HYDROBORATION OF TERPENES

I. THE SELECTIVE HYDROBORATION OF MYRCENE WITH DISIAMYLBORANE

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INTRODUCTION

The addition of diborane and its alkyl derivatives to olefins is a fast, quantitative reaction, of unusual broad generality and remarkably free from undesirable rearrangements or other side-reactions[1]. Moreover, the reaction involves a stereochemically *cis* addition from the less hindered side of the double bond, the boron atom becoming attached preferentially to the less substituted of the two carbon atoms of the double bond[1]. Finally, the resulting organoboranes are reactive intermediates which are readily transformed into other products of interest in organic synthesis, without rearrangement or loss of the stereospecific structure of the original hydroboration product. Consequently, the hydroboration reaction promises to be of major utility to the chemist interested in the synthesis of stereochemically defined products.

The main characteristics of the hydroboration reaction have been explored with a wide variety of simple, representative olefins[1]. It appeared of interest to establish whether the generalizations arrived at as a result of these initial studies were applicable to more complex systems.

The naturally occurring terpenes appear to provide an ideal testing ground for these generalizations. The terpenes are one of the most sensitive classes of organic compounds, subject to facile isomerization, cyclization, and skeletal rearrangement. Their hydroboration and subsequent conversion to other derivatives appear to offer unique possibilities for the preparation of terpenols and related derivatives, accessible only with difficulty by other routes. The products, being of defined stereochemistry, should permit reliable configurational assignments and structural correlations. Accordingly, we have undertaken a study of the hydroboration of a number of representative terpenes.

The present paper, the first of this series, reports our results on the selective hydroboration of myrcene†.

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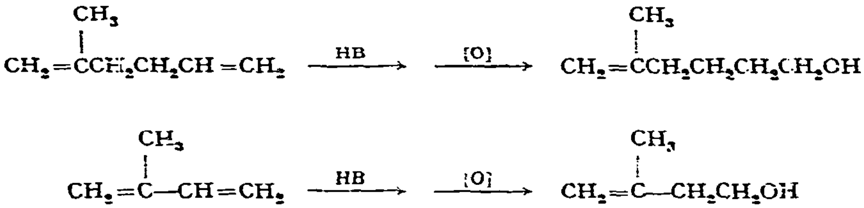
† A brief study of the hydroboration of myrcene was recently reported[2]. However, since our study differed somewhat in scope and objectives, it appeared desirable to record our observations in spite of the partial duplication which unfortunately occurred.

Previous studies with representative olefins established that disiamylborane [bis(3-methyl-2-butyl)borane] is a highly selective hydroborating agent which reacts selectively with the less substituted olefin in the presence of the more substituted[3].

$$RHC{=}CH_2 < R_2C{=}CH_2 < R_2C{=}CHR$$

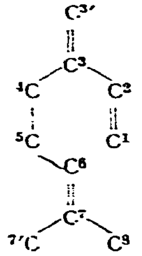
It was demonstrated that this generalization could be extended to both simple unconjugated and conjugated dienes[4]. Thus, hydroboration with disiamylborane followed by oxidation converts 2-methyl-1,5-hexadiene into 5-methyl-5-hexen-1-ol and isoprene into 3-methyl-3-buten-1-ol.



$$CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_2CH{=}CH_2 \xrightarrow{HB} \xrightarrow{[O]} CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_2CH_2CH_2OH$$

$$CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CH{=}CH_2 \xrightarrow{HB} \xrightarrow{[O]} CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CH_2CH_2OH$$

Myrcene offers three reactive double bonds.



On the assumption that the above generalization holds, the preference for attack by disiamylborane should be 1 > 3′ > 6. Unfortunately, a minor complication exists. The two more reactive double bonds are conjugated, and such conjugation reduces the activity of the unsaturated centers towards hydroboration and increases the difficulty of achieving the monohydroboration of the diene structure[4].

