The Synthesis of *trans,trans*-α-Farnesene[1]

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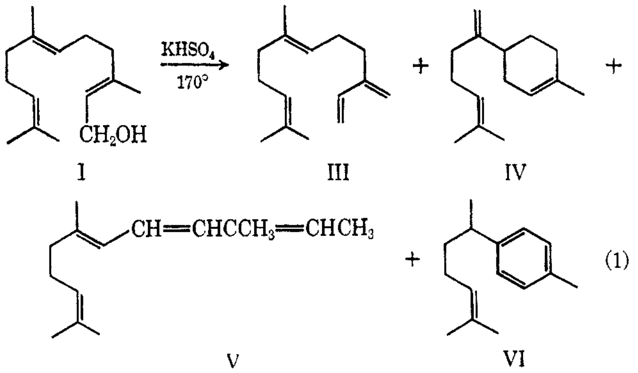
Received May 9, 1969

The stereospecific preparation of *tran,trans*-α-farnesene by rhodium chloride catalyzed isomerization of *trans*-β-farnesene is reported. In addition, conjugated isomers, probably allofarnesenes, are formed. The $KHSO_4$-catalyzed dehydration of nerolidol has been investigated, yielding products identified as α- and β-farnesene, β-bisabolene, and δ-bisabolene. The base-catalyzed dehydration of farnesol has been reinvestigated. Only β-farnesene is formed, along with a mixture of C_{14} hydrocarbons identified as 2,6,10-trimethylundeca-2,4,9-triene and 2,6,10-trimethylundeca-1,5,9-triene.

While β-farnesene has been known for a considerable time, and is in fact a constituent of several essential oils,[2] the corresponding α isomer has not been conclusively identified. Recently, α-farnesene has been discovered as a natural component of Granny Smith apple wax[3a,b] as well as in the glandular secretion of an ant, *Aphaenogaster longiceps* (F. Sm.).[3c] It seemed of interest, therefore, to prepare a synthetic specimen of α-farnesene.

We have accordingly examined the $KHSO_4$-catalyzed dehydration of nerolidol (I), a base-catalyzed dehydration of farnesol (II), and the isomerization of *trans*-β-farnesene (III), prepared by a method recently reported.[4]

Earlier workers have examined the dehydration of both farnesol[5] and nerolidol[6] with a variety of acidic catalysts. In the early work, mixtures of acyclic and monocyclic sesquiterpenes were reported. However, structural assignments were based principally on analogous reactions observed in the monoterpene series with linalool and geraniol. The considerable variations noted in the physical properties of these terpenes, such as β-farnesene, make it clear that these preparations were impure. A more recent study indicates that the mixture resulting from the $KHSO_4$-catalyzed dehydration of farnesol is in fact a complex mixture of at least twelve components, among which *trans*-β-farnesene (III), β-bisabolene (IV), allofarnesenes (V), and γ-curcurmene (VI) (reaction 1) were definitely identified, in addition to triterpene derivatives.[7]

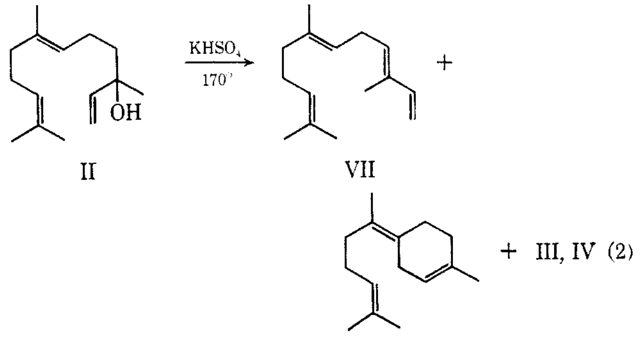


I III IV

V VI (1)

Recently the base-catalyzed dehydration of farnesol has also been reported, leading principally to the production of *trans*-β-farnesene (III), in addition to minor amounts of a product with one less carbon atom formulated as IX.[8]

Acid-Catalyzed Dehydration of Nerolidol.—Treatment of nerolidol with $KHSO_4$ at 170° results in a mixture of C_{15} hydrocarbons which, on gas chromatographic analysis, reveals four major components in the relative yields of 39.0 (III), 20.0 (VII), 19.0 (IV), and 22.0% (VIII) (reaction 2).



