Natural Abundance ^2H Nuclear Magnetic Resonance Study of the Origin of 2-Phenylethanol and 2-Phenylethyl Acetate

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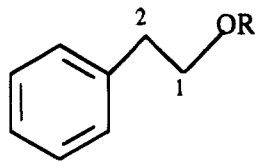
The site-specific natural abundance deuterium distribution of 2-phenylethanol (**1**) and 2-phenylethyl acetate (**2**) obtained through a variety of methods has been determined by ^2H NMR spectroscopy. This technique provided a means of distinguishing between "natural" materials isolated from natural sources or obtained by biodegradation of L-phenylalanine and other products of petrochemical origin or obtained from natural L-phenylalanine through nonenzymic controlled chemical processes.

Keywords: *SNIF-NMR; aromas; 2-phenylethanol; 2-phenylethyl acetate; authentication*

Recently, there has been legislative discrimination (*U.S. Code Fed. Regul.*, 1985) between chemically identical food aroma constituents of synthetic origin and those derived from natural sources. The latter products, labeled "natural", are receiving consumer preferences, and, therefore, it has become desirable to obtain substantial quantities of these valuable materials either by extraction from botanical sources or by biotransformations of abundant natural precursors (Stofberg, 1986). However, a major problem faced in this area is the occurrence of adulterations of these expensive natural substances with readily available "nature-identical" products of petrochemical origin. Moreover, in the case of the products available by enzymic transformation(s) of natural precursors, one should guarantee against the fraudulent use in the process of less expensive "non-natural" synthetic methods.

Among the several criteria proposed for the determination of the "naturalness" of the aroma components (Fuganti et al., 1993), the determination of the site-specific deuterium distribution data resulted among the most effective (Martin et al., 1982, 1983, 1986; Grant et al., 1982; Toulemonde and Horman, 1983; Hagedorn, 1992; Fronza et al., 1993). In the present paper we present a natural abundance ^2H nuclear magnetic resonance study of the origin of 2-phenylethanol (**1**) and



1 R = H
2 R = $COCH_3$

2-phenylethyl acetate (**2**) performed by comparison of synthetic products with materials obtained, respectively, by (i) extraction from botanical sources, (ii) biogeneration from natural L-phenylalanine, and (iii) transformation of the latter natural precursor through "non-natural" synthetic methods.

The presence in plants of products **1** and **2**, possessing rose-like/honey flavor, has been recognized nearly a century ago (von Soden and Rojahn, 1900; Brooks, 1911; Hall and Wilson, 1925), and, similarly, the derivation of their C_6-C_2 framework from L-phenylalanine by the action of fermenting yeasts has been reported by Ehrlich in pioneering work on the origin of the components of fusel oils (Ehrlich, 1907). 2-Phenylethanol (**1**) occurs in alcoholic fermented foods in amounts of 10–100 ppm (Kieser et al., 1964), and it is commercially available in natural form. Recently, the production of ca. 1.7 g/L of **1** and **2** at 24 h of incubation in different microorganisms fed with L-phenylalanine as the sole nitrogen source has been reported (Albertazzi et al., 1994). The high yields thus observed could possibly render the yeast biotransformation of natural L-phenylalanine as a means to access natural **1** and **2** and an alternative to the extraction from natural sources. Accordingly, we decided to carry out a SNIF-NMR study on products **1** and **2** designed to unequivocally identify their origin, and we report now the results obtained.

EXPERIMENTAL PROCEDURES

Deuterium NMR data (46.076 MHz) were recorded at 302 K on a Bruker AC300 spectrometer equipped with a process controller, a 10 mm selective deuterium probehead, and a ^{19}F lock channel, under broad-band proton decoupling conditions.