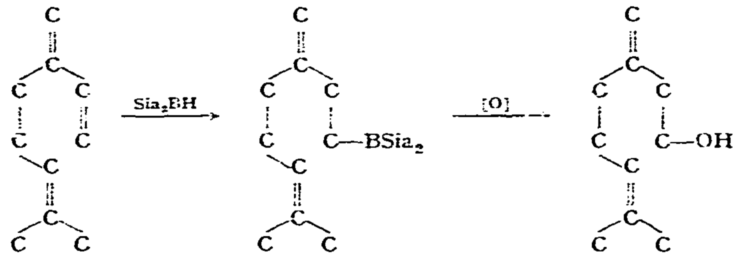
RESULTS AND DISCUSSION

In order to favor the formation of the monohydroboration product, an excess of myrcene (70 to 100 percent) in tetrahydrofuran at −10 to 0° was treated with disiamylborane in the same solvent. Oxidation of the hydroboration product yielded a crude myrcenol fraction which was purified by fractionation in a 100 plate Podbielniak column (b.p. 83–86° at 2 to 3 mm, n_D^{20} 1.4717) or by preparative vapor phase chromatography on either a Carbowax 20M or a tricyanoethoxypropane (TCEP) column (n_D^{20} 1.4711). The yields isolated in different preparations were in the range 55 to 65 percent.

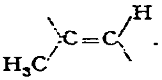
The product was homogeneous on a TCEP capillary column (150 ft.). Repeated recrystallization of the 3,5-dinitrobenzoate, m.p. 69–70°, followed by regeneration of the alcohol, yielded a material which was indistinguishable from the original product.

Hydrogenation of the product and a sample of authentic geraniol by the Brown procedure[5] afforded tetrahydro derivatives indistinguishable on a TCEP capillary column. Similarly, the partial hydrogenation of the product over Adams catalyst yielded DL-citronellol, identified through the allophanate, m.p. 104°, and comparison of the infrared spectrum with that of an authentic sample[6].

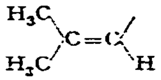
Finally, infrared and nuclear magnetic resonance spectra clearly support the product to be 7-methyl-3-methylene-6-octen-1-ol, "myrcenol", involving attack of disiamylborane at the least substituted of the three double bonds.



Thus the infrared spectrum is compatible only with the proposed formulation in that the C=C stretching frequency occurs at 1652 cm^{-1} and the =C–H stretching frequency at 3007 cm^{-1}, indicating a disubstituted double bond, whereas the CH_2 out-of-plane deformation (at 915–905 cm^{-1}) characteristic of the vinyl group, $-CH=CH_2$, is absent. An inflection at 987 cm^{-1} of medium intensity which could conceivably arise from the C–H out-of-plane deformation of the vinyl group may also be identified[7,8] with the grouping



Finally, the presence of a trisubstituted double bond is evident from the C–H out-of-plane deformation at 823 cm^{-1} and the inflection at 1678 cm^{-1}, the stretching frequency.

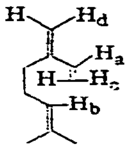


The nuclear magnetic resonance spectrum of myrcene shows four distinct vinyl protons, assigned[9] as summarized in Table 1.

In the NMR spectrum of myrcenol, absorption due to H_a, H_c is absent, striking substantiation that only the vinyl group ($-CH=CH_2$) has been hydroborated. H_d remains as a sharp singlet and H_b as a broad hump. The presence of only three vinylic hydrogen atoms in myrcenol was confirmed from a quantitative comparison of the integrated areas for methyl and vinyl proton absorption: methyl 6.00, vinyl 5.8 for myrcene; methyl 6.00, vinyl 2.8 for myrcenol. Similarly, the area ratio of 2.0 for H_d/H_b in myrcenol is significant.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRUM OF MYRCENE