II VII

VIII

Component III, on the basis of infrared (ir), nuclear magnetic resonance (nmr), and mass spectrometric analysis, is *trans*-β-farnesene.

The second component, VII, has a molecular weight of 204 according to mass spectrometric analysis. Its ultraviolet (uv) spectrum shows λ_{max} 232 mμ (ε 23,400). This suggests the presence of a conjugated diene grouping. The ir spectrum shows absorptions at 837 cm^{-1}, suggestive of the presence of trisubstituted double bonds. Bands at 893 and 990 cm^{-1}, as well as absorptions at 1609 and 1645 cm^{-1}, indicate the presence of a vinyl group. The nmr spectrum shows a multiplet at *ca.* τ 8.39 (9 H), a singlet at 8.27 (3 H), two peaks centered at 8.00, a triplet at 7.20 (J = 7.0 Hz, 2 H), a series of peaks in the olefinic region with a center approximately at 5.0 (5 H), and a quartet at 3.69 (1 H). This latter absorption supports the presence of a vinyl grouping. The other assignments agree substantially with those recently reported for a sample of α-farnesene isolated from natural sources.[3] We therefore consider *trans,trans*-α-farnesene as the most likely structure for component VII. The stereochemical assignment is discussed below. This evidence appears to establish for the first time definitively the production of α-farnes-

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[1] Portions of this work were presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

[2] W. Karrer, "Konstitution und Vorkommen der organischen Pflanzenstoffe," Birkhausser, Verlag, Basel, 1958.

[3] (a) F. E. Huelin and K. E. Murray, *Nature*, **210**, 1260 (1966); (b) K. E. Murray, *Aust. J. Chem.*, **22**, 197 (1969); (c) G. W. K. Cavill, P. J. Williams, and F. B. Whitfield, *Tetrahedron Lett.*, No. 23, 2201 (1967).

[4] G. Brieger, *J. Org. Chem.*, **32**, 3720 (1967).

[5] L. Ruzicka, *Helv. Chim. Acta*, **6**, 490 (1923); E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, 116 (1942); F. Šorm, J. Mleziva, Z. Arnold, and J. Pliva, *Collect. Czech. Chem. Commun.*, **14**, (1949); F. Šorm, M. Zaroal, and V. Herout, *ibid.*, **16**, 626 (1951); V. Herout, V. Benesova, and J. Pliva, *ibid.*, **18**, 297 (1953); F. Šorm, M. Vrany, and V. Herout, *ibid.*, **18**, 364 (1953).

[6] L. Ruzicka and E. Capato, *Helv. Chim. Acta*, **8**, 259 (1925).

[7] Y. Naves, *ibid.*, **49**, 1029 (1966).

[8] A. Bhati, *Perfum. Essent. Oil Record*, **54**, 376 (1963).

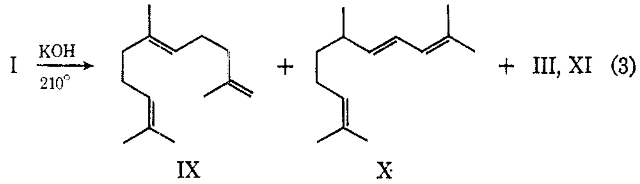
ene from the dehydration of nerolidol. Naves was unable to isolate or identify α-farnesene in the dehydration of farnesol with $KHSO_4$, but inferred its possible presence from uv spectral data.[7]

Component IV also shows a molecular weight of 204 by mass spectrometry. The ir spectrum shows bands in accord with those available for β-bisabolene.[7] The nmr spectrum of product IV is also essentially in agreement with that of β-bisabolene.[9]

Product VIII has a molecular weight of 204 (mass spectrometry). Its ir spectrum shows weak absorptions at 798, 826, and 1640 cm^{-1}, suggestive of a trisubstituted double bond in a six-membered ring, and an acyclic trisubstituted double bond. The nmr spectrum confirms this assignment, since there are only two broad peaks in the olefinic proton region at τ 4.92 and 4.66 (approximately 2 H), essentially identical in chemical shifts with absorptions found for β-bisabolene. These data, coupled with the observation that the mass spectrum closely resembles that of β-bisabolene, suggests that the fourth product, VIII, is in fact another isomer of bisabolene, most likely the δ isomer.

