mg of the product by vpc gave 7.4 mg of partially crystalline material having mp 93.5–95.5° (softens at 91°). Sublimation gave (+)-occidentalol (**2**) having mp 94.2–95.0°; uv max 263.5 nm (ϵ 4300, 3940); $[\alpha]^{26}\text{D}$ +364°, +360° (*c* 0.36, $CHCl_3$). The nmr (microcavity tube) and ir spectra of synthetic (+)-occidentalol were essentially identical with spectra determined on a sample of authentic (+)-occidentalol (kindly supplied by Dr. E. von Rudloff) which exhibited mp 94–95.5°; $[\alpha]^{26}\text{D}$ +341° (*c* 0.53); uv max 263.5 nm (ϵ 4450).

C.—Treatment of the mixture (230 mg) containing (+)-**12** (*ca.* 86 mg) from photolysis run C with CH_3Li in Et_2O followed by preparative vpc afforded 35 mg of (+)-occidentalol (**2**), $[\alpha]^{27}\text{D}$ +290° (*c* 2.92); vpc showed ≥85% purity. Further purification of 29.2 mg of (+)-**2** by vpc gave 14.7 mg of a partly crystalline glass, $[\alpha]^{25}\text{D}$ +352° (*c* 0.19, $CHCl_3$). Sublimation of the glassy material gave (+)-occidentalol (**2**) as needles, mp 91.0–92.5°, uv max 264 nm (ϵ 3905).

(+)-11-Hydroxy-5*β*,7*αH*-eudesma-1,3-diene [(+)-1] [7-Epi-(−)-occidentalol].—A solution of (−)-**11** (40 mg from run A in 2 ml of Et_2O at 0°) was treated with methyllithium (1 ml of 2.3 *M* solution in Et_2O) under N_2. A normal work-up gave an oil which was purified by glpc (XE-60, column 190°, head 216°)[42] to yield 28 mg (70%) of (+)-**1** as a viscous liquid: $[\alpha]^{25}\text{D}$ +60.7° (*c* 0.15); uv max 266 nm (ϵ 4900) and 273 (shoulder); ORD (*c* 0.0029) $[\phi]_{286}$ +13,300°, $[\phi]_{266}$ 0°, $[\phi]_{234}$ −28,300°; CD (*c* 0.0029) $[\theta]_{261}$ +27,600°, $[\theta]_{270}$ +24,500° (shoulder), and inflections at 255 and 285 nm; nmr δ 1.10 (s, 3, H-14), 1.14 (s, 6, H-12 and H-13), 1.81 (br s, 3, H-15), and 5.1–5.8 (m, 3, H-1,2,3); mass spectrum molecular ion theoretical 220.182, found 220.170.

(−)-11-Hydroxy-5,7*αH*-eudesma-1,3-diene [(−)-14] [(−)-*trans*-Occidentalol].—A solution of 191 mg (0.87 mmol) of diene **9** (prepared by method A) in 10 ml of Et_2O was treated with 5 ml of 2.3 *M* methyllithium in Et_2O. The mixture was poured into ice water and worked up in the normal manner to yield 187 mg (98%) of solid. Recrystallization from hexane afforded 81 mg (42%) of (−)-*trans*-occidentalol (**14**) as white needles: mp 94–95.5°; $[\alpha]^{25}\text{D}$ −47° (*c* 0.32); ir ($CHCl_3$) 3620, 3480, 1645, and 1590 cm^{-1}; uv max 264 nm (ϵ 4700); ORD (*c* 0.0043) $[\phi]_{272}$ −8100°, $[\phi]_{255}$ 0°, $[\phi]_{225}$ +25,000°; CD (*c* 0.0043) $[\theta]_{250}$ −21,400°, $[\theta]_{210}$ +7200°; nmr ($CDCl_3$) δ 0.79 (s, 3, H-14), 1.22 (s, 6, H-12 and H-13), 1.38 (s, 1, OH), 1.80 (d, 3, J = 1.4 Hz, H-15), and 5.39–5.98 (m, 3, H-1,2,3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; mol wt, 220.183. Found: C, 81.85; H, 10.86; mol wt, 220.203 (mass spectrum).

Photolysis of (−)-*trans*-Occidentalol [(−)-14].—A solution of trans-fused alcohol (−)-**14** (110 mg) in 270 ml of deoxygenated Et_2O at −78° was irradiated (4.1 hr)[45] as described above for the diene **9** (run A). Warm up (25°) and concentration of the solution afforded 115 mg of oil which consisted of (+)-occidentalol (**2**) (30%), 7-epi-(−)-occidentalol [(+)-**1**] (44%), (−)-*trans*-occidentalol (**14**) (24%), and a minor impurity (2%) as determined by vpc analysis on 10% XE-60[42] (column 190°, head 220°; retention times—**2**, 15.9 min; **1**, 20.9 min; **14**, 23.6 min; impurity, 28.0 min).

Registry No.—(+)-**1**, 29484-47-7; (−)-**2**, 29484-46-6; (+)-**2**, 473-17-6; (−)-**3**, 18508-76-4; **4**, 37573-94-7; **5**, 37573-95-8; **6**, 37573-96-9; **7**, 37573-97-0; **7** (3,5-DNB), 37573-98-1; **8**, 37573-99-2; **9**, 37574-00-8; (−)-**11**, 29484-53-5; (+)-**12**, 37574-02-0; (−)-**14**, 37574-03-1.

Acknowledgment.—We thank Professor S. I. Weissman for a loan of equipment for the low-temperature uv experiments.

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[45] Preliminary experiments (see footnote 9 in ref 7) indicated that the photostationary state was probably achieved after about 3.7 hr.

