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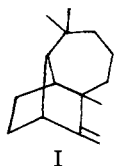
Synthetic Transformation of Natural Products. I. 1-Methylene-2,10-methano-5,5,9-trimethyldecahydronaphthalene

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RECEIVED JULY 1, 1963

In an effort to obtain longifolene (I), geraniol was coupled with cyclopentadiene, and the resulting product was subjected to an internal Diels-Alder reaction. The adduct V was converted to the corresponding olefin VIII which was identified as 1-methylene-2,10-methano-5,5,9-trimethyldecahydronaphthalene.

The biosynthetic pathways leading to the formation of sesquiterpenes have been the subject of considerable speculation.¹ Up to this point experiments have established that isopentenyl, 3,3-dimethylallyl, and geranyl pyrophosphate serve as intermediates in the synthesis of farnesyl pyrophosphate.² The further transformation of farnesol to other sesquiterpenes has not been examined *in vivo*, although very preliminary tracer studies for longifolene (I) have been reported.³ We have sought to utilize the established building block of nature, geraniol, in synthetic attempts to build the complex carbon skeleton of longifolene (I).



It was our intention to couple a derivative of geraniol with cyclopentadiene and perform an internal Diels-Alder reaction leading to the carbon skeleton of longifolene (I) according to Fig. 1.

Although hydrochlorides of terpenes have been used as derivatives for identification,⁴ it has never been established whether selective addition of HCl to a polyunsaturated system is possible.⁵ We were able to add HCl selectively to geranyl acetate to give only terminal hydrochloride II. Its structure was established by n.m.r. and pyrolytic dehydrohalogenation which regenerates geranyl acetate. The n.m.r. of the haloacetate II shows a clean triplet in the vinyl proton region, instead of the overlapping pair of triplets associated with geranyl acetate. The allylic protons appear as an unchanged doublet. These data, taken together, establish conclusively that selective addition of HCl to the terminal double bond has taken place.

The hydrochloride II reacted with excess cyclopentadienyl magnesium bromide to give the coupled product III in 28% yield. The structure of III is supported by its infrared spectrum which contains bands at 6.02 and 6.3 μ arising from the conjugated double bonds.⁶ The n.m.r. spectrum also contains new vinylic absorption peaks amounting to three protons. The peaks are not sufficiently resolved, however, to establish rigorously the relative amounts of the two possible double bond isomers. It was hoped that thermal equilibration would provide a small amount of the 5-cyclopentadienyl derivative, which would undergo the internal Diels-Alder reaction in the desired fashion to give IV.

(1) L. Ruzicka, *Experientia*, **9**, 357 (1953); G. Ourisson, *Bull. soc. chim. France*, 895 (1955); J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(2) F. Lynen, B. W. Agranoff, H. Eggerer, U. Henning, and E. M. Möslein, *Angew. Chem.*, **71**, 657 (1959).

(3) W. Sandermann and K. Burns, *Tetrahedron Letters*, **7**, 261 (1962).

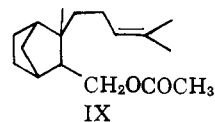
(4) J. L. Simonsen, "The Terpenes," 2nd Ed., Vol. I, Cambridge University Press, New York, N. Y., 1947.

(5) A. Verley (*Bull. soc. chim. France*, [IV] **25**, 68 (1919)) has reported selective addition of HI to geraniol, but the structure was not rigorously established.

(6) L. G. Bellamy, "The Infrared Spectra of Organic Molecules," Methuen and Co., Ltd., London, 1959, pp. 40-41.

In fact, refluxing III in pseudocumene (b.p. 176°) gave a nearly quantitative yield of a crystalline isomer with a comparable vapor phase chromatographic retention time. Its n.m.r. spectrum differed substantially from that of the starting material, having only a doublet in the vinyl absorption region. The n.m.r. spectrum, as well as certain infrared absorption bands, are closely related to those obtained with the Diels-Alder adducts of geraniol and cyclopentadiene.⁷ Only two isomers come into question as Diels-Alder products—IV and V. Subsequent transformations established that the isomer which was obtained did not have the desired structure IV. Therefore, we assign structure V to the Diels-Alder adduct. While in principle both the *exo* and *endo* addition products could be formed, only one isomer was observed in vapor phase chromatography. The isomer forms an addition product with mercuric salts. Since it has been established that the *endo*-hydroxymethyl group participates in the mercuration of bicyclo[2.2.1]hept-5-en-2-yl-methanol,⁸ the formation of an adduct with V also implies the presence of an *endo*-hydroxymethyl group. We, therefore, assign to V the stereochemistry resulting from an internal *endo* Diels-Alder addition. The subsequent transformation of V proceeded as follows.