It appears then that the course of $KHSO_4$-catalyzed dehydration is somewhat different from that for farnesol, in that detectable amounts of α-farnesene are formed in addition to the expected β-farnesene and the isomeric bisabolenes.

Base-Catalyzed Dehydration of Farnesol.—When farnesol is treated with KOH at 210°, a mixture of hydrocarbons is formed. Gas chromatographic analysis of the products indicates the presence of four components in the relative yields of 14.0 (IX), 4.2 (XI), 25.0 (X), and 62.0% (III) (reaction 3).



Component IX, according to mass spectrometric analysis, has a molecular weight of 192, indicating the loss of one carbon atom. Its ir spectrum shows peaks at 828 (trisubstituted double bond) and 887 and 1645 cm^{-1} (terminal methylene). The nmr spectrum shows a singlet at τ 5.38 (2 H), suggestive of a methylene group, and a broad peak centered at 4.94 (2 H). These observations are in accord with a structure proposed by Bhati for the substance he calls "*nor* farnesene" (2,6,10-trimethylundeca-1,5,9-triene), although his structural proposal was based principally on analogy to products obtained from phytol with KOH.[8]

The minor component XI was not further investigated. However, its gas chromatographic retention time suggests that it is also a C_{14} product.

Component X has again a molecular weight of 192 (mass spectrometry). It shows a uv spectrum with λ_{max} 238 mμ (ε 25,000), suggestive of a conjugated diene system. In accord with this are ir absorptions at 960 and 989 (*trans*-disubstituted conjugated double bond) and bands at 1650 and 1610 $cm.^{-1}$ The nmr spectrum shows a poorly resolved triplet at τ 4.92 (1 H), another triplet at 4.65 (J = 7.5 Hz, 1 H), a doublet at 4.33 (1 H), and a quartet at 3.89 (1 H). A structure consistent with this data would be 2,6,10-trimethylundeca-2,4,9-triene (X). In support of such a proposal, the ir spectrum closely resembles that of alloocimene, and bands at τ 4.65 and 4.33 are also found in the nmr of alloocimene.

The major component is *trans*-β-farnesene (III). The base-catalyzed dehydration of farnesol is then characterized by considerable cleavage. A mechanism which accounts for the observed products proceeds by oxidation of the primary alcohol to a carboxylic acid, followed by decarboxylation of the isomeric β,γ-unsaturated acid.[8,10] In the presence of strong base and high temperatures, double-bond isomerization is facile.[11] No α-farnesene was detected.

Isomerization of *trans*-β-Farnesene.—Since the dehydration of nerolidol leads only to a small amount of α-farnesene, the transformation of the more readily available β-farnesene[4] was also investigated. Several compounds derived from group VIII metals have been reported as active in olefin isomerization.[12] These include derivatives of Pt, Pd, Rh, and Ir. Recently, rhodium chloride trihydrate was used in a synthesis of α-sinesal.[13]

We applied this method to *trans*-β-farnesene. After treatment for 30 min at 70°, *trans*-β-farnesene is quantitatively isomerized. The major component (57%) has bands in the ir at 3091, 1645, 1609, 989, 893, and 839 cm^{-1}. The nmr spectrum shows a quartet at τ 3.68, characteristic of the lone proton of a vinyl group, a triplet at 4.60, attributed to the proton on the trisubstituted double bonds (J = 7.0 Hz), several bands between 4.85 and 5.20 (5 H in all), a triplet at 7.19 (J = 7.0 Hz, 2 H) attributable to the methylene flanked by two double bonds, absorption at 8.00 due to the remaining methylene protons, a peak at 8.26 (3 H), and a multiplet at 8.39 (9 H).

