Chemical Structure-Odor Correlation in Series of Synthetic Methylene Interrupted n-Nonadien-l-ols

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Z. Naturforsch. 51c, 841–848 (1996), received August 7/August 31, 1996

Structure-Odor Relation. Synthesis, Nonadienols, Principal Component Analysis

Chemical structure-odor correlations in the isomers of n-C₉-methylene interrupted dienols were explored using synthetic nine isomers of these alcohols. The synthetic dienols were purified by recrystallization or column chromatography of their 3,5-dinitrobenzoate derivatives.

Chemical structure-odor correlations in all the isomers of the purified n-nonadien-l-ols were analyzed by treating the data obtained statistically with the principal component analysis method (Sakoda et al., 1995; Cramer et al., 1988) in comparison with those of n-nonen-l-ols. The odor profiles of the n-nonadien-l-ols were attributable largely to the geometries of the isomers, compared with n-nonen-l-ols (Sakoda et al., 1995). With the principal component analysis, the odor profiles of the series of the dienols were successfully integrated into the first and the second principal components. The first component (PC 1) consisted of combined characteristics of fruity, fresh, sweet, herbal and oily-fatty, and the second component (PC 2) leaf or grassy and vegetable-like. Of the methylene interrupted dienol isomers, (2E,6Z)- and (3Z,6Z)-nonadien-l-ols which are natural products and have (6Z) in the same, deviated markedly from the other isomers as seen in (6Z)-nonen-l-ol of n-nonen-l-ols. That suggests that the double bond of (o3Z) was an important factor for natural characteristic odor.

Introduction

Recently, the relations between the characteristic odor and position and/or geometry of a double bond in various isomers of n-C₉- and C₉-mono­enols were successfully evaluated (Hatanaka et al., 1992; Sakoda et al., 1995). With these investigations, it has been revealed that the position and the geometry of double bond in primary alcohol has a significant and regular effect on its odor profile. Interestingly, naturally occurring (3Z)-hexen-l-ol, which is known as “leaf alcohol”, and naturally occurring (6Z)-nonen-l-ol were found to be deviated markedly from the relationship and showed a unique odor profile. These findings indicated that (o3Z)-moiety in a primary alcohol had rather specific interaction with human odor-sen­sory system.

Reprint requests to Prof. Dr. Tadahiko Kajiwara.

Materials and Methods

IR spectra were recorded on a JIR 100 FT-IR spectrometer (JEOL, Tokyo, Japan). ¹H NMR and ¹³C NMR spectra were obtained on a JNM-EX

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Preparation of (2E,6E)- and (2Z,6E)-nonadien-1-ols

As an α-site counterpart, propargyl alcohol was protected with 3,4-dihydro-2H-pyran to give 2-(2-propynlyoxy)-tetrahydropyran in 88% yield. On the other hand, as an ω-site counterpart, 3-butyln-1-ol was prepared by coupling of ethylene oxide with sodium acetylide in liquid ammonia. The ynol was protected with 3,4-dihydro-2H-pyran to give 2-(3-butylnlyoxy)-tetrahydropyran in 90% yield. Acetylenic coupling of the tetrahydropyran with ethyl bromide gave 2-(3-hexynlyoxy)-tetrahydropyran in 60% yield. The pyranyl ether was converted to 3-hexyn-1-ol with 30% (w/w) phosphoric acid-methanol in 81% yield. The ynol was hydrogenated over Lindlar catalyst to give (3Z)-hexenyl tosylate in 90% yield. Bromination of the tosylate with sodium bromide gave (3Z)-hexenyl bromide in 70% yield. The 2-(2-propynlyoxy)-tetrahydropyran was converted to its lithium salt with n-butyllithium in tetrahydrofuran (THF) and coupled with (3Z)-hexenyl bromide in hexamethyolphosphoric triamide (HMPA) to give 2-[(3Z)-hexen-2-ynyloxy]-tetrahydropyran in 25% yield. The pyranyl ether was converted to (6Z)-nonen-2-yn-1-ol with 30% phosphoric acid in 83% yield. The ynol was hydrogenated over Lindlar catalyst to give (2Z,6Z)-nonadien-1-ol in 93% yield. (2E,6Z)-nonadien-1-ol was obtained by reduction with lithium aluminum hydride in ether in 91% yield.