Hydrogenation, with 10% Pd/CaCO₃, gave the dihydro compound VI which was acetylated with acetic anhydride and pyridine to give the acetate VII. Pyrolysis of the acetate at 575° gave a moderate yield of an olefin C₁₅H₂₄. A close structural analog IX has been pyrolyzed to give *d,l*- β -santalene.⁷ Since pyrolysis of



a primary acetate appears to give little or no rearrangement,⁹ we assign structure VIII to the olefin.

The infrared contains strong bands at 6.06 and 11.4 μ as well as a weak band at 5.7 μ —all indications of an unsymmetrical methylene absorption.⁵ These bands are identical with those reported for longifolene.¹⁰ However, there are sufficient differences in the C-H deformation frequencies as well as in the fingerprint region to permit the conclusion that the olefin is not longifolene.

The n.m.r. spectrum of VIII supports the structure which we assign to it. There are two sharp peaks at 5.03 and 5.41 τ , respectively, which are assigned to the terminal methylene protons. The allylic bridgehead proton appears at 7.11 τ . The methylene protons appear as a broad band with maximum at 8.19 τ . The angular methyl appears at 8.66 τ while the *gem*-dimethyl group gives rise to two bands at 8.42 and 8.61 τ ,

(7) G. Brieger, "A New Synthesis of *d,l*- β -Santalene and *d,l*-*epi*- β -Santalene," to be published shortly.

(8) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).

(9) D. H. Froensdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Am. Chem. Soc.*, **81**, 643 (1959).

(10) G. Dupont, R. Dulov, P. Naffa, and G. Ourisson, *Bull. soc. chim. France*, [V] **21**, 1075 (1954).

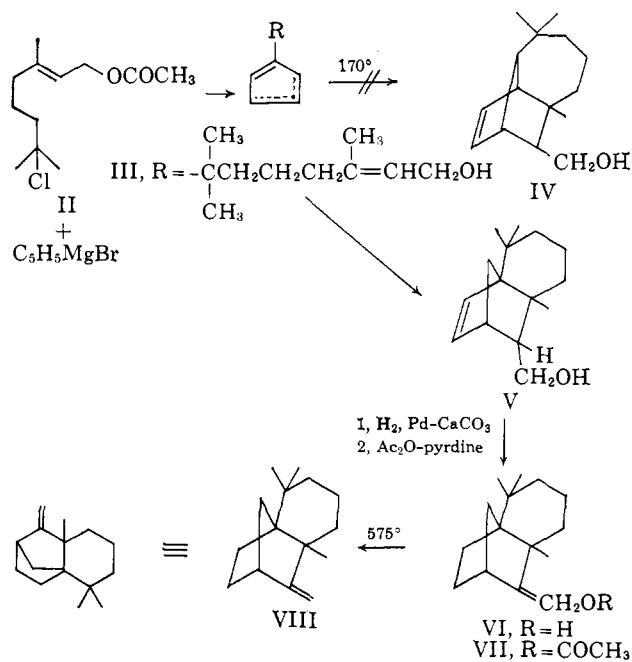


Figure 1.

respectively. It is not surprising that a large separation for the *gem*-dimethyl group is observed, as compared to longifolene,¹¹ since the two methyl groups are in a much more unsymmetrical environment.

We are continuing our investigations to determine the scope of the internal Diels-Alder reaction and if 5-alkylcyclopentadienes can be transiently obtained.

Experimental

Melting points were taken in capillary tubes in a Büchi melting point apparatus. The n.m.r. spectra were measured at 60 Mc. on a Varian A-60, using neat or carbon disulfide solutions with internal TMS standards. Vapor phase chromatography utilized an Aerograph A-90.

Addition of HCl to Geranyl Acetate.—Geranyl acetate (11.0 g.) was dissolved in 20 ml. of glacial acetic acid and cooled to 0°. Gaseous anhydrous HCl was passed into the mixture with stirring until one equivalent had been absorbed. The mixture was stirred 2 hr., then poured on ice. The ether extract was washed with water, dried over MgSO₄, the ether removed *in vacuo*, and the residue distilled through a short fractionating column to give a clear liquid II, b.p. 92–94° (0.3 mm.), yield 6.0 g.

Anal. Calcd. for C₁₀H₂₁O₂Cl: Cl, 15.30; Found: Cl, 15.07.

A small amount of haloacetate was pyrolyzed in the injector of a vapor phase chromatograph. Geranyl acetate was the only detectable product. The n.m.r. spectrum (neat) contained a triplet centered about 4.95 τ (vinyl proton) and a doublet centered about 5.75 τ due to the allylic protons.