While comparison with the other possible stereoisomers is not at present possible, the evidence available suggests strongly that the isomer formed is exclusively the *trans,trans* form VII. In a careful study of the isomeric *cis* and *trans* forms of α- and β-ocimenes, Ohloff[14] found that the lone vinyl proton of the *cis* form absorbed consistently at the lower τ value ($\Delta\tau \approx 0.38$). This is the largest shift reported, and ought therefore to be of diagnostic value. The absolute value of τ 3.70 (*trans*-β-ocimene) and 3.69 (*trans*-α-ocimene) compares favorably with the value herein reported (3.68). The appearance of peaks for methyl protons in the ratio of 3:9 suggests that three of the methyl groups have similar stereochemical environments. The only other isomer which could exhibit this spectrum would be the unlikely *cis,cis* form.

The ir spectra of the isomeric ocimenes suggest that the stretching frequency of the conjugated double bond might also be used for stereochemical analysis. Both *trans* forms have the higher wavenumber assigned (1608 for *trans*-β-ocimene and 1605 cm^{-1} for *trans*-α-ocimene). Again the band found in the α-farnesene is consistent with this assignment (1609 cm^{-1}).

Within the limitations mentioned above, we therefore

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(9) The unpublished nmr spectrum was kindly provided by Dr. R. B. Bates.

(10) G. H. Hargreaves and L. N. Owen, *J. Chem. Soc.*, 750 (1947).

(11) R. T. Arnold, O. C. Elmer, and R. M. Dodson, *J. Amer. Chem. Soc.*, **72**, 4359 (1950).

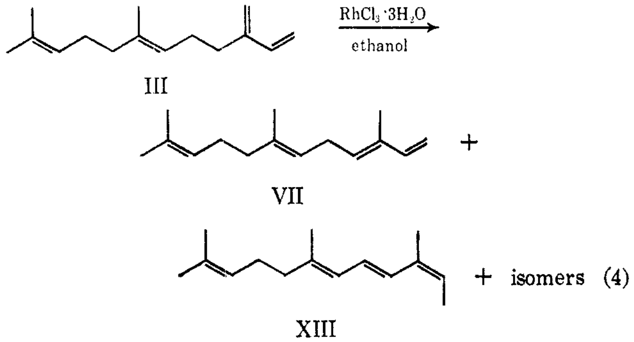
(12) J. F. Harrod and A. J. Chalk, *ibid.*, **86**, 1776 (1964).

(13) E. Bertele and P. Schudel, *Helv. Chim. Acta*, **50**, 2445 (1967).

(14) G. Ohloff, J. Seibl, and E. sz. Kovats, *Ann.*, **675**, 83 (1964).

assign the *trans,trans* stereochemistry to the α-farnesene produced by isomerization of *trans*-β-farnesene.

A second product is produced by the isomerization process. It has a uv spectrum showing a maximum of 280 mμ suggestive of more extensive conjugation. The ir spectrum shows bands which closely resemble those found in alloocimene with a *trans* orientation for the disubstituted double bond. A likely structure then is the C_{15} homolog of alloocimene, XIII. The stereochemistry has not been determined. Other more extensively conjugated isomers were also detected (reaction 4).



The rhodium chloride catalyzed isomerization of *trans*-β-farnesene then provides the most suitable method presently available, short of total synthesis, for the production of α-farnesene.

Experimental Section

All ir spectra were taken as thin films, unless otherwise indicated using either a Beckman IR-5 or IR-12 spectrometer. Nmr spectra were taken as approximately 10% solutions in CCl_4 with tetramethylsilane reference. Values are reported as τ values relative to tetramethylsilane.

Dehydration of Nerolidol.—A mixture of nerolidol (5.0 g) and $KHSO_4$ (5.0 g) in a distillation flask was placed into a preheated oil bath at 170°. Vacuum was applied and the crude products were separated by distillation. The product, bp 110–130° (15 mm), was dried over anhydrous K_2CO_3. The yield was 2.2 g or 43%. The product was analyzed on a 10 ft × $^1/_4$ in. column packed with 20% DEGS–60–80 mesh Chromosorb W for 5 ft and 20% Apiezon L–60–80 mesh Chromosorb W for 5 ft, revealing four components, III, VII, IV, VIII, which were collected for analysis. Relative abundance follows: 39.0 (III), 20.0 (VII), 19.0 (IV), and 22.0% (VIII).