(2Z,6E)-nonadien-1-ol: b.p. 69.0–70.0 °C/0.27 mmHg; purity 99.6%; m.p. of 3,5-DNB 21.6−23.0 °C; IR (film) cm⁻¹: 3334 (O-H), 2963 (C-H); 13C NMR (CDCl₃/TMS): δ = 13.9, 25.6, 27.6, 32.4, 58.6, 128.1, 128.7, 132.4, 133.0 ppm; 1H NMR (CDCl₃/TMS): δ = 0.96 (t, 3H, J = 6.4), 1.49 (br s, 1H), 2.17−1.97 (m, 6H), 4.17 (d, 2H, J = 4.4), 5.65−5.34 ppm (m, 4H).

(2E,6E)-nonadien-1-ol: b.p. 51.0–53.0 °C/0.025 mmHg; purity 99.9%; m.p. of 3,5-DNB 21.6−23.0 °C; IR (film) cm⁻¹: 3334 (O-H), 3006 (C=C-H), 2962, 2933 (C-H), 1670, 1652 (C=C), 1026 (C-O), 968 (E, CH=CH); 13C NMR (CDCl₃/TMS): δ = 14.3, 20.6, 27.0, 27.6, 58.5, 128.0, 128.9, 132.3, 132.6 ppm; 1H NMR (CDCl₃/TMS): δ = 0.96 (t, 3H, J = 7.3), 1.62 (br s, 1H), 2.02−2.15 (m, 6H), 4.17 (d, 2H, J = 6.4), 5.29−5.66 ppm (m, 4H).

Preparation of (2E,6Z)- and (2Z,6Z)-nonadien-1-ols

As an α-site counterpart, 3-hexyn-1-ol was hydrogenated over Lindlar catalyst to give (3Z)-hexen-1-ol in 98% yield. (3Z)-hexen-1-ol was tosylated with tosyl chloride (TsCl) to give (3Z)-hex-3-enyl tosylate in 90% yield. Bromination of the tosylate with sodium bromide gave (3Z)-hexenyl bromide in 70% yield. The 2-(2-propynlyoxy)-tetrahydropyran was converted to its lithium salt with n-butyllithium in tetrahydrofuran (THF) and coupled with (3Z)-hexenyl bromide in hexamethyolphosphoric triamide (HMPA) to give 2-[(3Z)-hexen-2-ynyloxy]-tetrahydropyran in 25% yield. The pyranyl ether was converted to (6Z)-nonen-2-yn-1-ol with 30% phosphoric acid in 83% yield. The ynol was hydrogenated over Lindlar catalyst to give (2Z,6Z)-nonadien-1-ol in 93% yield. (2E,6Z)-nonadien-1-ol was obtained by reduction with lithium aluminum hydride in ether in 91% yield.

(3E,6E)-nonadien-1-ol: b.p. 45.0–56.0 °C/0.25 mmHg; purity 99.3%; m.p. of 3,5-DNB 21.6−23.0 °C; IR (film) cm⁻¹: 3334 (O-H), 3006 (C=C-H), 2962, 2933 (C-H), 1670, 1652 (C=C), 1026 (C-O), 968 (E, C=C), 715 (Z, CH=CH); 13C NMR (CDCl₃/TMS): δ = 14.3, 20.6, 27.0, 27.6, 58.5, 128.0, 128.9, 132.3, 132.6 ppm; 1H NMR (CDCl₃/TMS): δ = 0.96 (t, 3H, J = 7.3), 1.62 (br s, 1H), 2.02−2.15 (m, 6H), 4.17 (d, 2H, J = 6.4), 5.29−5.66 ppm (m, 4H).