Conformational Isomerism in Dihydropregeijerene and Hedycaryol[1,2]

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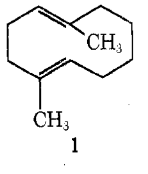
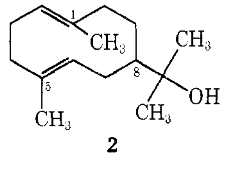
Conformations available to the 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene sesquiterpenes dihydropregeijerene (**1**) and hedycaryol (**2**) are discussed in terms of the cubic array of Chart 1. Conformers have either a crossed or parallel relation of the double bonds in association with arrangements of the C-7,8,9,10 methylene segment which are described as chair, twist-boat, and twists. They are interconverted by three processes: rotation of each of the double bonds through the ring and inversion of the C-8,9 unit. Variable-temperature nmr spectra of **1** and **2**, particularly of samples deuterated at C-2, were helpful in assessing conformer populations and interconversions. All interconversions rates are rapid at 90°; all are slow at −30°. The conformational compositions of both **1** and **2** consist of a mixture of crossed chair and approximately equal amounts of parallel twists *T′* and *T″* with a temperature-dependent composition favoring the parallel set at higher temperatures. However, the relative amounts of the crossed and parallel sets differ for the two molecules: for **1** the parallel set increases from 15% at −70° to 35% at 0°; for **2** the parallel set already predominates to the extent of 75% at −30°. The demonstration of the existence of specific conformers of hedycaryol provides an experimental basis for biogenetic speculations which have invoked stereospecific, conformationally controlled reactions.

Since 1959 many sesquiterpene *trans,trans*-1,5-cyclodecadienes (members of the germacrane class) have been isolated. Following the establishment of constitution and configuration, data have started to accumulate on conformations and their relation to reactivity, an area of considerable biogenetic importance.[3] This article provides data pertinent to the conformations in solution of two of the simplest sesquiterpene *trans,trans*-1,5-cyclodecadienes, dihydropregeijerene (**1**) and hedycaryol (**2**).



1



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Hedycaryol is the simplest known representative of sesquiterpene *trans,trans*-1,5-cyclodecadienes which contain one or more chiral centers (in hedycaryol at C-8) in addition to the potential chirality of the ring system itself. Dihydropregeijerene is an even simpler molecule, lacking any chiral center and indeed any substitu-

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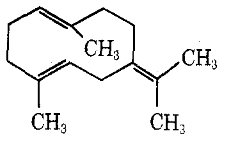
[1] The investigation was supported by Public Health Service Research Grant GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service.

[2] The article is abstracted from the Ph.D. theses of Y. C. P. and H. C. K., Wesleyan University, 1971.

[3] For a review see W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 321 (1967). The earliest significant speculation is that of J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

tion on saturated carbon. However, the characteristic methyls present on the two double bonds are attached unsymmetrically to C-1 and C-5, thereby making nonequivalent the otherwise equivalent double bonds.

It has been recognized that sesquiterpene *trans,trans*-1,5-cyclodecadienes may adopt conformations in which the two double bonds face each other across the ring in either a crossed or parallel relation. X-Ray analyses have shown that crystalline silver nitrate complexes of germacrene B (**3**) and pregeijerene (**4**) consist of racemic mixtures of crossed conformations.[4,5] (At the same time interesting distortions of the double bonds have been revealed.) Costunolide (**5**) has similarly been shown to exist in a crossed conformation.[6] In solution, application of the nuclear Overhauser effect has led to the assignment of crossed conformations to furanodienone (**6**)[7], dihydrotamaulipin A acetate (**7**),[8] and linderalactone (**8a**).[9] In a few instances interconvertible conformations have been demonstrated. Urospermal (**9**) extraordinarily exists in two isolable, crystalline forms, each stabilized in a crossed conformation by hydrogen bonding.[10] The two forms equilibrate in solution and the equilibrium constant is solvent dependent. Isabelin (**10**) and litsealactone (**8b**) have been observed by nmr spectroscopy at room temperature to consist of pairs of nonisolable conformers in ratios of $\sim$60:40 and 85:15, respectively.[9,11] The major isomers have been assigned crossed conformations. The minor forms of **10** (interestingly, probably the only conformer present in the crystalline state) and **8b** appear to be parallel conformers. In this work the structurally simple molecules of dihydropregeijerene (**1**) and hedycaryol (**2**) are shown to consist of mobile equilibria in solution of crossed and parallel conformers.



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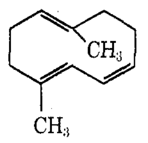

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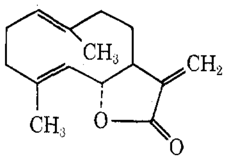

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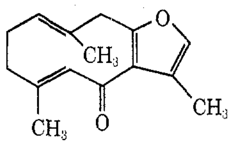

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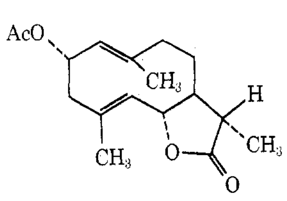

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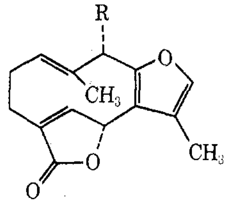
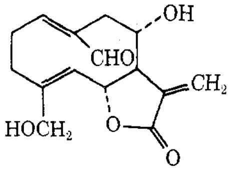


8a, R = H
b, R = OAc



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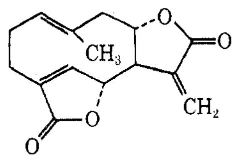

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Dihydropregeijerene (1). Conformational Analysis—Although conformational analysis of cyclodecane[12] is complex, the introduction of double bonds imposes geometric restrictions which make it progressively simpler for *trans*-cyclodecene[13] and *trans,trans*-1,5-cyclodecadiene. The analysis carried out in the present work was based on mechanical models from which conformers were generated and their interrelationships noted. The models consisted of normal, *i.e.*, undistorted, bond angles even though considerable deviations are known to occur in medium rings.[5,12] The experimental data did not demand more precise geometry and no specific distortions were considered to be justified.

