dimethyl sulfoxide under reflux gave an equilibrium mixture containing the isomeric olefins in 91:9 proportions with only traces of β -thujene. Conjugation of the double bond with the cyclopropane ring may provide an explanation of the unusually large amount of the exocyclic isomer (in contrast, α -pinene and β -pinene occur in the ratio 99:1 at equilibrium), but this distribution could also arise from the greater strain of accommodating a double bond in what is essentially a five-membered ring.⁷

Treatment of the *p*-toluenesulfonylhydrazone of thujone with sodium in glycol gave α -thujene (42%), β -thujene (16%), and α -terpinene (13%); however, with acetamide as solvent over 80% of the first product resulted.⁷³ Other applications of this reaction are in eq 5 and eq 6; thus bicyclic ketones with



the carbonyl group α to the small ring predominantly underwent ring scission to acetylenic products, unlike those without a conjugated carbonyl group which reacted without ring opening. The proposed mechanism⁷⁴ for the former type is shown in eq 5.

(63) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3244 (1961).

(64) S. Winstein, E. C. Friedrich, R. Baker, and Y. I. Lin, *Tetrahedron, Suppl.*, **8** (II), 621 (1966).

(65) E. J. Corey and H. Uda, *J. Amer. Chem. Soc.*, **85**, 1788 (1963).

(66) Y. I. Lin, Thesis, University of California at Los Angeles, 1967; quoted by S. Winstein, *Quart. Rev., Chem. Soc.*, **23**, 150 (1969).

(67) S. Forsen and T. Norin, *Tetrahedron Lett.*, 4183 (1966).

(68) D. V. Banthorpe and H. ff. S. Davies, *J. Chem. Soc. B*, 1339 (1968).

(69) A. J. Birch, *ibid.*, 809 (1945).

(70) J. W. Daly, F. C. Green, and R. H. Eastman, *J. Amer. Chem. Soc.*, **80**, 6330 (1958).

(71) M. Muehlstaedt and K. Walter, *Z. Chem.*, **3**, 389 (1963).

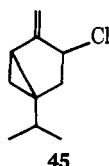
(72) J. N. Lowe, *Diss. Abstr.*, **25**, 840 (1964).

(73) J. E. Baldwin and H. C. Krauss, *J. Org. Chem.*, **35**, 2426 (1970).

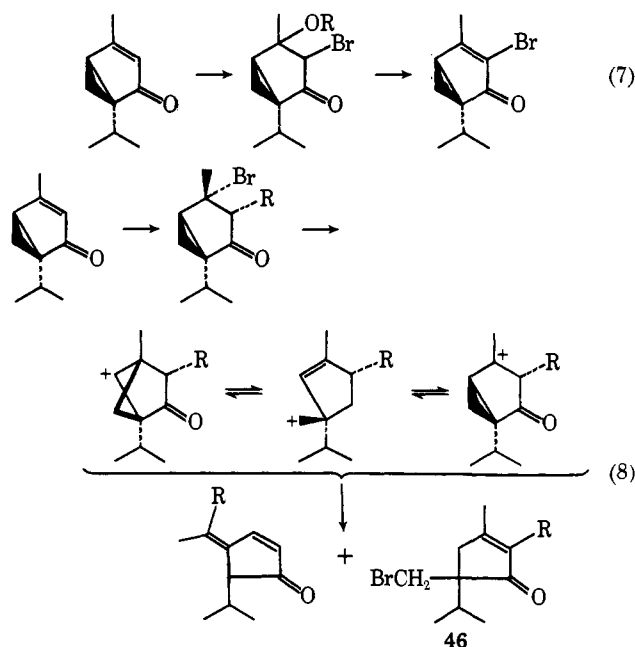
(74) J. W. Wheeler, R. H. Chung, Y. N. Vaishnav, and C. C. Shroff, *ibid.*, **34**, 545 (1969).