(2E,6Z)-nonadien-1-ol: b.p. 51.0–53.0 °C/0.025 mmHg; purity 99.9%; m.p. of 3,5-DNB 21.6−23.0 °C; IR (film) cm⁻¹: 3334 (O-H), 3006 (C=C-H), 2962, 2933 (C-H), 1670, 1652 (C=C), 1026 (C-O), 968 (E, C=C), 715 (Z, C=C); 13C NMR (CDCl₃/TMS): δ = 14.3, 20.6, 27.0, 27.6, 58.5, 128.0, 128.9, 132.3, 132.6 ppm; 1H NMR (CDCl₃/TMS): δ = 0.96 (t, 3H, J = 7.6), 1.55 (br s, 1H), 2.15−2.00 (m, 6H), 4.08 (d, 2H, J = 4.9), 5.42−5.29 (m, 2H), 5.72−5.66 ppm (m, 2H).

Preparation of (3E,6E)- and (3Z,6E)-nonadien-1-ols

As an ω-site counterpart, acetylenic coupling of the 2-(2-propynlyoxy)-tetrahydropyran with ethyl...
bromide gave 2-(2-pentyloxy)-tetrahydropyran in 90% yield. The pyranyl ether was converted to 2-pentyn-1-ol with 5% (w/w) PTS-methanol in 90% yield. (2E)-penten-1-ol was obtained by Birch reduction in 85% yield. Bromination of the (2E)-penten-1-ol with phosphorus tribromide gave (2E)-pentenyl bromide in 74% yield. 2-[6Z]-nonen-3-ynyl]-tetrahydropyran was prepared by Grignard coupling of 2-(3-butylnyloxy)-tetrahydropyran with (2E)-pentenyl bromide in 86% yield. The pyranyl ether was converted to (3Z)-nonadien-1-ol in 97% yield. The ynol was hydrogenated over Lindlar catalyst to give (3Z,6Z)-nonadien-1-ol in 97% yield. 

Preparation of (3Z,6Z)-nonadien-1-ol

As an α-site counterpart, acetylenic coupling of 2-(2-propynylxloxy)-tetrahydropyran with propyl bromide gave 2-(2-hexynylxloxy)-tetrahydropyran in 79% yield. The pyranyl ether was converted to 2-hexyn-1-ol with 5% (w/w) PTS-methanol in 97% yield. Bromination of the 2-hexyn-1-ol with phosphorus tribromide gave 2-hexynyl bromide in 66% yield. 2-[6Z]-nonadienylxloxy]-tetrahydropyran was prepared by Grignard coupling of 2-(2-propynylxloxy)-tetrahydropyran with 2-hexynylbromide in 73% yield. The pyranyl ether was converted to (2,5)-nonadiyn-1-ol with 5% PTS-methanol in 92% yield. The ynol was hydrogenated over Lindlar catalyst to give (2Z,5Z)-nonadien-1-ol in 95% yield.

Preparation of (2Z,5Z)-nonadien-1-ol

As an ω-site counterpart, acetylenic coupling of 2-(2-propynylxloxy)-tetrahydropyran with propyl bromide gave 2-(2-hexynylxloxy)-tetrahydropyran in 79% yield. The pyranyl ether was converted to 2-hexyn-1-ol with 5% (w/w) PTS-methanol in 91% yield. Bromination of the 2-hexyn-1-ol with phosphorus tribromide gave 2-hexynyl bromide in 66% yield. 2-[2,5]-nonadienyloxy]-tetrahydropyran was prepared by Grignard coupling of 2-(2-propynylxloxy)-tetrahydropyran with 2-hexynylbromide in 73% yield. The pyranyl ether was converted to (2,5)-nonadiyn-1-ol with 5% PTS-methanol in 92% yield. The ynol was hydrogenated over Lindlar catalyst to give (2Z,5Z)-nonadien-1-ol in 95% yield.