It is useful to start by describing the interconversion operations rather than the conformers themselves. There are three: rotation of the C-1,2 double bond through the ring; rotation of the C-5,6 double bond through the ring; and a change of the C-7,8,9,10 methylene chain which is described as C-8,9 inversion. The conformers so interrelated are not immediately and precisely defined by mechanical models which exhibit considerable flexibility. However, a good chemical and representational assumption is that C-3,4,7,10 lie approximately in a plane. The X-ray data published for costunolide[6] are in accord with this assumption, which corresponds to maximizing separation of the two sides of the ring (as defined by the planes of the two double bonds C-4,5,6,7 and C-10,1,2,3). There are eight low-energy conformers, each capable of conformational change *via* any one of the three interconverting operations. They are represented in Chart I as a cubic array in which each of the three sets of parallel edges of the cube corresponds to an interconverting operation.

So-called crossed conformers have identical planar chirality for the two double bonds, which can therefore be designated R-1, R-5 and S-1, S-5 or, more briefly, RR and SS. Independently, the C-7,8,9,10 methylene segment may resemble a cyclohexane chair (*C*) or twist-boat (*TB*), the two being related *via* C-8,9 inversion. (In some ways the *trans,trans*-1,5-cyclodecadiene system resembles a cyclohexane which has been stretched by insertion of two double bonds.) The total number of crossed possibilities is thus RR-*C* and its enantiomer SS-*C*; and RR-*TB* and its enantiomer SS-*TB*. It is interesting and probably important that the chair is associated with almost ideal staggering of the methylene segments C-3,4 and C-7,8,9,10 whereas the twist-boat has an unfavorable C-8,9 eclipsing. The angles of inclination of the double bond planes to the basal plane of the ring C-3,4,7,10 are not precisely defined because

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[4] F. H. Allen and D. Rogers, *Chem. Commun.*, 588 (1967).

[5] J. McClure, G. A. Sims, P. Coggon, and A. T. McPhail, *ibid.*, 128 (1970).

[6] F. Sorm, M. Suchy, M. Holub, A. Linek, I. Hadinec, and C. Novak, *Tetrahedron Lett.*, 1893 (1970).

[7] H. Hikino, C. Konno, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, *Chem. Commun.*, 662 (1969).

[8] N. S. Bhacca and N. H. Fischer, *ibid.*, 68 (1969).

[9] K. Takeda, K. Tori, I. Horibe, M. Ohtsuru, and H. Minato, *J. Chem. Soc. C*, 2697 (1970).

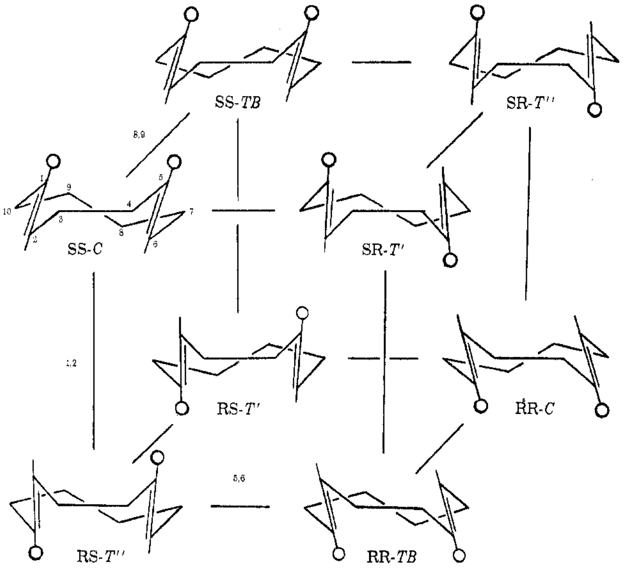
[10] R. K. Bentley, J. G. St. C. Buchanan, T. G. Halsall, and V. Thaller, *Chem. Commun.*, 435 (1970).

[11] H. Yoshioka, T. J. Mabry, and H. E. Miller, *ibid.*, 1679 (1968).

[12] See J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964).

[13] G. Binsch and J. D. Roberts, *ibid.*, **87**, 5157 (1965).

CHART I
CONFORMATIONS OF 1,5-DIMETHYL-1,5-*trans,trans*-CYCLODECADIENES AND THEIR INTERRELATIONSHIPS[a]



[a] ○ designates the methyl groups; 1,2 and 5,6 denote rotation of the C-1,2 and C-5,6 double bonds through the ring, and 8,9 denotes inversion of the C-7,8,9,10 methylene segment. Conformations: *C*, chair; *T*, twist; *TB*, twist-boat.

of a certain amount of flexibility associated with their pivoting about C-3,10 and C-4,7. However, the C-5,6 double bond must be inclined in the sense of the C-5 methyl pointing away from the center of the ring and the C-6 hydrogen into the center of the ring because rotation of the C-5 methyl to a perpendicular position is resisted by stretching of the C-7,8,9,10 segment. The plane of the C-1,2 double bond is similarly influenced but it is likely to be more nearly perpendicular than the C-5,6 double bond because of methyl–methyl repulsion. Crossed conformers in Chart I are drawn for representational convenience with similarly inclined planes, each conformer thereby possessing a pseudo[14]-C_2 axis of symmetry passing through the midpoints of bonds C-3,4 and C-8,9: the methyl–methyl separation is 3.0 Å compared to 3.5 Å measured by X-ray analysis for the silver nitrate complex of pregeijerene.[5]

Parallel conformers are generated from crossed conformers by C-1,2 or C-5,6 rotation through the ring, with the vinyl hydrogen necessarily passing through the ring in each case because the methyl groups are too bulky. Models suggest that, of the two, C-5,6 rotation may be somewhat more facile.