E. ADDITION

Except for the hydroborations previously discussed and the hydrations to be considered shortly, few studies of additions are available. Nitrosyl chloride was claimed to add to α -thujene in accordance with the Markovnikov rule,⁷⁵ but no evidence for the structure of the product was presented. Chlorination of α -thujene in the presence of buffer⁷⁶ formed the allylic product **45**, although whether electrophilic addition with elimination into the exo branch of the initially formed cation occurred or whether a dichloride was formed which lost hydrogen chloride is open to question.

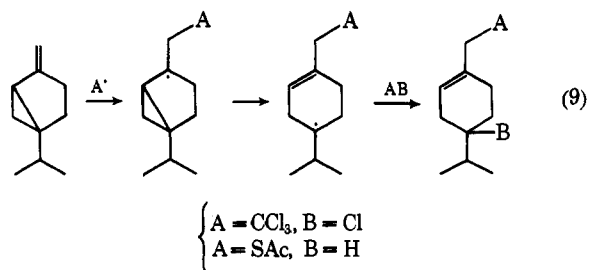


N-Bromosuccinimide and (-)-umbellulone reacted in water or methanol to give⁷⁷ a mixture of epimers which readily underwent elimination on warming (eq 7), but when hydrogen bromide or bromine in carbon tetrachloride at 0° was the reagent, deep-seated rearrangements to cyclopentyl compounds occurred with backside participation of the cyclopropane ring to form either classical ions as shown in eq 8 or nonclassi-



cal species. Treatment of **46** with base is reported to regenerate the thujane skeleton.³

Addition of carbon tetrachloride or thiols to sabinene under conditions favoring the formation of radicals led uniquely to products of ring opening^{78,79} (eq 9), although no

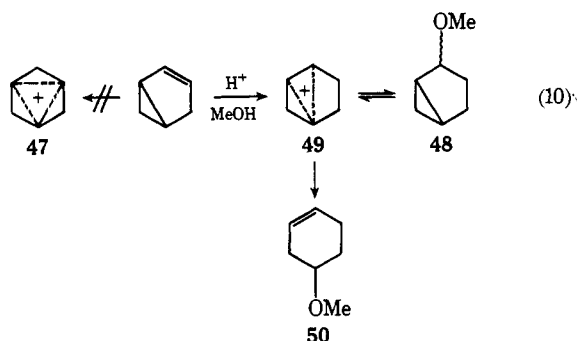


cyclopentane derivatives akin to those obtained on hydrogenation were found. Ring opening presumably relieved strain in the thujane radical and was much faster than chain transfer. Radicals formed from similar additions to β -pinene were less strained and could be trapped to give products in which the bicyclic skeleton was preserved.⁷⁹

Few other additions have been reported, the only one of note being the condensation of sabinene with diazoacetic esters to give good yields of spiro compounds.⁸⁰

F. ACID-CATALYZED ISOMERIZATIONS

The reactions of thujenes with mineral acids closely parallel reactions of bicyclo[3.1.0]hex-2-ene.^{81,82} Addition of methanol to the latter in the presence of sulfuric acid showed no trace of reaction through the trishomocyclopropyl cation **47** (eq 10) but proceeded entirely in the opposite direction to give **48**. The stereospecificity of the reaction implies stabilization of the intermediate, which is probably the ion **49**. The final product was not, however, stable but rearranged to the monocyclic product **50**.



Addition reactions of the thujenes in the presence of acids followed this general pattern, but invariably led to ring-opened products, since the presence of a methyl group on C(4) makes this position tertiary. Derivatives of sabinene hydrate, formed by reaction at this carbon atom, were readily rearranged,⁷⁰ although sabinene hydrate could be isolated when sabinene was hydrated with mercuric acetate as catalyst.⁸³ Hydration⁸⁸ of either sabinene or α -thujene with 1% aqueous sulfuric acid gave, under similar conditions, identical mixtures of terpinen-4-ol (**51**), α -terpinene (**52**), γ -terpinene (**53**), and terpinolene (**54**). Markovnikov addition of a proton to either substrate presumably generated a common ion, for

(75) R. D. Shrivastara and S. S. Deshapande, *Proc. Nat. Inst. Sci. India, Part A*, **31**, 180 (1965).

