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149. Ken'ichi Takeda, Hitoshi Minato, Satoko Nosaka, and Ichiro Ishizuka: Studies on Sesquiterpenoids. V.[1] The Structure of a Double Bond Isomer of α-Dihydroguaiene.[2]

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As reported earlier,[2] guaiol (I) was easily dehydrated with thionyl chloride in pyridine to give α-guaiene (II) as the major product together with a small amount of isopropylidene isomer, β-guaiene (III).[3] α-Guaiene (II) afforded only α-dihydroguaiene (IV) by catalytic hydrogenation with palladium charcoal under alkaline conditions, but under acid or neutral conditions it gave a mixture of α-dihydroguaiene (IV) and its double bond isomer (V, VI, VII, or VIII); this mixture showed two peaks at retention times of 8.8 and 11.25 minutes in the gas chromatogram. α-Dihydroguaiene having a peak at the retention time of 8.8 minutes was isolated by fractional distillation and elucidated to be represented by structure (IV). On the other hand, it was assumed that an isomer having a peak at the retention time of 11.25 minutes mights be represented by structure (V).

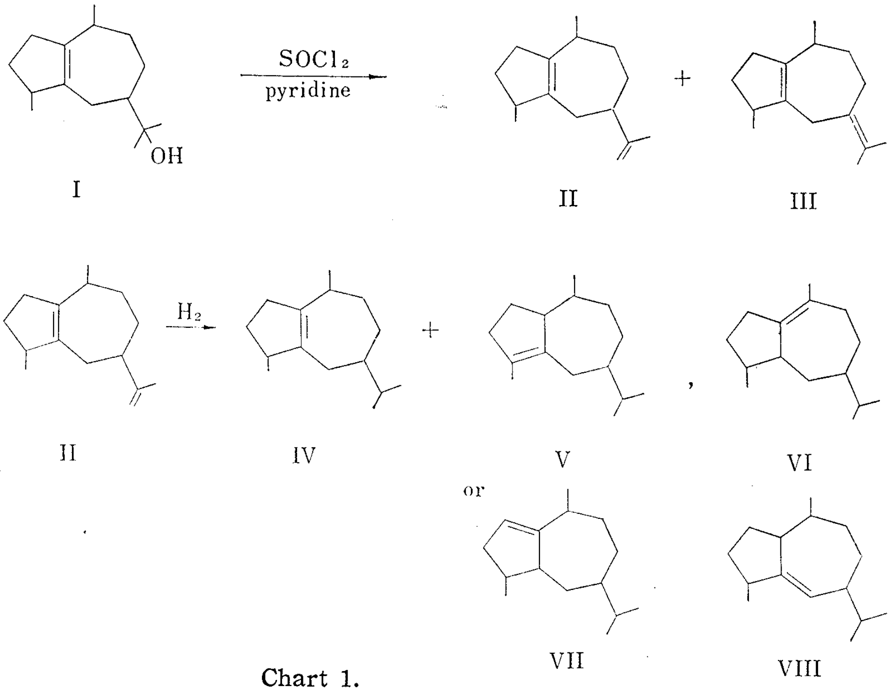

Chart 1.

We should now like to present chemical and spectroscopic evidence which established unambiguously the structure of this double bond isomer.

When α-guaiene (II) was hydrogenated in ethyl acetate with palladium charcoal as a catalyst under neutral condition, 1 mole of hydrogen was taken up smoothly and a colorless mobile oil, b.p$_2$ 76~92° was obtained. This oil showed two peaks at retention times of 15.1 and 19.5 minutes,[*2] whose ratio of peak heights was 1:1.58 in the gas chromatogram (see Fig. 1).

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[*2] In the previous paper it showed at retention times of 8.8 and 11.25 min.

1) Part IV. H. Minato: Tetrahedron, **18**, 365 (1962).

2) K. Takeda, H. Minato, S. Nosaka: *Ibid.*, **13**, 308 (1961).

3) R.B. Bates, R.C. Slagel: J. Am. Chem. Soc., **84**, 1307 (1962).