Parallel conformers have double bonds of opposite chirality and both RS and SR combinations are possible: they are pseudo[14] meso forms. Independently, the C-7,8,9,10 segment can be in one of two enantiomeric twist (*T*) forms[15] yielding a total set of RS-*T'* and RS-*T''* which are pseudo[14]-enantiomeric, and related *via* C-8,9 inversion, and the corresponding pair SR-*T'* and SR-*T''*. They all have eclipsing interactions of the C-3,4 and C-8,9 units but there is no methyl–methyl repulsion. The double bonds are quite flexible with respect to pivoting about C-3,10 and C-4,7 and their inclinations in Chart I are rather arbitrarily drawn.

Results and Discussion

Roberts[13] has shown by nmr that the double bond of *trans*-cyclodecene rotates through the ring with an energy of activation of 10.7 kcal mol^{-1} and furthermore that inversion of the C-6,7 methylene segment opposite the double bond requires a comparable energy of activation. Thus all three operations interconverting conformers of dihydropregeijerene might be expected to contribute to the temperature-dependent nmr spectrum.

At ambient temperature the 60-MHz nmr spectrum of **1** shows distinct absorptions corresponding to two vinyl methyls at δ 1.41 and 1.48 ppm, each appearing as a sharp doublet with $J = 1$ Hz; eight allylic hydrogens as a fairly sharp envelope centered at δ 2.1 ppm; and two vinyl hydrogens as a broad, structureless band with a width of 45 Hz. Both raising and lowering the temperature from ambient leads to marked changes, clearly indicating the existence of interconverting conformers, but overlap of absorptions of the two vinyl hydrogens does not allow more than this generalization. However, examination of the absorption patterns of the individual vinyl hydrogens was rewarding and was made possible by the synthesis of selectively deuterated compounds.

The spectrum changes shown in the pattern of the C-6 vinyl hydrogen of **1**-*2-d* were particularly significant. Cooling in carbon disulfide solution led to the formation of two separate areas of absorption centered at δ 4.3 and 5.0. The high-field area developed continuously as a doublet with $J = 10$ Hz with widths at half-height of 6 Hz at −70°. The low-field area first developed a structure with three prominent peaks, it then yielded a coalescence envelope, and finally developed more structure at −70°. At −70° the area ratio of high- to low-field absorptions was 85:15 but the ratio changed continuously with increasing temperature, attaining 65:35 at 0°. (It should be noted here that the trend and approximate ratios are definite and significant but no great accuracy is claimed for either the temperatures or ratios.) Heating in carbon tetrachloride yielded a symmetrical triplet ($J = 7$ Hz) of quartets ($J = 1$ Hz) which was very well defined at 90°.

By comparison the pattern of the C-2 vinyl hydrogen of **1**-*6-d* was uninteresting. Cooling in carbon disulfide led to the development of structure but no separation into two areas of significantly different chemical shift occurred, the maximum of absorption remaining almost invariant at δ 4.8 ppm, and heating in carbon tetrachloride yielded, at 90°, a triplet which was poorly defined with only indications of further structure.

Other parts of the spectrum also showed a temperature variation, and the patterns and behavior of the vinyl methyls are significant, each appearing at ambient temperature as a doublet with $J = 1$ Hz in undeuterated **1**. In **1**-*2,6-d_2* there are two sharp singlets which are resolved by cooling into a major pair absorbing at δ 1.32 and 1.48 and a minor pair at 1.40 and 1.45. The highest field absorption at δ 1.32 appears as a singlet in the spectrum of **1**-*2-d* and a doublet in the spectrum of **1**-

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[14] Pseudosymmetry refers to the symmetry of the ring carbons or, equivalently, the total system in which the methyls have been replaced by hydrogens.

[15] All-eclipsed parallel conformers possessing a pseudo[14]-plane of symmetry bisecting the C-3,4, and C-8,9 bonds were rejected as too high in energy to contribute to the ground-state population. They may resemble the transition states in the C-8,9 operation interconverting *T'* and *T''* conformers.

6-d and is therefore assigned to the C-1 methyl; the methyl absorption at 1.48 shows the opposite behavior.[16]

The data do not justify calculations of enthalpies and entropies for equilibria or rates and they do not justify exhaustive logical argument. They *are* qualitatively interpretable in terms of the array of Chart I with significant results.

At high temperatures all three interconverting operations are expected to be rapid[17] with the consequent rapid interconversion of conformers diagonally related across the body of the cube of Chart I. Such conformers are enantiomeric and their rapid interconversion makes the methylene hydrogens of C-7 enantiotopic, thereby explaining the symmetrical triplet pattern ($J = 7$ Hz) of the C-6 vinyl hydrogen at 90°. The triplet is further split into quartets ($J = 1$ Hz) by the C-5 methyl hydrogens. The pattern of absorption for the C-2 vinyl hydrogen is less well defined because of virtual coupling of the methylene hydrogens of C-3 with those on C-4 (both pairs are allylic).