Preparation of (4Z,7Z)-nonadien-1-ol

As an ω-site counterpart, 2-(4-pentyloxy)-tetrahydropyran was obtained in 44% yield by chlorination of tetrahydrofurlyl alcohol with thionyl chloride in pyridine, followed by cleavage of tetrahydrofurlyl chloride with sodium amide in liquid ammonia and subsequent protection (4-pentyn-1-ol) with 3,4-dihydro-2H-pyran. On the other hand, as an ω-site counterpart, 2-(2-propynylxloxy)-tetrahydropyran was converted to its lithium salt with n-butyllithium in tetrahydrofuran (THF) and coupled with methyl iodide in hexamethylphosphoric triamide (HMPA) to give 2-(2-butyloxy)-tetrahydropyran in 80% yield.
tetrahydropyran in 57% yield. The pyranyl ether was converted to 2-butyln-1-ol with 5% (w/w) PTS-methanol in 98% yield. Bromination of the 2-hexyn-1-ol with phosphorous tribromide gave 2-butylnyl bromide in 78% yield. 2-[(4,7)-nona-diynyl-oxy]-tetrahydropyran was prepared by Grignard coupling of 2-(4-pentylnoxy)-tetrahydropyran with 2-butylnyl bromide in 63% yield. The pyranyl ether was converted to (4,7)-nonadiyn-1-ol with 5% PTS-methanol in 90% yield. The ynol was hydrogenated over Lindlar catalyst to give (4Z,7Z)-nonadien-1-ol in 97% yield (Lindlar, \textit{et al.}, 1966).

(4Z,7Z)-nonadien-1-ol: b.p. 61.0–65.0 °C/0.8 mmHg; purity 96.9%; IR (film) cm⁻¹: 3352 (O−H), 3035 (C=CH−H), 2945, 2875 (C−H), 1660 (C=−C), 1054 (C−H), 695 (Z, CH=CH);¹³C NMR (CDCl₃/TMS): δ = 12.7, 23.6, 25.3, 32.6, 62.4, 124.1, 128.7, 129.2 ppm;¹H NMR (CDCl₃/TMS): δ = 1.76–1.62 (m, 6H), 2.78–2.12 (m, 2H), 2.80 (t, 2H, J = 6.0), 3.65 (t, 2H, J = 6.4), 5.46–5.53 ppm (m, 4H).

\textit{Purification of n-nonadien-1-ols}

A C₉-unsaturated alcohol (10.0 g, 70.4 mmol) synthesized as above was added into a solution of 3,5-dinitrobenzoyl chloride (17.8 g, 77.4 mmol) in benzene (100 ml). Pyridine (6.1 ml) was added into the mixture and stirred at room temp. The reaction mixture was extracted with ether. The extract was washed with sat. NaHCO₃ soln. and brine, dried over Na₂SO₄ (anhdyrous), and evaporated \textit{in vacuo} to give a crude 3,5-dinitrobenzoate. It was repeatedly recrystallized from ethanol to give pure 3,5-dinitrobenzoate derivatives in 89–99% yield.

The purified 3,5-dinitrobenzoate derivative (4.0 g, 11.9 mmol) was added into 10% NaOH soln. (150 ml) and then stirred at room temp. The mixture was extracted with ether and washed with brine. The extract was dried over Na₂SO₄ (anhdyrous) and concentrated \textit{in vacuo} to give highly pure \textit{n}-nonadien-1-ols (over 96.9% purity) in 82–92% yield (1.4–1.6 g, 97.5–11.0 mmol).

