Tetrahedron. Vol 32, pp 2875 to 2877. Pergamon Press 1976. Printed in Great Britain

THE STEREOISOMERS OF 3,7,11-TRIMETHYLDODECA-2,6,10-TRIENE

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(*Received in USA* 14 *May* 1976; *Received in UK for publication* 13 *July* 1976)

Abstract—Four geometrical steroisomers of 3,7,11-trimethyldodeca-2,6,10-triene have been synthesized. The PMR and ^{13}C NMR spectra of these compounds provide important information on the geometry of Me substituted double bonds, while the mass spectra distinguish (E and Z,E)-isomers from (E and Z,Z)-isomers.

Following the identification of (E)-β-farnesene (**1**) as a natural aphid alarm pheromone,[1] we have discovered that a *nor*-farnesene [(E) - 2,6,10 - trimethylundeca - 1,5,9 - triene (**2**)] also possesses the alarm pheromone activity.[2] Studies with analogs of **2** revealed that the geometrical configuration of the double bonds in the molecule is highly critical to alarm pheromone activity.[2]

Since the stereoisomeric 3,7,11 - trimethyldodeca - 2,6,10 - trienes were considered suitable model compounds to clarify the relationships between biological activity and geometrical configuration, the four possible isomers, (E,E)-(**3**), (Z, E)-(**4**), (E,Z)-(**5**) and (Z,Z)-isomer (**6**), were synthesized. Identification of these isomers presented unique problems. We wish to report the successful identification of these geometrical isomers by the PMR, ^{13}C NMR (CMR), and mass spectra.

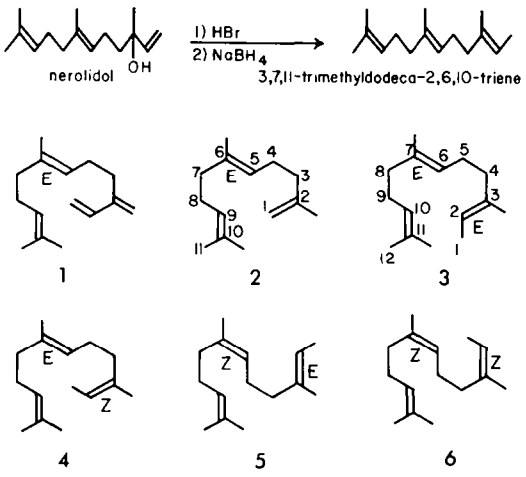
(E)-Nerolidol, on treatment with hydrobromic acid, gave a bromide. The bromide, reduced with sodium borohydride in dimethylformamide, was purified by Florisil column chromatography. The hexane eluate afforded a 3.5:1 mixture of **3** and **4**. The mixture chromatographed over Florisil-silver nitrate three times, using hexane–chloroform–ether solvent system (stepwise elution), gave (E,E) - 3,7,10 - trimethyldodeca - 2,6,10 - triene (**3**) and (Z,E)-isomer (**4**). Similarly, from (Z)-nerolidol, (E,Z)- and (Z,Z) - 3,7,10 - trimethyldodeca - 2,6,10 - trienes (**5** and **6**) were obtained. (-,Z)-isomers showed shorter retention times than the corresponding (E)-isomers by GLC on OV-225.

The IR spectra of the four isomers in Table 1 gave characteristic absorption due to trisubstituted double bonds in 1600 and 800 cm^{-1} regions, however, no basic difference was detectable among the isomers.

PMR spectra. The PMR spectra of the compounds allowed partial differentiation of the geometrical conformers in the vinyl Me resonance region. In all compounds,

Table 1. IR absorptions of trisubstituted double bonds (cm^{-1}) of isomeric 3,7,11-trimethyldodeca-2,6,10-trienes

Isomer	RCH = CR'R"		
	νC=C	2 × δ CH	δ CH
3 (E,E)	1675	1630	835
4 (Z,E)	1675	1640	840
5 (E,Z)	1675	1645	835
6 (Z,Z)	1675	1630	830



Me signals were recorded in only two regions, in 1.60–1.61 and 1.68–1.69 ppm (Table 2).

Bates *et al.*[3] studied the stereochemistry of the trisubstituted double bond presented by A-$CH_2C(CH_3)$=CH-CH_2-B, and recognized differences in the chemical shift of Me protons depending upon their geometrical configurations in the PMR spectra using carbon tetrachloride solution.