At low temperatures slow[17] rates are expected for all three interconverting operations. A slowing down of both C-1,2 and C-5,6 rotations is first seen, thereby separating crossed and parallel sets of conformers and then, at somewhat lower temperatures, C-8,9 inversion is observably slowed, thereby allowing observation of the individual C, TB, T' and T'' conformers which are present.[17,18] Crossed and parallel sets are distinguished by the relatively high field absorption of the C-6 vinyl hydrogen and C-1 methyl hydrogens of the crossed set which is accentuated by the specific inclination of the C-5,6 double bond.[19] By contrast, the C-2 vinyl hydrogen is not selectively shielded in either of the sets and no chemical shift separation is observed. Both T' and T'' conformers of the parallel set are significantly populated. Their rapid interconversion *via* C-8,9 inversion at temperatures around 0° leads to structured absorption for the C-6 vinyl hydrogen which arises from rapid averaging. Coalescence then occurs and is followed by the reappearance of structure which is the superposition of absorptions of T' and T'' conformers which are expected to have similar chemical shifts but appreciably different coupling. By contrast the high-field absorption of the C-6 vinyl hydrogen of the crossed set progressively develops into a sharper and sharper symmetrical doublet ($J = 10$ Hz) with no intermediate line shape changes. At $-70°$ each half of the doublet has a half-height width of 6 Hz for which coupling with the C-5 methyl hydrogens is largely responsible. The barrier to C-8,9 inversion in the parallel and crossed sets would not appear to be very different and the presence of both C and TB conformers should have led to a phenomenologically similar, unsymmetrical, temperature-dependent spectrum. The observed pattern is consistent with the presence of only one of them.[20] This must be the chair, which does not possess the unfavorable C-8,9 eclipsing interaction of the twist-boat. Moreover, the model of the chair shows dihedral angles of *ca.* 200 and 80° for the C-7 methylene hydrogens consistent with the observed pattern, with coupling for the 80° relation close to zero. The corresponding dihedral angles for the twist-boat are *ca.* 30 and 150° and are inconsistent with the observed pattern.[21]

The equilibrium constant for the crossed and parallel sets is temperature dependent; the crossed set predominates at low temperatures but the parallel set contributes equally at temperatures not much above room temperature. The crossed set is thus favored by enthalpy, the parallel set by entropy, and a significant contribution to the entropy difference must be the population of two parallel conformers but only one crossed.

Hedycaryol (2).—Hedycaryol isolated from natural sources[22] is the *d* isomer, $[\alpha]_D$ +30.8°; our synthetic material is the *dl* racemate. The hydroxypropyl group attached to C-8 makes that carbon asymmetric and the array of Chart I now refers separately to the individual enantiomers of hedycaryol, with all conformers of a given enantiomer diastereomerically related. Conformers situated on the front and back faces of the cube are distinguished by the pseudoequatorial and pseudoaxial nature of the hydroxypropyl substituent and its bulk effectively removes the pseudoaxial set from the ground-state population, and thereby eliminates C-8,9 inversion as an operator contributing to the temperature-dependent nmr spectrum. The effect of C-1,2 and C-5,6 rotations are still observable with crossed and parallel sets emerging from the ambient temperature coalescent pattern of the C-6 vinyl hydrogen of *2-2-d* as two distinct areas centered at δ 4.4 and 5.0 ppm. The same trend in temperature-dependent population is observed, higher temperatures favoring the parallel set, but it is interesting that the parallel set already predominates to the extent of 75% at $-30°$. If an explanation for the relative favoring of parallel forms by the hydroxypropyl groups is called for (the energy difference being very small), it is worth noting that the nonbonded interactions of the substituent with the C-7,8,9 segment are relieved somewhat in going from the staggered–staggered arrangement of the crossed chair to the staggered–eclipsed arrangement of the parallel twists. This effect should also make the crossed twist-boat relatively more stable, but the effect is too small to be observable; the pattern for the C-6 vinyl hydrogen of the crossed set develops as a doublet, $J = 10$ Hz, very similar to that of dihydropregeijerene. The corresponding pattern for the parallel set develops structure, which does not go through a coalescence phase, consistent with population of two twist conformers which can only average *via* a crossed conformer. At 90° the conformational composition consists almost completely of these parallel twists, averaging rapidly *via* C-1,2 and C-5,6 rotations, and the spectrum of the C-6 vinyl hydrogen is a much distorted triplet of quar-

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[16] Methyl assignments for germacrane sesquiterpenes have been made by R. N. Sathe, G. H. Kulkarri, and G. R. Kelkar, *Chem. Ind.* (*London*), 448 (1968).

[17] Rapid and slow rates refer to the nmr time scale only.

[18] Although C-8,9 inversion is observable at a lower temperature than double-bond rotation, this does not necessarily imply a faster rate constant for C-8,9 inversion because a smaller Δν is averaged.

[19] The assumption is made that chemical shift differences are largely caused by differential shielding by the opposed double bonds and not by differential distortion effects of the attached double bonds. Consistent with this assumption are the similar and almost normal chemical shifts of *trans*-cyclooctene and *trans*-cyclodecene (δ 5.4 ppm); *cf.* cyclohexene (5.6). The absorptions of *trans,trans*-1,5-cyclooctadiene (4.9) and *trans,trans*-1,5-cyclodecadiene (4.7) are at significantly higher field.

[20] No useful upper limit can be set on the amount of twist–boat present.

[21] For a summary of the angular dependence of coupling, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

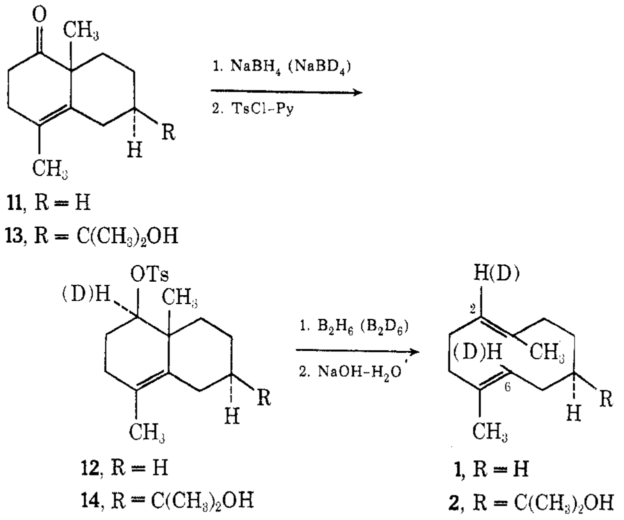
[22] R. V. H. Jones and M. D. Sutherland, *Chem. Commun.*, 1229 (1968).

tets as might be expected from roughly equal amounts of the individual twist conformers with complementary but not equivalent coupling of the C-7 methylene hydrogens.