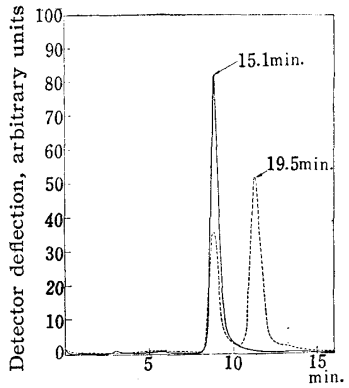

Fig. 1. Gas Chromatogram of Hydrogenation Products of α-Guaiene

—— : alkaline condition
------ : neutral condition

This mixture was fractionated through a column packed with Dixon packing, and further redistilled by Podbielniak column distillation to give a compound having a peak at the retention time of 19.5 minutes only (see Tables Ⅲ and Ⅳ). Thus-obtained purified oil no longer showed absorption bands corresponding to the isopropenyl functions in the infrared spectrum, and showed the following physical data: b.p$_2$ 94~95°, n_D^{25} 1.4916, d_4^{25} 0.90893, $[\alpha]_D$ +117.4°, UV : λ_{max} 208 mμ (ε 5.990); and the analytical values of this oil coincided well with those of dihydroguaiene. Although this compound showed no other characteristic band corresponding to the trisubstituted double bond in the infrared spectrum, a strong line at 1670 cm^{-1} related to the C=C double bond was observed in the Raman spectrum.

From these results may be excluded structures (Ⅶ and Ⅷ) out of the four possible structures as cited above for this compound.

Osmium tetroxide oxidation of the above-mentioned compound afforded a dihydroxy compound (Ⅸ), m.p. 136~137°, which was oxidized with sodium periodate to give a diketone (X), b.p$_1$ 115~116°.

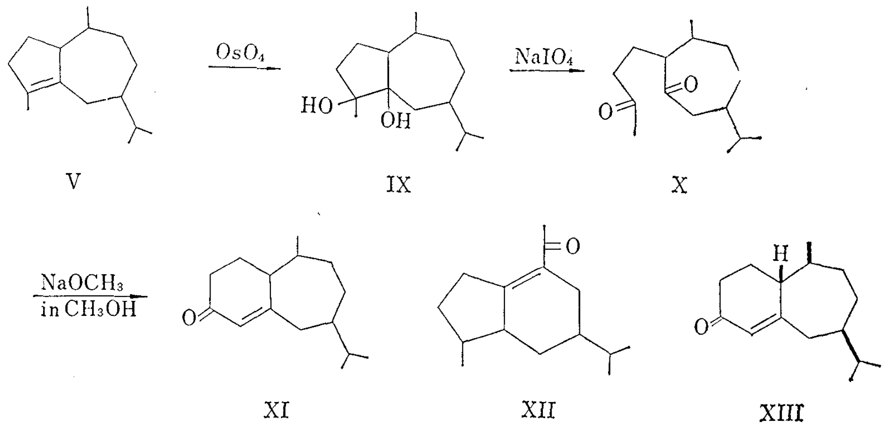

Chart 2.

This compound (X) showed the carbonyl absorption bands at 1717 and 1698 cm^{-1}, not corresponding to the five-membered ring ketone,*³ and showed negative to Fehling's and Tollen's reagents. The results of the spectroscopic examination and aldehyde test showed that this substance has neither a five-membered ring ketone nor an aldehyde

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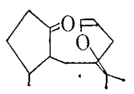
*³ L. Dolejs, A. Mironov, F. Šorm : Tetrahedron Letters, No. 11, 18 (1960).