7-Cyclopentadienyl-6,7-dihydrogeraniol (III).—A Grignard reagent was formed in the standard manner from 5.0 g. of Mg and 16 ml. of ethyl bromide; 10 ml. of freshly distilled cyclopentadiene was added dropwise over a 1-hr. period. The mixture was

refluxed 6 hr. with ethane evolution. After cooling to 0° 6.54 g. of geranyl acetate hydrochloride was added with stirring. The mixture was then stirred overnight. A yellow precipitate appeared.¹² The entire mass was poured into a mixture of ice and ammonium chloride, taken up in additional ether, washed twice with H₂O, dried over MgSO₄, and evaporated *in vacuo*. The residue was distilled to give 1.72 g. (yield 28%) of a pale yellow oil, b.p. 106–110° (0.3 mm.). The n.m.r. spectrum had the same absorption as II, plus a doublet at 4.09 τ and a multiplet at 3.73 τ . The infrared spectra had absorption bands at 6.02 and 6.3 μ . The vapor phase chromatographic retention time (on a 4-ft. column with 20% Aprizon L on HDMS treated Chromosorb W, temperature 178°, flow 100 ml. of He/min.) was 26 min.

Anal. Calcd. for C₁₅H₂₄O: C, 81.81; H, 10.91. Found: C, 81.97; H, 11.06.

Isomerization of 7-Cyclopentadienyl-6,7-dihydrogeraniol.—Alcohol III (1.57 g.) was refluxed for 48 hr. in 10 ml. of pseudocumene in presence of a trace of quinoline under N₂. The pseudocumene was distilled *in vacuo* and the residue chromatographed. The vapor phase chromatogram (4-ft. column, 20% Aprizon L on HDMS treated Chromosorb W, temperature 188°, flow 100 ml. of He/min.) showed only one major peak with retention time of 30 min., 15 sec. The purified material was crystalline, m.p. 30–32°. The molecular weight was 220 as determined by mass spectrometry.¹³ A yield of 90% was obtained. The n.m.r. spectrum contained only a doublet at 4.28 τ in the vinyl proton region. The infrared had only weak absorption, *ca.* 6.1 μ , but strong new bands at 13.5 and 13.7 μ .

Mercuric chloride derivative of V, m.p. 232–233°.

Anal. Calcd. for C₁₅H₂₃OHgCl: C, 39.56; H, 5.06. Found: C, 39.63; H, 5.50.

Hydrogenation of Isomer V.—Isomer V (1.27 g.) was hydrogenated in 10 ml. of absolute ethanol with 10 ml. of absolute ethanol with 10% Pd-CaCO₃. The ethanol was removed under reduced pressure to give a crystalline alcohol VI, m.p. 62–64° (yield 1.073 g.). The bands at 13.5 and 13.7 μ in the infrared, as well as the weak absorption, *ca.* 6.1 μ , had disappeared.

Anal. Calcd. for C₁₅H₂₆O: C, 81.08; H, 11.71. Found: C, 80.71; H, 11.55.

Acetylation of VI.—Alcohol VI (1.07 g.) was dissolved in 5 ml. of pyridine plus 1 ml. of acetic anhydride and let stand overnight with stirring. The mixture was then poured on ice, extracted with ether, washed with H₂O and dilute HCl followed by dilute NaHCO₃, dried over MgSO₄, and stripped to give a pale oil. A sample purified by vapor phase chromatograph (4-ft. column, 20% Aprizon L on HDMS treated Chromosorb W, temperature 218°, flow 100 ml. of He/min.) had a retention time of 24 min. The infrared spectrum had a strong band at 5.75 μ .

Anal. Calcd. for C₁₇H₂₈O₂: C, 77.27; H, 10.60. Found: C, 77.45; H, 10.43.

1-Methylene-2,10-methano-5,5,9-trimethyldecahydronaphthalene (VIII).—Acetate VII (250 mg.) was pyrolyzed in a short column containing a mixture of glass beads and helices. The products were chromatographed to give unchanged acetate plus 50 mg. of olefin VIII with a retention time of 13 min., 10 sec. (4-ft. column of 20% Aprizon L on HDMS treated Chromosorb W at 180°, flow 100 ml. of He/min.). The infrared spectrum had a weak band at 5.7 μ . The n.m.r. showed strong bands at 5.03 (1 proton) and 5.41 τ (1 proton). Three unsplit peaks appeared at 8.42 (3 proton), 8.61 (3 protons), and 8.66 τ (3 protons), and a broad peak at 8.19 τ (12 protons).

Anal. Calcd. for C₁₅H₂₄: C, 88.23; H, 11.77. Found: C, 88.14; H, 11.73.

(12) R. Riemschneider, A. Reisch, and H. Horak, *Monatsh.*, **91**, 805 (1960).

(13) For which we thank Dr. A. L. Burlingame of this Department.

(11) S. Dev, *Tetrahedron*, **9**, 1 (1960).