In conclusion, it can be stated that the use of deuterium substitution proved to be very effective in outlining conformational relationships of dihydropregeijerene and hedycaryol, although they have not been fully dissected. Experimental substance has been provided for biogenetic suggestions which have invoked stereospecific, conformationally dependent reactions and it is now clear that hedycaryol, in particular, can readily adopt three conformations, one crossed chair and two parallel twists.

Synthetic Work—*dl*-Hedycaryol (2) was synthesized as previously described[23] and 2-*2*-*d* was prepared by using sodium borodeuteride in the conversion **13** → **14** (see Scheme I). Dihydropregeijerene (1) was obtained for the first time by the same overall procedure. 4-Methyl-$\Delta^{4(10)}$-1-octalone (**11**) was reduced with sodium borohydride in ethanol to a mixture of two alcohols (82:18). It was anticipated that the major isomer would have a cis relationship of the angular methyl and hydroxyl, the methyl sterically favoring trans delivery of hydride. Tosylation of the mixture and subsequent crystallization gave a single tosylate (**12**) in 68% yield, showing an nmr chemical shift for the distinctive methine hydrogen of δ 4.35 ppm, with a width at half-height of 18 Hz. The corresponding chemical shift of the minor tosylate in the mother liquor was δ 4.46 ppm, with a width at half-height of 11 Hz, thus confirming the cis stereochemistry of the major alcohol.[21] Fragmentation of the tosylate was carried out by first treating with excess diborane and then adding aqueous sodium hydroxide;[24] after 6 hr at 70°, work-up, including distillation, afforded a 75% yield of crude product which was purified by silver nitrate extraction and redistillation. The product, isolated in 40% yield, was found to be homogeneous by capillary glpc at 80°; its analysis was consistent with a formula composition of $C_{12}H_{20}$; and spectroscopic data were consistent with its formulation as dihydropregeijerene. Thermally, after 6 hr at 140°, it yielded a Cope-related product, the nmr spectrum of which was found to be in accord with that reported for authentic dihydrogeijerene.[25]

SCHEME I



Syntheses of **1**-*2*-*d*, **1**-*6*-*d*, and **1**-*2,6*-d_2 were accomplished by selective deuteration, a C-2 vinyl deuterium being introduced in the conversion **11** → **12** by using sodium borodeuteride, and a C-6 vinyl deuterium by the use of deuterated diborane in the conversion **12** → **1**.

Experimental Section

Physical Data.—Melting points were determined using a Thomas Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained using a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were recorded using a Varian A-60A spectrometer employing tetramethylsilane as an internal reference. Varian unit V-6040 was used for variable-temperature nmr studies. For low-temperature runs both spinner air and coolant nitrogen were predried by passing through Drierite towers and coolant nitrogen was further dried by passing through a liquid nitrogen trap. Temperatures were calibrated by determining the temperature-dependent shift differences in the spectra of methanol and ethylene glycol. Spinning band distillations were performed using a 24-in. Nester-Faust NFT-50 Teflon spinning band column fitted with an automatic reflux ratio control. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph, Model A-90-P, and Perkin-Elmer, Model F-11, units, using packed and capillary columns, respectively. Peak areas were calculated using a Disc chart integrator. The columns used were (1) 5 ft × 0.25 in. 5% Carbowax M on Chromosorb T (40/60); (2) 1 ft × 0.25 in. SF-96 on Chromosorb P (60/80); (3) 150 ft × 0.01 in. SF-96.

Materials.—Solvents were dried and/or distilled before use with the exception of ether and ethanol. Magnesium sulfate was used as a drying agent.

4,9-Dimethyl-$\Delta^{4(10)}$-1-octalone (11) was prepared by modifications of a procedure previously described.[26,27] 1-Acetylcyclohexene was first prepared and then converted to 1-isopropenylcyclohexene by the procedure of Wittig and Schollkopf.[28] Into a 12-l., three-neck flask equipped with mechanical stirrer, condenser, nitrogen inlet, and a solid sample addition device was placed 900 ml (2.02 mol) of a 2.25 *M* solution of *n*-butyllithium in hexane (Alfa) and then 6000 ml of anhydrous ether. A total of 747 g (2.21 mol) of solid methyltriphenylphosphonium bromide (Aldrich, crystallized from ethanol, mp 230–231°) was added slowly with rapid stirring and the resulting orange-red mixture was stirred for 5 hr at room temperature. A total of 175 g (1.41 mol) of 1-acetylcyclohexene,[29] bp 74–77° (10 mm), was added slowly with ice cooling. The resulting suspension was stirred at gentle reflux overnight, and then cooled to room temperature and worked up, eventually yielding a total of 113 g (66%) of 1-isopropenylcyclohexene.[26]

In a 100-ml flask, fitted with condenser and nitrogen inlet, was placed 17.33 g (0.142 mol) of 1-isopropenylcyclohexene, prepared as described above. Ethyl α-acetoxyacrylate[30] (22.45 g, 0.142 mol) and 0.72 g of 3,5-di-*tert*-butylcatechol (Aldrich) were then added. The mixture was thoroughly flushed with nitrogen and then stirred at 160° for 24 hr. Direct distillation at 0.5 mm gave 5.1 g of forerun, bp 46–110°; and then 30.4 g (77%) of cycloadduct: bp 110–112°; nmr (CCl_4) δ 4.15 (q, 2, J = 7 Hz), 1.64 (b, 3), 1.25 (t, 3, J = 7 Hz), and 2.0 ppm (2 sharp s, 3, separated by 2 Hz, in a 75:25 ratio).