According to their results, in the case of terpene hydrocarbons (A=H or isoprene unit, B = isoprene unit) (E)-Me protons resonate at higher field (1.59–1.60 ppm) whereas (Z)-Me protons resonate at lower field (1.66 ppm).

Table 2. Chemical shifts (ppm) of methyl protons of isomeric 3,7,11-trimethyldodeca-2,6,10-trienes

Isomer	$(CH_3)CH=C<$ and $-(CH_3)C=CH<$ (E)	$(CH_3)C=CH<$ (Z)
3 (E,E)	1.60 (12H, s.[a])	1.68 (3H, b.s.)
4 (Z,E)	1.61 (9H, d.[b], J[c]=1.5)	1.68 (6H, d.[b], J=1.5)
5 (E,Z)	1.60 (9H, b.s.)	1.68 (6H, s.)
6 (Z,Z)	1.61 (6H, b.s.)	1.69 (9H, d.[b], J=1.5)

a: Singlet, doublet, and broad singlet are abbreviated to s., d., and b.s.

b: When olefinic protons at 5.15 ppm were irradiated, these doublet signals changed to sharp singlet signals.

c: In Hz.

By analogy, signals observed at 1.60 or 1.61 ppm, and 1.68 or 1.69 ppm in **3**–**6** were assignable to (E)-Me and (Z)-Me protons, respectively. By PMR, however, we could not differentiate between the Me's substituted on each configurational double bond. Moreover, the resonance of the Me protons at C-1 overlapped at 1.60–1.61 ppm complicating assignments at this position.

CMR spectra. The CMR spectra of the four isomers showed clearly separated chemical shifts (Table 3).

A signal for each vinyl Me appeared in the 13, 17 and 25 ppm regions for all isomers, and we were easily assignable to C-1, (E)-Me attached to C-11, and (Z)-Me attached to C-11, respectively. Two other kinds of vinyl Me's which were observed in all isomers in the 15 and 23 ppm

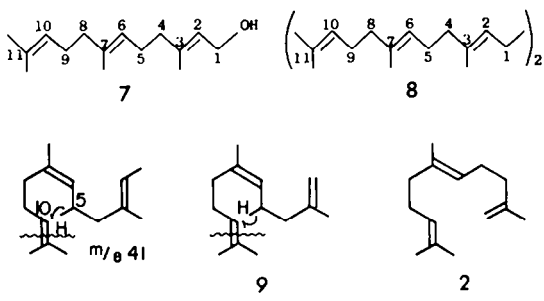
Table 3. CMR chemical shifts (ppm) of isomeric 3,7,11-trimethyldodeca-2,6,10-trienes

3 (E,E)	4 (Z,E)	5 (E,Z)	6 (Z,Z)
135.53	135.75	135.53	135.77
134.65	134.92	134.82	136.05
130.93	131.03	131.19	131.30
124.34	124.34	125.03	124.93
124.23	124.14	124.32	124.19
118.17	118.94	118.14	118.86
39.78	39.83	40.07	31.92
39.78	31.62	32.03	31.87
26.81	26.80	26.69	26.66
26.70	26.35	26.64	26.16
25.67	25.69	25.69	25.68
17.64	23.42	23.39	23.39
15.96	17.67	17.59	23.39
15.64	15.95	15.66	17.69
13.33	13.27	13.33	13.24

regions indicated (E)- and (Z)-Me carbon signals, respectively. In **4**, the Me carbon on the central (E)-double bond resonated at 15.95 ppm. On the other hand, in **5** the Me carbon on C-3 [(E)-double bond] was observed at 15.66 pp. Therefore, the signal at 15.96 ppm could be assigned to the Me carbon on C-7, whereas the signal at 15.64 ppm was due to the Me on C-3 in the (E,E)-isomer (**3**).

A signal due to each of the olefinic carbons in the 118 and 131 ppm regions appeared throughout all spectra and were assigned to C-2 and C-11, respectively. In general, a disubstituted olefinic carbon $\left(\diagup\!\!\diagdown C{=}C\right)$ resonates at lower field than a monosubstituted olefinic carbon (–CH=C).[4,5] Therefore, signals in the 124 ppm region are assignable to either C-6 or C-10 in these isomers. In the case of farnesol (**7**)[4] and squalene (**8**),[4] the C-10 carbon resonates at somewhat lower field (125.6 in farnesol, 125.5 ppm in squalene),† compared with the C-6 carbon (124.9 in farnesol, 125.5 ppm in squalene).† Therefore, in the present four isomers, the 124 ppm signal at lower field can be assigned to C-10 while another 124 ppm signal can be attributed to C-6. Although the signals in the 134–135 ppm region are due to the carbons at C-3 and C-7, they are not distinguishable.