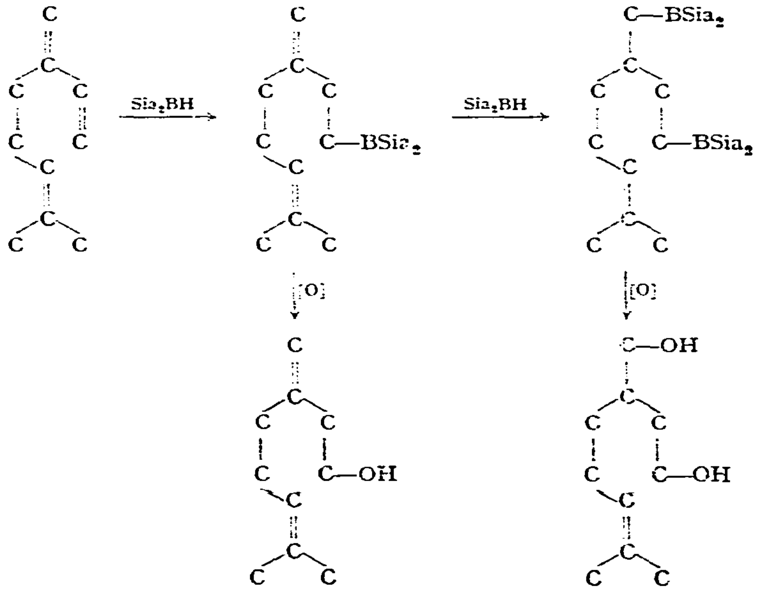
Shift p.p.m.	*Appearance*	*Assignment*	
6.08 6.26 6.38 6.55	Two doublets	H_a	
5.32	Apparent doublet	H_b	
5.07	Center of multiplet	H_c	
4.94	Single peak — no splitting	H_d	

Treatment of myrcene with two moles of disiamylborane, followed by oxidation, resulted in the formation of a 78 percent yield of a diol, b.p. 119–121° at 0.2 mm, n_D^{20} 1.4787, bis-α-naphthylurethane, m.p. 87–89°.

The structure of the product as 7-methyl-3-hydroxymethyl-6-octan-1-ol, "myrcenediol", involving attack at the 1- and 3'-positions of the vinyl and methylene groups, was based upon the nuclear magnetic resonance and infrared spectra. In the NMR spectrum, vinyl proton absorption occurs as a broad band at 5.07 p.p.m. The sharp absorption anticipated for the unsaturated methylene group, $>C{=}CH_2$, is absent. Similarly, the absence of a monosubstituted or 1,1-disubstituted double bond was confirmed by the infrared spectrum of the diol. Weak absorption bands, characteristic of the trisubstituted double bond, occur at 1798 cm^{-1} and 826 cm^{-1}.

Hydroboration–oxidation of myrcenol with disiamylborane yielded the same diol, as confirmed by a gas chromatographic comparison.

Consequently, the data clearly support the conclusion that the reaction of disiamylborane with myrcene proceeds stepwise, with addition occurring preferentially at the vinyl group, followed by reaction at the methylene group.



EXPERIMENTAL PART

Materials

The purification of diglyme, tetrahydrofuran, boron trifluoride etherate, and the preparation of diborane and disiamylborane were carried out as described in earlier studies[3,4]. Myrcene was a commercial sample from The Glidden Co. (n_D^{20} 1.4758, purity 80 percent by gas chromatographic examination). Distillation through a 12-in. vacuum jacketed packed column yielded a product, b.p. 89°–92° at 70 mm, n_D^{20} 1.4706, 87 percent purity. Distillation through a 150 cm Podbielniak column yielded a product, n_D^{20} 1.4690, 95 percent purity (reported[10] for pure myrcene: n_D^{20} 1.4680). We observed no significant difference in results with these different samples of myrcene.

Monohydroboration of myrcene

Disiamylborane (100 mmoles) was prepared by adding 54.4 ml of 1.84 *M* BH_3 in tetrahydrofuran (100 mmoles BH_3) to 21 ml of 2-methyl-2-butene (200 mmoles) in tetrahydrofuran at 0°. After standing for 3 hours, the solution of the reagent was slowly added under nitrogen to 34 ml of freshly distilled myrcene (200 mmoles) in tetrahydrofuran at 0°. The reaction mixture was maintained at 0–10° for 4 hours. It was then treated with 5 ml of water to hydrolyze any residual hydride, followed by 32 ml of 3*N* sodium hydroxide and 32 ml of 30 % hydrogen peroxide. The latter was added slowly (vigorous reaction!), maintaining the reaction temperature at 25 to 50° by external cooling. After 1.5 hours at room temperature, the reaction mixture was extracted with ether, the ether layer washed with brine, followed by ice-cold water. The ether layer was dried over anhydrous magnesium sulfate and distilled. There was obtained 10.5 g of myrcenol, b.p. 83–86° at 2 to 3 mm, n_D^{20} 1.4717, a yield of 68%. (Found: C, 17.94; H, 11.62. $C_{10}H_{18}O$ calcd.: C, 17.89; H, 11.76 %.)