\textit{Odor characteristics}

\textit{Sensory evaluation}

Paper strips dipped in 1% triethyl citrate solutions of the synthesized alcohols were sniffed by three trained flavorists. They were asked to describe the sensory characteristics using eight sensory descriptive terms: leaf or grassy green an image of grasses, stems, and leaves; vegetable-like an image of vegetable, i.e., tomatoes, green peppers, cabbages etc.; fruity an image of fruits, i.e. apples, berries, pears etc.; sweet degree of sweetness; fresh degree of freshness; spicy an image of pepper, nutmeg, cinnamon etc.; oily-fatty, waxy, rancid; herbal an image reminiscent of bitterness of crude drugs. Score sheets with four-point scale ranging from threshold to very intense: i.e. 0 = threshold, 1 = very weak, 2 = intense, 3 = very intense, were used for the evaluation of the test samples. The average scores of three panellers were adopted as the odor-strength of the sensory attributes.

\textit{Statistical analysis}

We applied the average scores from sensory evaluation to principal component analysis using \textquoteleft ANALYST\textquoteright (analyzer programs for statistical data, Fujitsu, Tokyo, Japan) on a FACOM M-308 computer (Fujitsu, Tokyo, Japan).

The data from sensory evaluation were statistically analyzed using principal component analysis, one of the multivariate analyses, to characterize the odor profiles of the tested nine compounds using the eight explanatory variables.

\textit{Results and Discussion}

In this study, nine isomers of \textit{n}-nonadien-1-ols were synthesized in odor to analyze their odor-structure relationship. Because there could be as much as 52 isomers possible, we selected these nine methylene-interrupted diene isomers such as analogous to naturally occurring isomers, i.e., (2E,6Z)-nonadien-1-ol (cucumber alcohol) and (3Z,6Z)-nonadien-1-ol.

Odor specificity analysis: odor characteristic of each \textit{n}-nonadien-1-ol was described by using the eight sensory descriptive terms of leaf or grassy, vegetable-like, fruity, sweet, fresh, spicy, oily and herbal. The odor strength in each descriptive term was scored as 0 threshold; 1 very weak; 2 intense; 3 very intense. The average of three trained flavorists was plotted on the radar chart (Figs. 1 and 2). This analysis showed that, if the geometry of double bond was different, the odor characteristic was quite different. The position of each double
Fig. 1. Odor profiles of 6-nonenyl (1-(2,6E)-, (2E,6Z)-, (2Z,6E)- and (2Z,6Z)-nonadecan-1-ol) and 6-nonenyl-1-ol. Eight sensory descriptive terms were used for the sensory characteristics: leaf or grassy green an image of grasses, stems, and leaves; vegetable-like an image of vegetable, i.e., tomatoes, green pepper, cabbages etc.; fruity an image of fruits, i.e., apples, berries, pears etc.; sweet degree of sweetness; fresh degree of freshness; spicy an image of pepper, nutmeg, cinnamon etc.; oily-fatty, waxy, rancid; herbal an image reminiscent of bitterness of crude drugs. Score sheets with four-point scale ranging from threshold to very intense: i.e. 0 = threshold, 1 = very weak, 2 = intense, 3 = very intense, were used for the evaluation of the test samples. The average scores of three panellers were adopted as the odor-strength of the sensory attributes.
bond also have quite effects on its odor. Vegetable-like factor was strongest with (2E,6Z)-nonadien-1-ol. The vegetable-like factor was weakened, in the order of (2Z,6Z)-, (2E,6E)- to (2Z,6E)-nonadien-1-ols. Among the isomers analyzed (3Z,6Z)-nonen-1-ol showed pleasant flavor having high fruity, sweet and fresh factors, and (2E,6Z)-nonen-1-ol showed pleasant flavor having high vegetable-like factor. It should be noted that these are both the naturally occurring compounds.
Principal Component Analysis of C₉- Unsaturated Alcohols

Fig. 3. The score plots and the vectors of the eigenvalues on the plane of the first principal component vs. the second principal component in n-nonen-1-ols, n-nonanol, and isomers of (2E,6Z)- and (3Z,6Z)-nonadien-1-ols.