Phenylethanol samples were prepared by carefully weighing pure (>97% GC) phenylethanol (about 3 g), hexafluorobenzene for ^{19}F lock (150 mg, Merck), and acetonitrile as internal (D/H) standard (600 mg, Fluka). Phenylethyl acetate samples were prepared by carefully weighing pure (>97% GC) phenylethyl acetate (about 3 g), hexafluorobenzene for ^{19}F lock (150 mg, Merck), and 1,4-dioxane as internal (D/H) standard (600 mg, Fluka). Acetonitrile and dioxane were previously tested by isotope ratio mass spectrometry (IRMS) and showed averaged (D/H) values of 113.6 and 150.5 ppm [standard mean ocean water (SMOW)], respectively.

The NMR measurement of samples composed of acetonitrile/official TMU or dioxane/official TMU [tetramethylurea, Community Bureau of References, BCR EC010, (D/H) = 136.67 ppm] gave (D/H) values consistent with the IRMS ones. Ten spectra were run for each sample, collecting 400 scans and using the following parameters: 6.8 s acquisition time, 0.05 s relaxation delay, 1200 Hz spectral width, 16K memory size,

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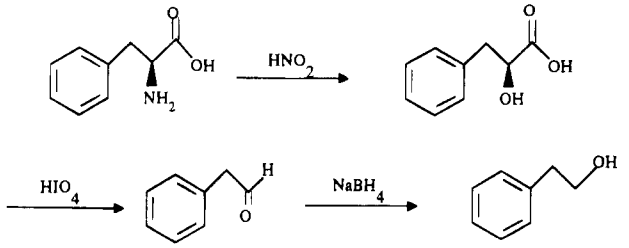
Scheme 1



15 μs (90°) pulse length. Each FID was Fourier transformed with no zero filling (0.15 Hz/point digital resolution) and line broadening of 2 Hz, manually phased, and integrated. S/N was >120 (phenyl peak).

Molar fractions f_i were calculated from the integrated areas

$$f_i = S_i/\sum_i S_i \quad (1)$$

where S_i is the area of the ith peak.

Internal isotopic ratios are

$$R_{ij} = n_i S_i/S_j \quad (2)$$

The absolute values of the site-specific (D/H) ratios were calculated according to the formula (Martin et al., 1985)

$$(D/H)_i = n_{WS} g_{WS} (MW_L) S_i (D/H)_{WS} / n_i g_L (MW_{WS}) S_{WS} P_L \quad (3)$$

where WS stands for the working standard (dioxane or acetonitrile) with a known isotope ratio $(D/H)_{WS}$ and L for the product under examination; n_{WS} and n_i are the number of equivalent hydrogens of dioxane or acetonitrile and of the ith peak; g_{WS} and g_L are the weights of the standard and the sample; MW_L and MW_{WS} are the corresponding molecular weights; S_i and S_{WS} are the areas of the ith peak and of the standard, respectively; P_L is the purity of the sample. $(D/H)_{WS}$ is the working standard isotope ratio as determined by isotope ratio mass spectrometry on the SMOW scale (Gonfiantini, 1978).

Samples 1–7 of 2-phenylethanol present the following origin. The products 1 and 2 are synthetic, commercially available materials obtained from BBE and Adrian, respectively. Samples 3 and 4 arise from synthetic phenylacetaldehyde (1.6:0.4 mixture with methanol, Givaudan) reduced with fermenting bakers' yeast and $NaBH_4$, respectively. To this end, sample 3 was prepared upon slow addition of 25 mL of the above phenylacetaldehyde/methanol mixture to a stirred suspension of 500 g of bakers' yeast in 3 L of tap water containing 100 g of D-glucose. After 16 h at 28–30 °C, to the fermentation mixture are added Celite, 500 g, and 1 L of ethyl acetate. The resulting emulsion was broken by filtration under vacuum through a thick Celite pad using a large Büchner funnel. The organic phase that separated was evaporated and the residue distilled under vacuum to provide sample 3 in ca. 50% yield.