In a similar preparation, utilizing distilled myrcene of n_D^{20} 1.4706, there was isolated by preparative gas chromatography a 55 % yield of myrcenol, n_D^{20} 1.4711.

Hydroboration of 51.8 mmoles of myrcene of 95 % purity with 30.7 mmoles of disiamylborane provided 12.5 mmoles of pure myrcenol, a 53 % yield relative to the myrcene consumed.

Myrcenol was converted into the 3,5-dinitrobenzoate by the procedure of Brewster and Ciotti[11]. (Found: C, 58.75; H, 5.94; N, 8.13. $C_{17}H_{20}N_2O_2$ calcd.: C, 58.59, H, 5.79; N, 8.05 %.)

Hydrogenation of myrcenol

Both myrcenol and geraniol were hydrogenated by the internal procedure using platinum on carbon catalyst and acetic acid in ethanol as the hydrogenation medium[5]. In each case the theoretical amount of hydrogen was absorbed for complete hydrogenation. Tetrahydrogeraniol, n_D^{20} 1.4344, and tetrahydromyrcenol, n_D^{20} 1.4359, appeared to be identical, as down by the formation of only a single peak in a gas chromatographic examination on a TCEP capillary column.

Similarly, the half hydrogenation of myrcenol produced citronellol[6], n_D^{20} 1.4576, allophanate, m.p. 104°, with an identical infrared spectrum to that published for the pure compound[6].

Dihydroboration of myrcene

To a stirred solution of disiamylborane, 87.5 mmoles, at —20° was added a solution of 41 mmoles of myrcene (89% purity). After 0.75 h at —10 to —20°, followed by 1.25 h at 0°, water was added to destroy residual hydride. Oxidation was effected at 30–50° with 37 ml of 3*N* sodium hydroxide and 37 ml of 30% hydrogen peroxide. After 2 h, the aqueous phase was saturated with potassium carbonate, separated from the organic phase, and extracted further with tetrahydrofuran. The combined organic phases were dried over anhydrous potassium carbonate. Distillation yielded 28 mmoles of myrcenediol, b.p. 119–121° at 0.2 mm, n_D^{22} 1.4787, a yield of 77%. (Found: C, 70.20; H, 11.97. $C_{10}H_{20}O_2$ calcd.: C, 69.70; H, 11.71%.)

The bis-3,5-dinitrobenzoate was a liquid which could not be crystallized. Treatment of the diol purified by chromatography on alumina (eluted with methanol from Grade IV alumina) with α-naphthyl isocyanate yielded the bis-α-naphthylurethane, m.p. 87–89° from petroleum ether (b.p. 65–67°). (Found: C, 75.13; H, 6.41; N, 5.33. $C_{32}H_{34}N_2O_4$ calcd.: C, 75.25; H, 6.72; N, 5.49%.)

Hydroboration of myrcenol

Myrcenol in tetrahydrofuran at 0° was treated with sufficient disiamylborane to react with the hydroxyl group and one double bond. After oxidation, the diol was isolated as above. Gas chromatographic analysis of the diol mixed with the diol derived from the dihydroboration of myrcene (Carbowax 20*M* on silanized firebrick) at 170°, showed only a single peak.

SUMMARY

The reaction of disiamylborane with myrcene (7-methyl-3-methylene-1,6-octadiene) occurs selectively to place the boron atom at the 1-position. Oxidation of the resulting organoborane with alkaline hydrogen peroxide yields myrcenol (7-methyl-3-methylene-6-octen-1-ol) identified by infrared and nuclear magnetic resonance spectra. Further hydroboration of myrcenol with disiamylborane, or dihydroboration of myrcene with the reagent, results in selective reaction at the 3-methylene group. Oxidation of the products yields the diol, 7-methyl-3-hydroxymethyl-6-octan-1-ol. Consequently, the three double bonds of myrcene exhibit a tendency to undergo attack in the order, $RCH_2{=}CH_2 > RR'C{=}CH_2 > R_2C{=}CHR'$, as predicted from competitive experiments with simple model systems.

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