†Values were given by substituting the original chemical shift (δ_{CS_2} in Ref. 4) into the equation, $\delta_{TMS} = 193.8 - \delta_{CS_2}$ (Ref. 5).



We can classify the chemical shifts of the allylic methylene carbon into three signal species, in the regions of 26, 31–32, and 39–40 ppm. Analysis[5] of these three signals reveals that a methylene carbon attached to a (Z)-double bond bearing a Me group [–$\underset{}{C}H_2$–$(CH_3)\overset{(Z)}{C}$=CH–] resonates in the 31–32 ppm region. On the other hand, a methylene carbon attached to an (E)-double bond bearing a Me group [–$\underset{}{C}H_2(CH_3)\overset{(E)}{C}$=CH–] appears at 39–40 ppm. The remaining 26 ppm signals are due to a methylene carbon attached to a double bond substituted with a proton [–$\underset{}{C}H_2$–CH=C]. The exact assignment between the two 26 ppm signals in each isomer is still ambiguous.

All CMR signal assignments are shown in Fig. 1.

Mass spectra. Some peaks in the mass spectra of the isomers are listed in Table 4. The most remarkable distinction is the intensity of the *m/e* 41 ion species in the isomers. This ion species, $[C_3H_5]^+$, is greater in the isomers possessing the (Z)-configurational double bond at C-6 [**5**(100) and **6**(90%)] than in the corresponding (E)-isomers [**3**(42) and **4**(64%)]. It is possible to consider that a

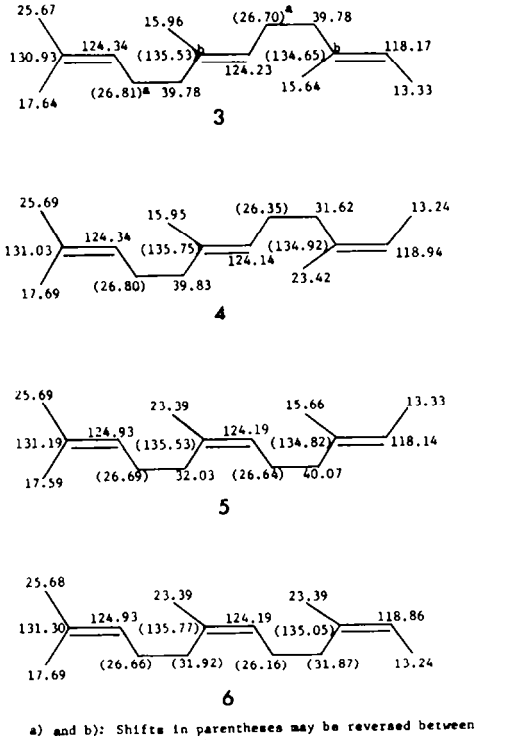


Fig. 1. CMR chemical shift assignments for isomeric 3,7,11-trimethyldodeca-2,6,10-trienes.

Table 4. Relative intensities (%) of some mass spectral peaks of isomeric 3,7,11-trimethyldodeca-2,6,10-trienes

	m/e					
Isomer	41	69	81	95	137	206 (M^+)
3 (E,E)	42	100	11	6	4	1
4 (Z,E)	64	100	12	8	3	2
5 (E,Z)	100	43	23	15	13	6
6 (Z,Z)	90	100	51	19	6	5

proton on C-5 which lies close to C-10 in the (-, Z)-isomers accelerates the fission of the C-10–C-11 double bond by rearrangement of the proton on C-5 to C-10. This speculation was supported by the mass spectra of the *nor*-sesquiterpenes, in which the *m/e* 41 peak was observed to be large in **9** (66%), (Z)-isomer compared with **2** (51%), (E)-isomer.

Birch *et al.*[6] isolated **3** and **4** from the plant, *Santalum spicatum*, and synthesized both compounds from farnesyl acetate. Compound **3** was also found in cigarette smoke by Dare *et al.*,[7] who prepared it from farnesyl bromide. Thus, farnesyl derivatives are good sources of the corresponding sesquiterpene hydrocarbons. In order to obtain stereoisomeric hydrocarbons, nerolidols are more favorable starting materials, since commercial farnesol contains only (E)-configurational isomers at C-6.