(76) D. Tishchenko and T. Danilova, *Zh. Obshch. Khim.*, **23**, 783 (1953).

(77) R. T. Gray and H. E. Smith, *Tetrahedron*, **25**, 3161 (1969).

(78) E. A. Tolstikov and M. I. Goryaev, *Zh. Obshch. Khim.*, **33**, 2061 (1963).

(79) J. A. Claisse, D. I. Davies, and L. T. Parfitt, *J. Chem. Soc. C*, 258 (1970).

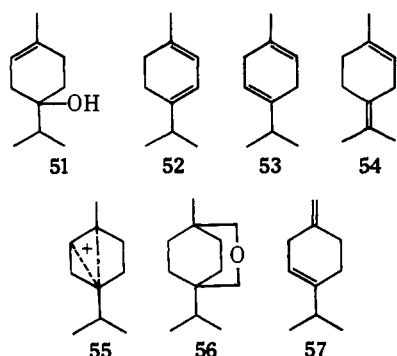
(80) M. I. Goryaev and G. K. Tolstikov, *Zh. Obshch. Khim.*, **32**, 310 (1962).

(81) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *J. Org. Chem.*, **30**, 771 (1965).

(82) P. K. Freeman, F. A. Raymond, and M. F. Grostic, *ibid.*, **32**, 24 (1967).

(83) G. F. Russell and W. G. Jennings, *J. Agr. Food Chem.*, **18**, 733 (1970).

which a structure **55** has been proposed,⁸⁴ analogous to **49**. This is also consistent with the observation⁸⁵ that reactions of α -thujene in acid proceeded more rapidly than the corresponding reactions of limonene by a factor of 1000. With 20% aqueous phosphoric acid,⁸⁶ the main product was 1,4-cineole (**56**), and mixtures of all the products mentioned also resulted from treatment of the olefins with ion-exchange resins⁸⁷ and with titanous acid.⁸⁸ Treatment of sabinene with silica gel gave⁸⁹ some β -terpinene (**57**) presumably as the

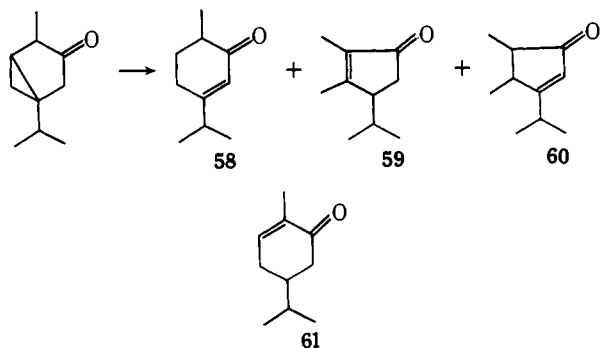


partially conjugated double bond-cyclopropyl system is attached *en bloc* to the surface of the silica gel, where the cyclopropyl system reacts preferentially (*cf.* section IV.A).

Acid-catalyzed addition of alcohol to sabinene led⁹⁰ to ring opening even at -15° , and addition of hydrogen chloride to give supposedly sabinene hydrochloride actually formed⁹¹ 4-chloromenth-1-ene.

Thujanes can be treated with 6 *N* sulfuric acid at 140° and recovered unchanged, although resinification occurred with more concentrated acid, but reaction with halogen acids resulted mainly in ring fission to form cyclopentane derivatives,⁴ sometimes accompanied by dehydration to *p*-cymene.

The thujones do not add hydrogen chloride,⁴ but the aqueous acid catalyzes rearrangement to a mixture of carvenone (**58**) and the cyclopentane derivatives **59** and **60**; **59** was often referred to as "isothujone" in the earlier literature.



(84) G. A. Tolstikov, L. N. Lishtanova, and M. I. Goryaev, *Zh. Obshch. Khim.*, **33**, 683 (1963).

(85) P. Loftus and D. Whittaker, unpublished results.

(86) K. K. Sugathan and J. Verghese, *Curr. Sci.*, **33**, 711 (1964).

(87) M. I. Goryaev, V. I. Shabalina, and A. D. Dembitskii, *Dokl. Akad. Nauk SSSR*, **158**, 155 (1964).