Sample 4 was prepared upon $NaBH_4$ reduction of the phenylacetaldehyde/methanol mixture (8 g of hydride for 50 mL of substrate in 200 mL of ethanol at 10 °C). Once the reduction was complete, the reaction mixture was diluted with ice–water and extracted twice with CH_2Cl_2 (300 mL). The residue obtained upon evaporation of the washed and dried organic phase was distilled under vacuum to afford the above-mentioned specimen. Samples 5 and 6 are commercial samples sold as natural 2-phenylethanol, whose origin is not specified, provided by San Giorgio Flavors and Daniel, respectively.

Sample 7 has been obtained through the sequence of Scheme 1 from natural L-phenylalanine provided by Rindex. To this end, L-α-hydroxyphenyllactic acid was prepared from L-phenylalanine exactly as reported (Winitz et al., 1956). The crystalline hydroxy acid, 12 g, in 250 mL of THF was treated with 1.05 mol equiv of periodic acid under stirring at room temperature. At the end of the reaction the precipitate was removed by filtration and the solution, diluted with an equal volume of ethanol, was treated with 4 g of $NaBH_4$. After 2 h, the reaction mixture was brought to small volume under vacuum and the residue was partitioned between equal volumes of water and CH_2Cl_2 (150 mL). The residue obtained upon evaporation of the dried organic phase was distilled under vacuum to provide the required 2-phenylethanol, possessing the natural skeleton, but prepared through unnatural procedures in 45% overall yield.

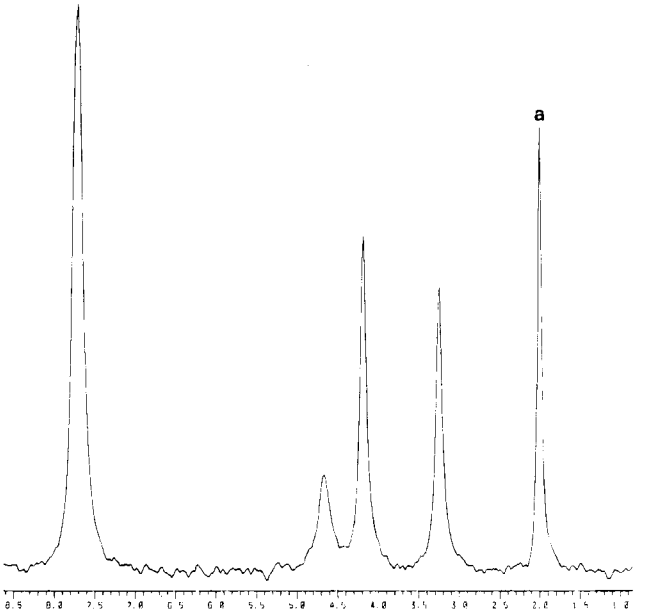


Figure 1. Natural abundance ^2H NMR spectrum of 2-phenylethanol (sample 1): (a) signal of acetonitrile used as internal standard.

2-Phenylethyl acetate samples 8–11 were obtained from L-phenylalanine in *Kloeckera saturnus* CBS 5761 exactly as recently reported (Albertazzi et al., 1994). Sample 12 is a synthetic commercial sample from Aldrich, whereas sample 13 was obtained upon acetylation (Ac_2O/pyridine) of synthetic 2-phenylethanol from Fluka.

RESULTS AND DISCUSSION

The assignment of the signals appearing in the ^2H NMR spectra of 2-phenylethanol (**1**) (Figure 1) and of 2-phenylethyl acetate (**2**) (Figure 2) is reported in Table 1. The analyzed samples of **1** included the following: (i) synthetic commercial samples from different suppliers (samples 1 and 2); (ii) the product obtained from synthetic phenylacetaldehyde upon bakers' yeast reduction (sample 3); (iii) the material obtained from the same aldehyde upon $NaBH_4$ reduction (sample 4); (iv) two specimens of commercial natural 2-phenylethanol (samples 5 and 6); and (v) 2-phenylethanol prepared from natural L-phenylalanine through the chemical transformations indicated in Scheme 1 (sample 7). The analyzed samples of 2-phenylethyl acetate (**2**) were the following: (i) four specimens of ester obtained in *K. saturnus* CBS 5761 from natural L-phenylalanine (the amino acid for samples 8 and 9 was from Rindex; those for samples 10 and 11 were from Fluka and from a nonidentified producer, obtained through a dealer) and (ii) a commercial sample from Aldrich (sample 12) and a material obtained from synthetic 2-phenylethanol (Fluka) esterified upon acetylation with Ac_2O/pyridine (sample 13).