$\nu_{C=O}$ 1744 cm^{-1}

function. Moreover, it was established that this compound has the CH_3CO group by iodoform test. As structures (VI, VII and VIII) for the double bond isomer of α-dihydroguaiene (IV) do not satisfy the above-mentioned results, structure (V) is most likely. In order to confirm this assumption, this diketone (X) was treated with an alkali. When X was treated with sodium methoxide in methanol, an α,β-unsaturated ketone (XI), b.p$_{0.5}$ 91~92°, was obtained (2,4-dinitrophenylhydrazone: red needles m.p. 118~119°). This α,β-unsaturated ketone (XI) showed absorption bands at 244 mμ (ε 15,600) in the ultraviolet spectrum, and at 1666 ($\nu_{C=O}$) and 1620 cm^{-1} ($\nu_{C=C}$) in the infrared spectrum. As the absorption band at 244 mμ is in agreement with the band of the type (XI),4) the type (XII) should therefore be excluded. This result also proves the correctness of the assumed structure (V) for the isomeric α-dihydroguaiene. The stereochemistry of XI was established by its optical rotatory dispersion curve shown in Fig. 2. The curve of the ketone (XI) is of the same type as those given by Δ^4-3-oxosteroids, thus the configuration of an angular hydrogen atom between five- and seven-membered ring should be expressed to be β-oriented as shown in XIII. Since the configurations of the methyl5) and the hydroxyisopropyl1) groups in guaiol (I) were both already confirmed, this α,β-unsaturated ketone (XI) should be represented as XIII.

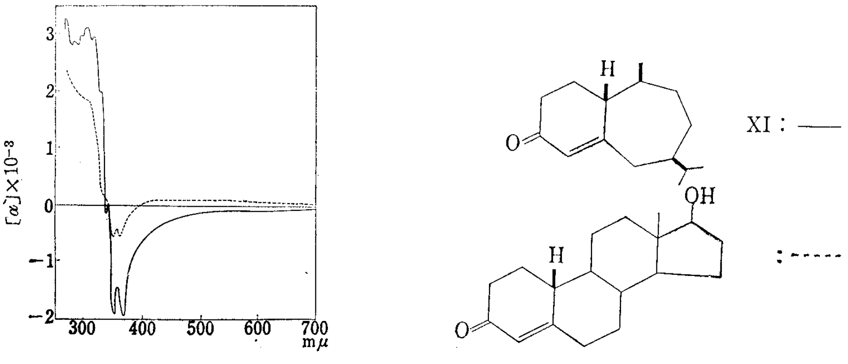


Fig. 2. RD Curves (Dioxane) of XI and 19-nor-Testosterone

One may have the question as to whether such tetrasubstituted double bonds between five- and seven-membered ring as that of guaiol (I) or α-dihydroguaiene (IV) migrate, when these compounds are shaken in hydrogen atmosphere with palladium charcoal catalyst. Then, we examined the migration reactions of the double bonds of guaiol (I) and α-dihydroguaiene (IV). When these compounds were shaken in hydrogen atmosphere with 10% palladium charcoal as a catalyst for 30 hours under neutral or acid condition respectively, the gas chromatography of α-dihydroguaiene (IV) showed the appearance of a peak having r.r.t.[*4] of 1.11 in addition to the peaks of the starting material (IV, r.r.t., 1.00) and the double bond isomer (V, r.r.t., 1.29), as shown in Table I. In the case of guaiol (I), the gas chromatography showed the peak of the starting material (I, r.r.t., 1.00) and three new peaks having r.r.t. of 1.11, 1.20, and 1.34, as shown in Table II.

From these results, it is ovbious that the double bonds of these compounds migrated undoubtedly.

Confirmation of the structures of these double bond migrating compounds is now in progress.

[*4] r. r. t. = relative retention time.

4) M. Palmade, G. Ourisson : Bull. soc. chim. France, **1958**, 886.

5) H. Minato : This Bulletin, **9**, 625 (1961).

Table I. Gas Chromatogram of the Products of the Double Bond-migration Reactions of α-Dihydroguaiene (IV)

Reaction times	Ratio of peak heights at r.r.t. of		
	1.00	1.11	1.29
Starting material (IV)	1.00[a]	0	0.17[b]
30 hr. (neutral condition)	1.00	0.98	1.10
60 hr. (〃)[c]	1.00	1.27	1.14
30 hr. (acid condition)	1.00	1.13	0.99

a) Time, 15.1 min.

b) This peak is due to contamination of the starting material, α-dihydroguaiene (IV) with the compound (V).

c) Gas chromatogram of this product showed the shoulders at r.r.t. of 1.04 and 1.17.