EXPERIMENTAL

The PMR spectra were recorded in deuteriochloroform on a Varian XL-100 spectrometer at 100 MHz with TMS as internal standard. The CMR spectra were taken at 25.5 MHz on a Varian XL-100 using 25% solution in $CDCl_3$ in 5 mm sample tubes. Chemical shifts were measured from internal TMS. The mass spectra were measured on a Bendix Model 12 modified with a CVC Mark IV. Ionization was at 30° and 70 eV. The IR spectra were obtained as liquid films on a Perkin-Elmer Model 257 spectrometer.

(E,E)- and (Z,E) - 3,7,11 - Trimethyldodeca - 2,6,10 - triene (**3** *and* **4**). A mixture of (E)-nerolidol (4.0 g) and 48% hydrobromic acid (4 ml) was stirred for 30 min under ice-cooling, and then stirred for 2 hr at room temp. The mixture was extracted with ether, washed with water, and dried with Na_2SO_4. Removal of the ether gave a crude bromide. To a soln of the crude bromide in DMF (14 ml) was added dropwise a suspension of $NaBH_4$ (720 mg) in DMF (10 ml) under ice-cooling. After stirring at 5° for 30 min, the stirring was continued for 1 hr at room temp. The mixture was treated with water, extracted with hexane, washed with water and dried with Na_2SO_4. Evaporation of the solvent afforded an oily residue. Florisil (50 g) column chromatography of the residue gave a mixture of **3** and **4** from hexane eluate. The mixture was chromatographed over Florisil–silver nitrate (10%) (60 g), and eluted with 12 ml fractions of hexane containing increasing proportions (5, 10, 15, . . . , 90, 95, and 100%) of chloroform. Subsequently the column was eluted with a mixture of chloroform and ether, in which the concentration of ether was increased in successive 10% steps. Finally, the column was eluted with ether. The Florisil–silver nitrate column chromatography was repeated twice with the same solvent system. Compound **4** (106 mg) and **3** (435 mg) were eluted separately during the ether fractions.

(E,E) - 3,7,11 - Trimethyldodeca - 2,6,10 - triene (**3**): PMR; 1.60 (12H, s.), 1.68 (3H, b.s.), 2.15 (8H, b.s.), 5.15 ppm (3H, m.): MS; *m/e* 206 (M^+; $C_{15}H_{26}$), 137, 136, 123, 121, 95, 81, 69, 41. (Z,E)-3,7,11 - Trimethyldodeca - 2,6,10 - triene (**4**): PMR; 1.61 (9H, d., $J = 1.5$), 1.68 (6H, d., $J = 1.5$), 2.04 (8H, t., $J = 2$), 5.15 ppm (3H, m.): MS; *m/e* 206 (M^+; $C_{15}H_{26}$), 137, 136, 123, 121, 95, 81, 69, 41.

(E,Z)- and (Z,Z) - 3,7,11 - Trimethyldodeca - 2,6,10 - triene (**5** *and* **6**). (Z)-Nerolidol (3.5 g) afforded **6** (74 mg) (from 45 to 60% ether in chloroform fractions) and **5** (215 mg) (from ether fractions) by the same reaction and isolation procedures described above.

(E,Z) - 3,7,11 - Trimethyldodeca - 2,6,10 - triene (**5**): PMR; 1.60 (9H, b.s.), 1.68 (6H, s.), 2.05 (8H, d., $J = 2.5$), 5.15 ppm (3H, m.): MS; *m/e* 206 (M^+; $C_{15}H_{26}$), 164, 137, 136, 121, 95, 81, 69, 53, 41. (Z,Z) - 3,7,11 - Trimethyldodeca - 2,6,10 - triene (**6**): PMR; 1.61 (6H, b.s.), 1.69 (9H, d., $J = 1.5$), 2.05 (8H, d., $J = 2.5$), 5.15 ppm (3H, m.): MS; *m/e* 206 (M^+; $C_{15}H_{26}$), 163, 137, 136, 122, 121, 95, 81, 69, 53, 41.

Acknowledgements—The authors thank Drs. R. P. W. Scott, J. F. Bount and R. C. Pitcher, Hoffmann-LaRoche, Inc., for the PMR and CMR spectra. We are also indebted to Dr. T. E. Acree and Mr. R. M. Butts, Department of Food Science and Technology, New York State Agricultural Experiment Station, for the mass spectra. This research was supported by a grant from the National Science Foundation (GB 43193).

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