The ^2H spectra of 2-phenylethanol and 2-phenylethyl acetate have been divided in four regions defining different groups of isotopomers (Table 1). Accurate integration of the signals allows one to calculate the

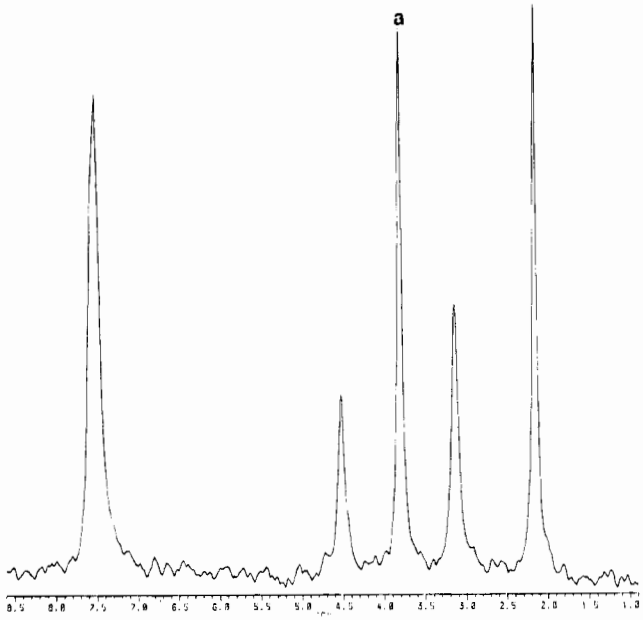


Figure 2. Natural abundance ^2H NMR spectrum of 2-phenylethyl acetate (sample 8): (a) signal of dioxane used as internal standard.

Table 1. Assignment of the Deuterium Spectra of 2-Phenylethanol (1) and 2-Phenylethyl Acetate (2)

	1		2	
group[a]	nucleus	δ^b	nucleus	δ^c
1	−Ph	7.5	−Ph	7.5
2	$-CH_2OH$	4.2	$-CH_2O-$	4.5
3	$-CH_2-$	3.3	$-CH_2-$	3.1
4	−OH	4.7	$-CH_3$	2.1

[a] Numbering of the different groups of nuclei used in Tables 2 and 3 for the isotopic parameters. [b] Chemical shifts referred to the internal acetonitrile signal taken at 2.0 ppm. [c] Chemical shifts referred to the internal dioxane signal taken at 3.8 ppm.

molar fractions f_i of each group and the absolute site-specific isotope ratios $(D/H)_i$. The data are reported in Tables 2 and 3. Since different internal standards have been employed for the calculation of D/H ratios for phenylethanols and phenyl acetates (see Experimental Procedures), these values are only used to compare the deuterium content of a given site among the samples of a single group of compounds.