(88) G. A. Rudakov, M. I. Goryaev, and G. A. Tolstikov, *Zh. Obshch. Khim.*, **32**, 312 (1962).

(89) R. E. Wrolstad and W. G. Jennings, *J. Chromatogr.*, **18**, 318 (1965).

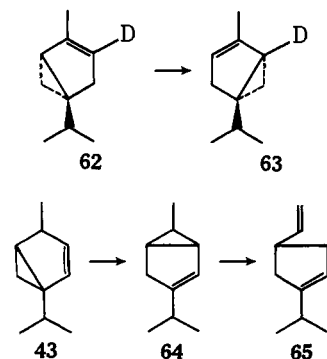
(90) M. I. Goryaev and G. A. Tolstikov, *Zh. Obshch. Khim.*, **33**, 1031 (1963).

(91) M. I. Goryaev and G. A. Tolstikov, *Dokl. Akad. Nauk SSSR*, **141**, 855 (1961).

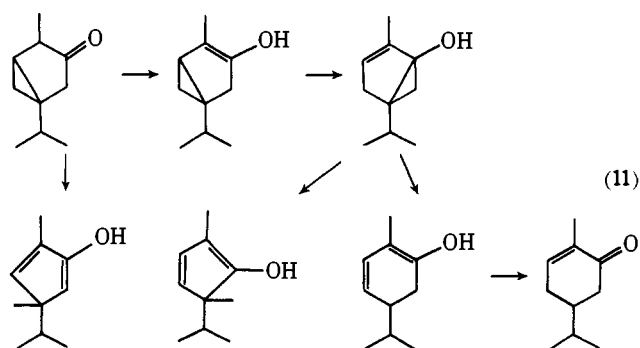
In these examples protonation took place on the cyclopropyl system so that both directions of ring opening were observed. Carvotanacetone (**61**) has been reported as a product of this reaction but is now known to arise from simultaneous thermal rearrangement.

G. PYROLYSIS

α -Thujene has long been known to racemize rapidly at 250° , and investigations^{92,93} using deuterium-labeled material have shown that the reaction was a degenerate example of the vinylcyclopropane rearrangement⁹⁴ in which **62** was converted into **63**. More recent investigations⁹⁵ have shown that the reaction is not a concerted process but consists of opening of the cyclopropane ring to give an intermediate consisting of two independent radicals. The intermediate may preserve or invert its conformation, the former process being slightly preferred. β -Thujene (**43**) underwent a similar reaction to form **64**, but now the product was unstable and rearranged further to yield **65**. Thujone rearranged through its enol



form, by a similar mechanism at little above room temperature,^{14,96} to form carvotanacetone (**61**) together with cyclopentane derivatives, in a series of steps involving hydrogen shifts (eq 11). Previous workers had supposed that the re-



actions of acids with thujone gave carvotanacetone by elimination of a proton from the ion formed by anti-Markovnikov protonation of the cyclopropane ring, but this reaction has been traced to a thermal rearrangement.

Although sabinene is also a vinylcyclopropane system, it

(92) W. von E. Doering and J. B. Lambert, *Tetrahedron*, **19**, 1989 (1963).

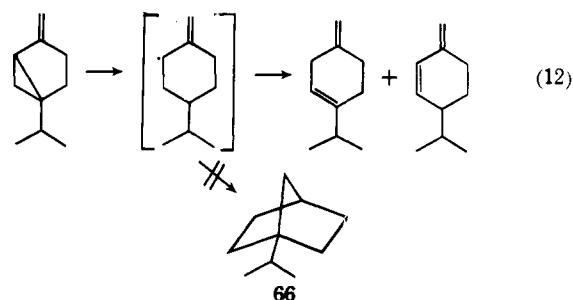
(93) D. L. Forbess, *Diss. Abstr.*, **26**, 4284 (1966); *Chem. Abstr.*, **64**, 19686 (1966).

(94) W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963).

(95) W. von E. Doering and E. K. G. Schmidt, *Tetrahedron* **27**, 2005 (1971).