Into a 5000-ml flask fitted with condenser, mechanical stirrer, and nitrogen inlet was placed 28.5 g (0.754 mol) of lithium alu-

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[23] P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.*, **37**, 34 (1972).

[24] J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 854 (1967).

[25] C. Ganter and B. Keller-Wojtkiewicz, *Helv. Chim. Acta*, **54**, 183 (1971).

[26] P. S. Wharton and C. E. Sundin, *J. Org. Chem.*, **33**, 4255 (1968).

[27] P. S. Wharton and B. T. Aw, *ibid.*, **31**, 3787 (1966).

[28] G. Wittig and U. Schollkopf, *Org. Syn.*, **40**, 66 (1960).

[29] J. H. Saunders, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 22.

[30] The ethyl ester was prepared by the procedure described for the methyl ester by J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).

minum hydride and 1000 ml of anhydrous ether. Cycloadduct, prepared as described above (141.0 g, 0.502 mol), was dissolved in 500 ml of ether and added dropwise at such a rate that gentle reflux was maintained and stirring was continued at room temperature for 2 hr after addition was completed. The reaction mixture was cooled in an ice bath, quenched with water, and stirred for 3 hr. Then 600 ml of 10% hydrochloric acid was added. Further work-up afforded 103.6 g of brown oil which was dissolved in 200 ml of hot acetone. Two crops of pale yellow solids, which rapidly whitened on exposure to air, were obtained, totalling 81.8 g (83%): mp 106–120°; nmr ($CDCl_3$) δ 3.5 (b, 2.0), 1.2–2.8 (m, 17.4 with broad s at 1.66 ppm).

Into a 2000-ml flask fitted with mechanical stirrer, nitrogen inlet, and dropping funnel was placed a solution of 35.0 g (0.178 mol) of the mixture of diols, prepared as described above, in 500 ml of 95% ethanol. A solution of 45.8 g (0.214 mol) of sodium metaperiodate (Baker) in 500 ml of water was added with vigorous stirring. The reaction mixture was stirred at room temperature for an additional 2 hr and was then poured into 2000 ml of brine containing a little sodium thiosulfate. Work-up afforded 26.3 g (90%) of 4-methyl-$\Delta^{4(10)}$-1-octalone:[26] bp 69–72° (0.2 mm); ir (film) 5.82 μ; nmr (CCl_4) δ 2.36 (broad s, 3) and 1.70 (s, 3) superimposed on a broad envelope at 1.0–3.0 ppm.

Into a 2000-ml flask fitted with mechanical stirrer, nitrogen inlet, addition funnel, thermometer, and ice bath was placed 600 ml of dimethoxyethane and then sodium hydride (0.358 mol) obtained by washing with pentane 15.9 g of a 54% dispersion of sodium hydride in mineral oil (Alfa). A solution of 53.5 g (0.326 mol) of octalone prepared as described above and 185 g (1.30 mol) of methyl iodide in 300 ml of dimethoxyethane was then added rapidly with stirring. The reaction mixture became green and eventually gray over a period of 4 hr. The total reaction mixture was treated with 50 ml of ethanol and 100 ml of a 10% solution of sodium hydroxide and then heated on a steam bath for 1 hr. After cooling it was poured into 1500 ml of brine containing a little sodium thiosulfate. Further work-up gave 70 g of yellow oil which was first simply distilled, affording 51.0 g (88%) of a mixture of ketones, bp 63–64° (0.1 mm). The distillate was further subjected to fractional distillation at 0.1 mm, yielding 0.45 g of forerun, bp 42–51°, and a residue of 2.1 g. The 38.0-g fraction of 4,9-dimethyl-$\Delta^{4(10)}$-1-octalone[27] was homogeneous by glpc on column 1 at 180°: ir (film) 5.84 μ; nmr (CCl_4) δ 0.8–2.8 ppm (complex with peaks at 1.68 and 1.18). Later fractions contained considerable quantities of materials with longer glpc retention times.

4,9-Dimethyl-$\Delta^{4(10)}$-1-octalyl *p*-Toluenesulfonate (12).—4,9-Dimethyl-$\Delta^{4(10)}$-1-octalone, prepared as described above (14.0 g, 78.9 mmol), was dissolved in 50 ml of absolute ethanol and placed into a 1000-ml flask fitted with a magnetic stirrer, nitrogen inlet, addition funnel, and ice bath. A solution of 1.50 g (39.4 mmol) of sodium borohydride in 400 ml of absolute ethanol was added with stirring and the resulting mixture was stirred for 2 hr at ice-bath temperatures and then at room temperature overnight. Water (10 ml) and acetic acid (30 ml) were then added and stirring was continued for 2 hr. Further work-up gave 13.5 g (83%) of clear liquid. Glpc analysis on column 1 at 160° showed the presence of three components with retention times of 5.5 (1%), 11 (17%), and 13 min (82%) and the three components were isolated by preparative glpc under the same conditions. The compound with a retention time of 5.5 min was shown to be identical with starting ketone, ir (CCl_4) 5.85 μ. The compound with a retention time of 11 min was characterized by ir (CCl_4) 2.80, 2.92 (OH), 3.45 (CH), 6.95, 9.40 μ; nmr (CCl_4) δ 3.34 (broad, $W_{1/2}$ = 10 Hz), 0.5–2.8 (complex, with a broad spike at 1.59 and sharp spike at 1.05 ppm). The compound with a retention time of 13 min was characterized by ir (CCl_4) 2.80, 2.92 (OH), 3.45 (CH), 6.87, 6.94 μ; nmr (CCl_4) δ 3.35 (complex, $W_{1/2}$ = 15 Hz), 0.5–2.8 (complex, with a broad spike at 1.55 and sharp spike at 0.98 ppm). Distillation of 8.12 g of the mixture of alcohols gave 5.97 g (33.1 mmol) of clear liquid, bp 83.5–84° (0.2 mm), which was dissolved in 12 ml of pyridine. The solution was cooled and then, with rapid stirring, 6.87 g (36 mmol) of *p*-toluenesulfonyl chloride (crystallized from hexane) was added. The resulting mixture was stored at −10° for 3 days, and then treated with a few drops of water. After the mixture became homogeneous, it was poured into 50 ml of water. Further work-up gave 11.0 g of pale yellow solid, crystallization of which from 35 ml of hot hexane gave two crops, 7.56 g, mp 87–89° dec, and 1.19 g, mp 61–78° dec. The first crop was characterized by nmr (CCl_4), δ 4.35 ppm (m, 1, $W_{1/2}$ = 15 Hz). An analytical sample, mp 89–90° dec, was prepared by recrystallizing twice from hot hexane.