Principal analysis: previous result of principal analyses concerning about C₆-monoenols and monoenals, and C₉-monoenols suggested that this analytical system can be properly used for the odor evaluation (Hatanaka et al., 1992; Sakoda et al., 1995). After the analysis, fresh, fruity and sweet factors were found to inversely contribute to PC 1, on the other hand, herbal, vegetable-like and leaf or grassy were found to positively contribute to PC 2. The contribution of PC 1 and PC 2 summed up to nearly 60% (Table). For convenient comparison, all the data previously obtained in our laboratory are simultaneously plotted. As shown in Fig. 3, it was indicated that 5-, 6- and 7-nonen-1-ols, which contain a double bond in w side had a positive value of PC 1, on the other hand, 2-, 3-, and 4-nonen-1-ols which contain a double bond in the α-terminal functional group side did a negative...
Table I. The principal component analyses of the odor of the n-nonen-1-ols, n-nonanol, and isomers of (2E,6Z)- and (3Z,6Z)-nonadien-1-ols.

<table>
<thead>
<tr>
<th>Odor description</th>
<th>PC 1</th>
<th>PC 2</th>
<th>PC 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>-0.674</td>
<td>0.516</td>
<td>0.115</td>
</tr>
<tr>
<td>Fruity</td>
<td>-0.697</td>
<td>0.420</td>
<td>0.364</td>
</tr>
<tr>
<td>Leaf or grassy</td>
<td>0.069</td>
<td>0.636</td>
<td>-0.509</td>
</tr>
<tr>
<td>Herbal</td>
<td>0.459</td>
<td>0.574</td>
<td>0.607</td>
</tr>
<tr>
<td>Oily-fatty</td>
<td>0.778</td>
<td>-0.219</td>
<td>0.202</td>
</tr>
<tr>
<td>Spicy</td>
<td>0.732</td>
<td>0.506</td>
<td>0.236</td>
</tr>
<tr>
<td>Sweet</td>
<td>-0.792</td>
<td>0.025</td>
<td>0.172</td>
</tr>
<tr>
<td>Vegetable-like</td>
<td>0.227</td>
<td>0.678</td>
<td>-0.467</td>
</tr>
<tr>
<td>Eigenvalue</td>
<td>2.978</td>
<td>1.941</td>
<td>1.118</td>
</tr>
<tr>
<td>Proportion</td>
<td>37.2</td>
<td>24.3</td>
<td>14.0</td>
</tr>
<tr>
<td>Cumulative proportion</td>
<td>37.2</td>
<td>61.5</td>
<td>75.5</td>
</tr>
</tbody>
</table>

PC: Principal component.

one. In the four geometrical isomers of 2,6-nonadien-1-ols, only (2E,6Z)-nonadien-1-ol located at especially high point of both PC 1 and PC 2. Both the components gradually decreased from (2Z,6Z)-, (2E,6E)- to (2Z,6E)-nonadien-1-ols. The spatial relationship between (2Z) and (2E) isomers in the 2,6-dienols highly correlated with that of (2Z)- and (2E)-nnonens. On the other hand, in the four geometrical isomers of (3E)-nonadien-1-ols, only (3Z,6Z)-nonadien-1-ol located apart at negative site of PC 1, while the others located at the positive site. PC 1 increased as number of (E)-geometry increased in the 3,6-nonadien-1-ols. Again, the spatial relationship between (3Z,6E) and (3E,6E) has high correlation with that of corresponding monoene isomers, i.e., (3E)- and (3Z)-nonen-1-ols. These analyses showed that, among these n-nonen-1-ols, (2E,6Z)- and (3Z,6Z)-nonadien-1-ols, which have a Z-double bond at w3 position had specific odor-character of both the first and the second principal components. This was also observed with (3Z)-hexen-1-ol and (6Z)-nonen-1-ol, which contain an w3Z double bond. From those results, that an w3Z-moiety in volatile alcohols has specific interaction with a sensory system of human was suggested intensely. This strategy was found to be interested in evaluating chemical structure-odor correlation.

Martin Y. C. (1978), Quantitative drug design; Marcel Dekker; New York.