trans-**β-Farnesene (III).**—Spectral data follow: uv max (*n*-heptane) 224 mμ (ε 14,000); ir (0.25-mm cell) 3095 (m), 2970 (s), 2930 (s), 2730 (w), 1790–1820 (w), 1670 (w), 1645 (w), 1630 (w), 1692 (s), *ca.* 1440 (s), 1378 (sh), 1372 (s), 1150 (w), 1105 (m), 990 (s), 900 (sh), 890 (s), 825–835 (m), 740–755 (w), *ca.* 670 cm^{-1} (w); nmr τ 8.42 and 8.35 (9 H), *ca.* 8.03 and *ca.* 7.80 (8 H), 5.07 (s), 4.95, and 4.70 (6 H), 3.70 (quartet, 1 H); mass spectrum, molecular ion at *m/e* 204.[15] This product was identical with trans-β-farnesene prepared as previously reported.[4]

trans,trans-α-**Farnesene (VII).**—Spectral data follow: uv max (95% ethanol) 232 mμ (ε 23,400); ir 3092 (w), 2975 (s), 2940 (s), 2880 (s), 1645 (m), 1609 (m), 1450 (s), 1379 (m), 1110 (m), 1090 (w), 990 (s), 893 (s), *ca.* 837 cm^{-1} (w); nmr τ 8.39 (m, 9 H), 8.27 (s, 3 H), 8.00 (d), 7.20 (t, 2 H, *J* = 7.0 Hz), several bands between 5.33 and 4.48 (5 H), 3.69 (quartet, 1 H); mass spectrum, molecular ion at *m/e* 204.[15]

β-Bisabolene (IV).—Spectral data follow: ir 3050 (w), 2950 (s), 2900 (s), 2840 (s), 1640 (m), 1440 (s), 1370 (m), 1150 (w), 1105 (w), 1050 (w), 1020 (w), 990 (w), 955 (w), 912 (w), 887 (s), 826 (w), 796 cm^{-1} (w); nmr τ 8.39 and 8.33 (9 H), 7.95, 5.34 (impurity?), 5.26 (s), 4.90 and 4.62 (2 H); mass spectrum, molecular ion at *m/e* 204.[15]

δ-Bisabolene (VIII).—Spectral data follow: ir 3020 (sh), 2970 (s), 2830 (s), 1640 (w), 1440 (s), 1370 (m), 1150 (w), 1105 (w), 1050 (w), 990 (w), 955 (m), 915 (w), 890 (w), 826 (w), 798 (w); nmr τ 8.37 (12 H), 7.36 (t, *J* = 7.0 Hz, 2 H), 4.90 and 4.62 (2 H); mass spectrum, molecular ion at 204 *m/e* 204.[15] This spectrum resembles that of IV.

Dehydration of Farnesol.—Farnesol (10.0 g) and KOH (80.0 g) were combined in a beaker and placed in an oil bath heated to *ca.* 210°, with vigorous stirring. After 10 min, the brown mixture was poured into 1 l. of ice water and extracted three times with 200 ml of ether. The combined ether extracts were evaporated and the residue was distilled to give 3.6 g of olefins, bp 80–90° (0.06 mm). The product was analyzed on a 10 ft × $^1/_4$ in. column containing 25% TCEP and 60–80 mesh Chromosorb W. Four components were detected in the following relative yields: 14.0 (IX), 4.2 (XI), 25.0 (X), and 62.0% (III). The products were separated by gas chromatography and analyzed.

2,6,10-Trimethylundeca-1,5,9-triene (IX).—Spectral data follow: ir 3050 (m), 2960 (s), 2940 (s), 2860 (s), 1760 (w), 1645 (m), 1440 (s), 1370 (m), 1110 (m), 1050 (w), 985 (w), 965 (w), 887 (s), 828 cm^{-1} (w); nmr τ 8.46 (s) and 8.35 (m, 12 H), *ca.* 8.0 (8 H), 5.38 (s, 2 H), 4.94 (2 H); mass spectrum, molecular ion at *m/e* 192.[15]

Anal.[16] Calcd for $C_{14}H_{24}$: C, 87.50; H, 12.50. Found: C, 87.75; H, 12.34.