Anal. Calcd for $C_{19}H_{26}O_3S$: C, 68.23; H, 7.84; S, 9.59. Found: C, 68.34; H, 7.86; S, 9.68.

In a separate run, the mother liquor remaining, after yielding two crops of the above crystals, was concentrated to an oil, nmr (CCl_4) δ 4.37 ppm (complex, 1, $W_{1/2}$ = 10 Hz).

Dihydropregeijerene (1).—To an ice-cooled solution of 5.00 g (15.0 mmol) of tosylate **12** prepared as described above in 20 ml of tetrahydrofuran was added, under a nitrogen atmosphere, 25 ml of a solution of borane 1.0 *M* in tetrahydrofuran (Alfa). The mixture was stirred for 4 hr. A solution of 9 g of sodium hydroxide in 30 ml of water was then added and the mixture was heated at 70° for 6 hr and then allowed to stand at room temperature overnight. The reaction mixture was heated with 10 ml of 30% hydrogen peroxide solution at 50° (other runs were carried out at room temperature) for 30 min and then poured into 100 ml of water and extracted three times with 25-ml portions of pentane. Most of the pentane was removed by evaporation and the remaining concentrated solution was cooled in Dry Ice–acetone. The clear superficial solution was decanted from insoluble gummy material and dried. Evaporation of solvent and distillation afforded 1.83 g (75%) of a clear liquid, bp 45–50° (0.1 mm). The insoluble gummy material was characterized by nmr (CCl_4) δ 7.30 and 7.75 (q, 4, AB quartet, J_{AB} = 8 Hz), 4.03–4.43 (b, 1, $W_{1/2}$ = 18 Hz), 2.46 (s, 3), and 0.50–2.35 (b, total integration 27.8, with sharp spikes at 0.90, 1.03, 1.04, and 1.07 ppm).

The distilled product, 1.83 g, was added to 200 ml of 20% silver nitrate solution and the solution was agitated with a Vibromixer (Chemapec Inc.). The resulting mixture was extracted once with 25 ml of pentane. The aqueous layer was added to 350 ml of cold concentrated ammonium hydroxide solution and the resulting turbid mixture was extracted with pentane. Further work-up afforded 1.05 g (43%) of clear liquid (distilled in a short path apparatus at 0.1 mm and a bath temperature of 45°) and 0.46 g of residue. Glpc on column 3 at 80° on the distillate indicated that it was 99% one component. The nmr spectrum is discussed elsewhere in this article.[31]

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.82; H, 12.16.

Samples of **1**-*2-d*, **1**-*6-d*, and **1**-*2,6-d_2* were obtained by procedures identical with those described above by using lithium aluminum deuteride and/or sodium borodeuteride (Alfa) at the appropriate stage of the synthetic sequence. Their nmr spectra are discussed elsewhere in this article.[31]

Dihydrogeijerene.—Dihydropregeijerene (0.40 g, 2.43 mmol), prepared as described above, was sealed in a glass tube under vacuum and heated in an oil bath at 140° for 6.5 hr. Short-path distillation at 0.1 mm and a bath temperature of 40° of the pyrolysate afforded 0.30 g (75%) of clear liquid and 0.09 g of residue. Preparative glpc on column 2 at 100° yielded a sample with ir (film) 3.30, 3.45, 3.55, 6.11, 11.0, and 11.25 μ; nmr (CCl_4) δ 5.78 (d of d, 1, J_1 = 18, J_2 = 10 Hz), 4.81 (d of d, 1, J_1 = 18, J_2 = 1.5 Hz), 4.80 (d of d, 1, J_1 = 10, J_2 = 1.5 Hz), *ca.* 4.7 (b, 1), 4.53 (b, 1), 1.68 (d, 3, J = 1 Hz), 0.99 (s, 3), with complex absorption from 1.2–2.0 with a maximum at 1.42 ppm. Closely similar data are reported in the literature.[25]

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 88.03; H, 12.18.

dl-**Hedycaryol (2)** was prepared as previously described: nmr (CS_2) δ 1.17 (s, 6 hydroxypropyl methyls), 1.3 (s, OH), 1.48 (d, C 5 methyl, J = 1 Hz), 1.57 (d, C-1 methyl, J = 1 Hz), 2.15 (eight allylic protons) and 4.9 (center of an envelope 45 Hz broad from C-2 and C-6 vinyl hydrogens). A sample of **2**-*2-d* was prepared by the same procedure by substituting sodium borodeuteride at the appropriate stage of the synthetic sequence.[31]

Registry No.—**1,** 33835-29-9; (±)-**2,** 32319-39-4; **11,** 17408-20-7; *cis*-**12,** 33835-31-3; *trans*-**12,** 33835-32-4; dihydrogeijerene, 37574-08-6.

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(31) Nmr spectra of the following will appear following these pages in the microfilm edition of this volume of the journal: **1** and **2** (ambient temperature); vinyl hydrogen region of **1**, **1**-*2-d*, **1**-*6-d*, and **2**-*2-d* (variable temperature). Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-735. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.