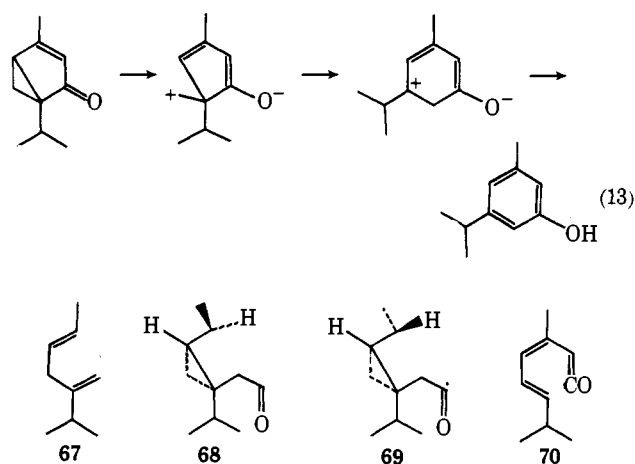
(96) W. von E. Doering, M. R. Willcott, and M. Jones, *J. Amer. Chem. Soc.*, **84**, 1224 (1962).

does not react by this mechanism. On decomposition at 600° a mixture of products was recovered in which β -terpinene and β -phellandrene predominated⁹⁷ and a biradical intermediate was likely (eq 12). Since the vinylcyclopropane rearrange-



ment is also believed to proceed by initial formation of a radical, it is possible that this reaction also could take place at lower temperatures, giving a similar intermediate, but the rigid stereochemistry of the ring system could prevent rearrangement to **66** and allow the intermediate either to return to sabinene or to decompose along conventional lines to β -phellandrene and β -terpinene. The cracking of thujanes was also considered to follow this latter route.⁹⁸

Sabinol rearranged on heating with zinc or copper to give thujone, and an initial isomerization to the enol of the latter is probable. Pyrolysis of umbellulone gave thymol together with traces of *p*-cymene and *sym*-thymol; the latter was probably⁹⁹ formed by the route in eq 13.



H. PHOTOLYSIS

Under uv irradiation,¹⁰⁰ thujone and isothujone cleaved to carbon monoxide and **67** together with the *cis* isomer of the latter.¹⁰¹ The first step of the reaction¹⁰² is probably production of the diradicals **68** and **69**; their reversible formation also provides a route for the simultaneous interconversion of thujone and isothujone. Although it is probably not a concerted process,¹⁰² this type of fragmentation appears to be

(97) B. M. Mitzner and E. T. Theimer, *J. Org. Chem.*, **27**, 3359 (1962).
 (98) V. N. Ipatieff and H. Pines, U. S. Patent 2399741; *Chem. Abstr.*, **40**, 4746 (1946).

(99) R. H. Eastman and J. W. Wheeler, *J. Amer. Chem. Soc.*, **81**, 236 (1959).

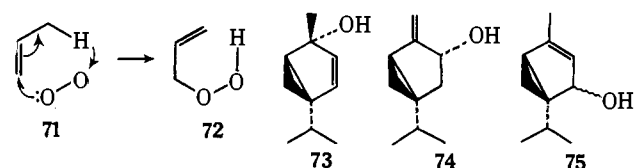
(100) R. H. Eastman, J. E. Starr, R. S. Martin, and M. K. Sakata, *J. Org. Chem.*, **28**, 2162 (1963).

(101) D. V. Banthorpe and K. W. Turnbull, *Chem. Commun.*, 177 (1966).