Table II. Gas Chromatogram[a] of the Products of the Double Bond-migration Reaction of Guaiol (I)

Reaction times	Ratio of peak heights at r.r.t of			
	1.00	1.11	1.20	1.34
Starting material (I)	1.00[b]	0	0	0
30 hr. (neutral condition)	1.00	2.53	0.82	1.24
30 hr. (acid condition)	1.00	2.27	0.74	0.97

a) For the analysis of products, a column, 3 m. in length with a 6 mm. i.d., consiting of Silicone oil KF-54 (Shinetsu Co.) on Chromosorb W. (30 to 60 mesh) was operated at 160° with a flow rate of 100 ml./min. of hydrogen.

b) Time, 11.3 min.

Experimental

The Shimadzu Gas Chromatograph-IA was used for all gas chromatographic determinations. For the analysis of products, a column, 3 m. in length with a 6 mm. i.d., consisting of Silicone 550 on Chromosorb W (30 to 60 mesh) was operated at 200° with a flow rate of 100 ml./min. of hydrogen. All melting points were measured by use of Kofler block ("mono-scope" Hans Bock Co., Ltd., Frankfurt am Main, Germany) and corrected. Rudolph Recording Spectropolarimeter was used for the optical rotatory dispersion measurement. Unless specified to the contrary, $[\alpha]_D$ are in EtOH; UV spectra were determined in 95% EtOH.

Hydrogenation of α-Guaiene (II)——To a solution of 31 g. of α-guaiene (II) in 300 ml. of AcOEt was added 3 g. of 10% Pd-C. The mixture was reduced by catalytic hydrogenation at room temperature and atmospheric pressure (uptake of H_2, 1.1 mole). The product was distilled at 76~92°/2 mm. Hg giving 30.5 g. of a mixture of IV and V. This mixture was redistilled through a column, 500 mm. high with a 15 mm. i.d., packed with Dixon packing (stainless steel, 1/16″), to furnish eight fractions (see Table III).

Table III. Distillation Products by Dixon Packing Column Distillation

Fraction No.	b.p$_4$ (°C)	Ratio of peak height at 15.1 min. : 19.5 min.	Yield (g.)
1	89.5	3.95 : 1	2.18
2	98.0	3.62 : 1	4.44
3	94.7	2.91 : 1	1.80
4	96.0	2.11 : 1	1.88
5	100.0	1.22 : 1	1.87
6	100.4	0.67 : 1	1.77
7	99.0	0.43 : 1	0.59
8	Residue	0.04 : 1	13.25

Fraction 8 was the residue of distillation, and rectified through Podbielniak column, 600 mm. high with a 8 mm. i.d., packed with Heli-grid, to furnish following nine fractions (see Table IV).

Fractions 7 and 8 were pure V, n_D^{25} 1.4916 (n_D^{20} 1.4940), d_4^{25} 0.90893, $[\alpha]_D^{23.5}$ +117.4°(±2°) (c=1.402), UV : λ_{max} 208 mμ (ε 5,990), Raman : ν_{max} 1670 cm.$^{-1}$ *Anal.* Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found : C, 87.30; H, 12.85.

TABLE IV. Distillation Products by Podbielniak Column Distillation

Fraction No.	b.p$_5$ (°C)	Ratio of peak height at 15.1 min. : 19.5 min.	Yield (g.)
1	90.0	0.25 : 1	0.9
2	121.0	0.18 : 1	0.45
3	120.0	0.065 : 1	0.49
4	120.5	0.044 : 1	0.46
5	120.0	0.027 : 1	0.48
6	117.0	0.016 : 1	0.23
7	118.0	0 : 1	1.81
8	116.5	0 : 1	1.10
9	Residue[a]	0 : 1	6.0

[a] The residue was distilled at 94~95°/2 mm. by usual manner giving a colorless oil (5.3 g.).