2,6,10-Trimethylundeca-2,4,9-triene (X).—Spectral data follow: uv max (95% ethanol) 238 mμ (ε 25,000); ir 3000 (m), 2960 (s), 2940 (s), 2850 (s), 1650 (w), 1610 (w), 1440 (s), 1370 (s), 1195 (w), 1095 (w), 1035 (w), 989 (m), 960 (s), 860 (m), 827 cm^{-1} (w); mass spectrum, molecular ion at *m/e* 192.[16]

Anal.[16] Calcd for $C_{14}H_{24}$: C, 87.50; H, 12.50. Found: C, 87.34; H, 12.67.

trans-β-**Farnesene (III).**—See properties given above.

Isomerization of *trans*-β-**Farnesene.**—*trans*-β-farnesene (1.97 g) was combined with 120 mg of rhodium chloride trihydrate in 16 ml of absolute ethanol. The mixture was heated and stirred under nitrogen at 70° for 30 min. The mixture was cooled, taken up in 30 ml of diethyl ether, and washed once with 75 ml of saturated $NaHCO_3$ solution and then several times with distilled water. The solvent was evaporated to give a quantitative recovery of material. Gas chromatography (25% TCEP and 30–60 mesh Chromosorb W 10 ft × $^1/_4$ in. column, 124°) showed two major components, XIII (24.5) and VII (57.3%).

allo-**Farnesene (XIII).**—Spectral data follow: uv max (95% ethanol) 280 mμ (ε 12,000); ir 3078 (w), 3047 (w), 2970 (s), 2924 (s), 2729 (w), 1665 (w), 1645 (m), 1594 (w), 1440 (s), 1378 (s), 1236 (w), 1110 (m), 987 (m), 958 (m), 900 (m), 827 (m), 797 cm^{-1} (w).

trans,trans-α-**Farnesene (VII).**—Spectral data follow: uv max (95% ethanol) 233 mμ (ε 27,000); ir 3091 (w), 2970 (s), 2930 (s), 2885 (s), 1645 (m), 1609 (m), 1445 (s), 1383 (s), 1110 (m), 1092 (m), 989 (m), 893 (s), 839 cm^{-1} (w) [reported ir spectra, 3085 (w), 1635 (m), 1600 (s), 985 (s), 890 (s), 835 (m),[3c,17] and 3093 (w), 1667 (w), 1642 (m), 1609 (s), 990 (s), 893 (s)[3b]]; nmr τ 8.40 (m, 9 H), 8.26 (3 H), 8.00 (4 H), 7.19 (t, *J* = 7 Hz, 2 H), 5.20, 5.11, 5.04, 4.85, and 4.60 (t, 3 H in all), 3.68 (quartet, 1 H) [reported nmr spectrum,[3b] 8.39, 8.36 (m, 9 H), 8.26 (3 H), 8.00 (d, 4 H), 7.19 (t, 2 H), 4.9 (m, 5 H), 3.68(quartet, 1 H)]; mass spectrum,[18] *m/e* 204 (p, 7.3%), 189 (2.3), 161 (5.8), 135 (7.3), 119 (31.1), 107 (40.4), 93 (82.2), 79 (36.4), 69 (51.8); 55 (50.2), 41 (100.0) (reported mass spectrum,[3b] *m/e* 204, 189, 161, 135, 119, 107, 93, 79, 69, 55, 41).

Registry No.—III, 502-60-3; IV, 21902-26-1; VII, 21499-64-9; VIII, 20266-07-3; IX, 13290-12-5; X, 21902-29-4; XIII, 21902-30-7.

Acknowledgment.—Technical assistance was provided by Messrs. B. Crawford and D. Hachey. The mass spectrometric determinations by R. Hites are gratefully acknowledged. This work was partially supported by the Petroleum Research Fund of the American Chemical Society.

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[15] The mass spectra were determined by Mr. R. Hites, at the Massachusetts Institute of Technology.

[16] Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

[17] The small discrepancies between the reported[3] values are apparently due to the use of a dilute carbon tetrachloride solution in one case.[3c] The spectra are identical as thin films (private communication, Professor G. W. K. Cavill).

[18] The analysis was kindly provided by Dr. D. deJong, Wayne State University.