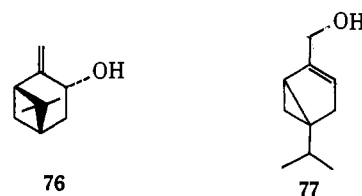
(102) R. S. Cooke and G. D. Lyon, *J. Amer. Chem. Soc.*, **93**, 3840 (1971).

common among bicyclo[3.1.0]hexanones,¹⁰³ but it is not universal for under similar conditions umbellulone formed thymol⁸⁸ in a reaction in which **70** has been implicated as an intermediate that could be trapped by reaction with methanol.¹⁰⁴

Photosensitized oxidation of thujenes led to hydroperoxides (which could be readily reduced to alcohols) that were formed with migration of the double bond in an "ene" reaction, **71** forming **72**. Reaction of (+)- α -thujene using Rose Bengal as

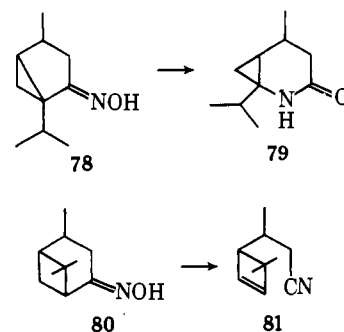


photosensitizer led to **73** and **74** in comparable amounts together with minor proportions of **75** that were probably the result of radical attack at the allylic position.¹⁰⁵ Another study² on (-)- α -thujene using the same photosensitizer gave a large (90%) yield of the optical isomer of **73**. These reactions are surprisingly stereoselective; the comparable reactions of α -pinene, although also involving the introduction of oxygen from the less hindered side of the ring, proceeded predominantly by attack at the less hindered end of the double bond to give *trans*-pinocarveol (**76**) (95% yield). Sabinene was attacked at the unhindered end of the double bond¹⁰⁶ to form essentially only **77**.



I. RING EXPANSION

Thujane derivatives have not been reported to undergo any ring expansion reactions yielding carbocyclic rings, but the Beckmann rearrangement of the oxime of dihydroumbellulone (**78**) gives the lactam **79** by migration of the cyclopropyl group.¹⁰⁷ Formation of a lactam from the oxime of a bicyclic ketone having a bridgehead α -carbon atom is unexpected. Most ketoximes of this type yield an unsaturated nitrile under



(103) J. E. Starr and R. H. Eastman, *J. Org. Chem.*, **31**, 1393 (1966).

(104) L. Barber, O. L. Chapman, and J. D. Lassila, *J. Amer. Chem. Soc.*, **90**, 5933 (1968).

(105) E. Klein and W. Rojahn, *Chem. Ber.*, **98**, 3045 (1965).

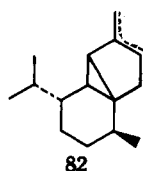
(106) H. Dasler, *Justus Liebigs Ann. Chem.*, **622**, 194 (1959).

(107) W. D. Burrows and R. H. Eastman, *J. Amer. Chem. Soc.*, **79**, 3756 (1957).

Beckmann rearrangement conditions, a typical example being the formation of **81** from verbanone oxime (**80**).

V. Sesquithujanes

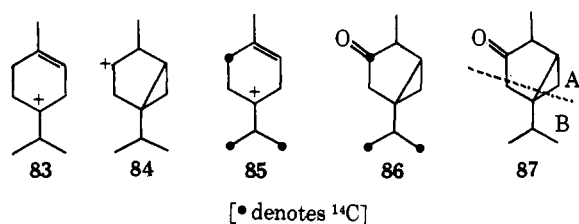
Higher terpenes containing the thujane skeleton are relatively uncommon, the best known examples of this type being the isomeric α - and β -cubebenes (**82**) which have been isolated



from oil of cubeb.¹⁰⁸ Total syntheses have been devised.¹⁰⁹

VI. Biosynthesis

An attractive hypothetical route for the biogenesis of thujane derivatives is bicyclization of the ion **83**, or its structural equivalent derived from terpinen-4-ol, to form **84** and functionalization of the latter.¹¹⁰ There is some experimental support for this idea; the time courses of incorporation of [¹⁴C]acetate into monoterpenes of *Tanacetum vulgare* were consistent with α -terpineol and terpinen-4-ol being precursors of thujone, and in addition invalidated a proposal that thujane derivatives and other bicyclic monoterpenes were directly formed



by condensation of C₅ moieties without the intermediacy of acyclic or monocyclic C₁₀ compounds.¹¹¹