Oxidation of V with Osmium Tetroxide——A solution of 2 g. of OsO_4 in 20 ml. of dry purified benzene was added to a solution of 1.6 g. of V in 30 ml. of the same solvent and 3 ml. of pyridine. The mixture was left at room temperature for 5 days and then saturated with H_2S. The black precipitate was filtered off and sufficiently washed with Et_2O. The filtrate and washing were washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. Crystallization from Et_2O and chromatography of its mother liquid over Al_2O_3 afforded colorless plates (IX, 1.01 g.) and an oily diketone (X, 150 mg.). IX was recrystallized from EtOH–light petroleum to give colorless plates, m.p. 136~137°, $[\alpha]_D^{23}$ $-51.4°(\pm 2°)$ (c=1.081), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3485, 1097. *Anal.* Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.74; H, 11.67.

Oxidation of IX with Sodium Periodate——A solution of 905 mg. (2 equiv.) of $NaIO_4$ in 10 ml. of H_2O was added to a solution of 410 mg. of IX in 30 ml. of MeOH and 2 ml. of dioxane. The solution was left at room temperature for 68 hr. and then heated at 55~65° for 16 hr. This mixture was evaporated *in vacuo* and extracted with Et_2O. The Et_2O extract was washed with 2*N* Na_2CO_3 and H_2O, dried over Na_2SO_4. and evaporated giving 380 mg. of a colorless oil. The residue was distilled at 115~116°/1 mm. Hg giving 340 mg. of a colorless oil (X), $[\alpha]_D^{21}$ $+100.7°(\pm 2°)$ (c=1.119), IR ν_{max}^{film} cm^{-1}: 1717, 1698, which showed negative results to Fehling's and Tollen's reagents and afforded iodoform, m.p. 118~119°, by NaIO oxidation. *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.69; H, 11.14.

Treatment of X with 0.1*N* MeONa in MeOH——A solution of 473 mg. of diketone (X) in 15 ml. of 0.1*N* MeONa in MeOH was refluxed in N_2 atmosphere for 2 hr., then evaporated *in vacuo* and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over Na_2SO_4, and evaporated leaving 418 mg. of a colorless oil. Chromatography of the residue over 12 g. of Al_2O_3 ("Woelm," grade III) afforded on elution with light petroleum and light petroleum-benzene (4:1 and 1:1) 370 mg. of a colorless oil (XI), b.p$_{0.5}$ 91~92°, $[\alpha]_D^{21.5}$ $-62.5°$ $(\pm 2°)$ (c=1.348), UV: λ_{max} 244 mμ (ε 15,600), IR ν_{max}^{film} cm^{-1}: 1666, 1620. RD (Fig. 2) in dioxane (c=0.246): $[\alpha]_{700}$ $-65°$, $[\alpha]_{372}$ $-1940°$, $[\alpha]_{363}$ $-1435°$, $[\alpha]_{356}$ $-1905°$, $[\alpha]_{345}$ $+12°$, $[\alpha]_{341}$ $-130°$, $[\alpha]_{328.5}$ $+2005°$, $[\alpha]_{328}$ $+1990°$, $[\alpha]_{318}$ $+2975°$, $[\alpha]_{315}$ $+2910°$, $[\alpha]_{307}$ $+3130°$, $[\alpha]_{300}$ $+2990°$, $[\alpha]_{298.5}$ $+3010°$, $[\alpha]_{291}$ $+2820°$, $[\alpha]_{285}$ $+2890°$, $[\alpha]_{281}$ $+2830°$, $[\alpha]_{270}$ $+3310°$. *Anal.* Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.93. Found: C, 81.76; H, 11.13. 2,4-Dinitrophenylhydrazone of IX: red needles, m.p. 118~119° (from Et_2O-EtOH), UV: λ_{max} 386 mμ (ε 32,000). *Anal.* Calcd. for $C_{21}H_{28}O_4N_4$: C, 62.98; H, 7.05; H, 13.99. Found: C, 63.02; H, 7.03; N, 13.95.

The autohrs are indebted to Dr. K. Kuriyama for the $[\alpha]_D$ and the RD measurements.

Summary

When α-guaiene (II) was hydrogenated with palladium charcoal as a catalyst under neutral or acid conditions, it gave a mixture of α-dihydroguaiene (IV) and its double bond isomer. The constitution of the latter was established as V.

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