On the basis of the probable mechanism, feeding of [2-¹⁴C]-mevalonic acid to an appropriate plant should lead to the intermediate cation and thujone being labeled as in **85** and **86**. Degradation to locate the tracer in thujone, isothujone, sabinene, sabinol, and sabinyl acetate obtained after administering tracer to certain *Tanacetum*, *Thuja*, and *Juniperus* species revealed that in every example the carbon corresponding to that of the carbonyl group in thujone was indeed labeled, but was so to the extent of 90–95% of the incorporated tracer; the moiety B of the skeleton **87** contained negligible or very low amounts of radioactivity.¹¹² This unexpected asymmetry

(108) Y. Ohta, K. Ohara, and Y. Hirota, *Tetrahedron Lett.*, 4181 (1968).

(109) E. Piers, R. W. Britton, and W. de Waal, *Can. J. Chem.* **49**, 12 (1971).

(110) L. Ruzicka, *Experientia*, **9**, 357 (1953).

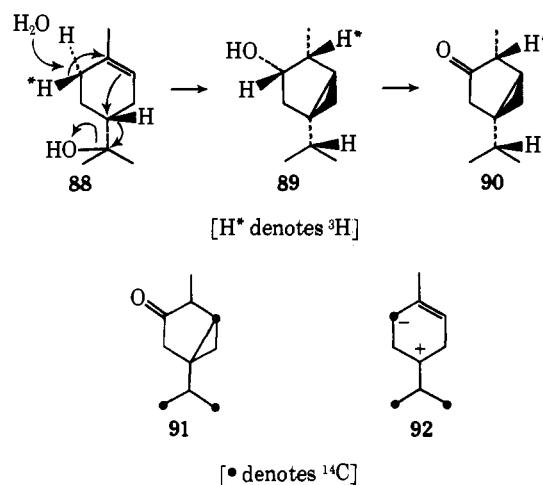
(111) D. V. Banthorpe and A. Wirz-Justice, *J. Chem. Soc. C*, 541 (1969).

(112) D. V. Banthorpe, J. Mann, and K. W. Turnbull, *ibid.*, 2689 (1970).

of labeling has been found in other types of monoterpenes¹¹³ and possible explanations of why the moieties A and B in **87** and related skeletons could be derived from separate metabolic pools have been outlined.¹¹²

Usually, the biogenetic route has been formally envisaged in terms of carbonium ions such as **83** or their structural equivalents, but concerted bicyclizations and hydride shifts, perhaps with concomitant introduction of oxygen as in the conversion of **88** into **89**, are an attractive alternative. In this latter mechanism, one hydrogen (starred in **88**) would shift to the C(4) position of thujone **90** whereas the other would be lost. The mechanism has been tested by feeding the 2*R* and 2*S* isomers of [2-³H₁]mevalonic acid to different specimens of *Tanacetum vulgare* so as to cause the appropriate hydrogens in **88** to be labeled in the two experiments. Feeding of one isomer led to the loss of essentially all the tracer en route to thujone, whereas tracer was incorporated from the other isomer and was situated at C(4) in the product.¹¹⁴

A completely different pattern of labeling was claimed in thujone biosynthesized from [2-¹⁴C]mevalonic acid by *Thuja occidentalis*. Incomplete degradation led to the presumed pattern **91**, and the product was supposed to be derived from



85 and the zwitterion **92** or its structural equivalent.¹¹⁵ However, repetition of the work under the same and other conditions of feeding gave the asymmetric pattern of labeling with all the tracer concentrated at the carbonyl carbon atom.¹¹³

Little is known of the metabolic significance *in vivo* of thujyl compounds (or indeed of other monoterpenes). Feeding of ¹⁴C-labeled thujone to *Tanacetum vulgare* and location of the tracer after various time intervals showed that a variety of interconversions within the monoterpenes as well as passage of tracer into pigments, sugars, and amino acids all occurred rapidly.¹¹¹

(113) D. V. Banthorpe and D. Baxendale, *ibid.*, 2694 (1970).

(114) J. Mann, Ph.D. Thesis, University of London, 1970.

(115) W. Sandermann and W. Schweers, *Tetrahedron Lett.*, 257 (1962).