From the data collected in Table 2 it can be seen that the molar fraction f_i (relative to the deuterium atoms located on the phenyl group) of 2-phenylethanols does not show significant variations throughout the examined samples. On the contrary, the molar fractions f_2 and f_3 show strong changes depending on the origin of the samples. Thus, the natural samples 5 and 6 display the lowest values of the molar fractions f_2 (ca. 0.13) and the highest values of f_3 (ca. 0.22) and can be easily discriminated from all other samples. The synthetic samples 1 and 2 are characterized by a high deuterium content at the hydroxymethylene group (f_2 = ca. 0.20). Sample 3, obtained from the reduction of synthetic phenylacetaldehyde by bakers' yeast, shows a deuterium distribution very similar to that of synthetic samples 1 and 2 from which it cannot be distinguished. On the contrary, the phenylethanol obtained from phenylacetaldehyde by $NaBH_4$ reduction (sample 4) shows a significantly lower deuterium content at the hydroxymethylene group (f_2 = 0.18) with respect to sample 3. Finally, the phenylethanol (sample 7) obtained from natural phenylalanine through nonenzymic controlled reactions shows a rather high value of f_3 (0.205), very near to that measured for the natural samples 5 and 6 but differs from samples 5 and 6 by a higher value of the mole fraction f_2 (0.17). In this instance the f_2 value is quite similar to that of sample 4, obtained from synthetic phenylacetaldehyde upon $NaBH_4$ reduction. In sample 7 one of the hydrogen atoms of the hydroxymethylene group arises, as above, from the natural hydride, whereas the second is the one originally present in L-phenylalanine (Scheme 1). It thus follows that particularly diagnostic for the authentication of the naturalness of phenylethanol samples is the deuterium content at the hydroxymethylene group. Indeed, this value reflects the way of reduction of phenylacetaldehyde, which is invoked as the key intermediate in the degradation of C_6-C_3 phenylpropanoid compounds to C_6-C_2 educts via phenyl pyruvate and decarboxylation (Albertazzi et al., 1994).

The authentication of the origin of the C_6-C_2 moiety by this technique, which works well in the case of 2-phenylethanols, can also be extended to 2-phenylacetates. Six different samples of 2-phenylacetate (**2**) have been analyzed (Table 3). Four of these samples (8−11) are of natural origin, and two (12 and 13) are synthetic. They can be distinguished from the deuterium content of the acetoxymethylene groups which show a lower value of f_2 (ca. 0.11) for the natural with respect to the synthetic samples (ca. 0.17). This behavior of natural 2-phenylethyl acetates parallels that of natural 2-phe-

Table 2. Site-Specific Deuterium Distribution in 2-Phenylethanols (1)

	mole fraction of deuterium[a] and absolute D/H value[a]				internal isotopic ratios[a]			
sample	f_1 $(D/H)_1$	f_2 $(D/H)_2$	f_3 $(D/H)_3$	$(D/H)^b$ m	R_{13}	R_{23}	R_{21}	R_{41}
1	0.548 (13)	0.196 (7)	0.180 (7)		6.09 (360)	2.18 (130)	1.80 (90)	0.69 (70)
	102.5	91.9	84.3	93.6				
2	0.556 (7)	0.210 (8)	0.170 (5)		6.54 (210)	2.46 (140)	1.86 (90)	0.57 (50)
	106.5	100.3	81.6	95.7				
3	0.535 (11)	0.214 (7)	0.177 (7)		6.05 (310)	2.41 (90)	2.00 (100)	0.69 (80)
	105.3	105.3	87.3	98.5				
4	0.544 (9)	0.186 (6)	0.188 (6)		5.80 (190)	1.98 (110)	1.70 (70)	0.76 (80)
	117.0	99.8	101.0	107.6				
5	0.568 (7)	0.138 (4)	0.213 (8)		5.35 (260)	1.30 (90)	1.22 (40)	0.72 (60)
	101.0	61.4	94.5	88.9				
6	0.554 (10)	0.131 (4)	0.226 (7)		4.90 (220)	1.16 (50)	1.18 (40)	0.80 (80)
	113.6	67.1	115.9	102.4				
7	0.535 (9)	0.173 (6)	0.205 (10)		5.24 (310)	1.70 (140)	1.62 (70)	0.82 (70)
	103.5	84.0	99.0	96.8				

[a] The values of the mole fractions (f_i), internal isotopic ratios (R_{ij}), and absolute D/H values are averaged over 10 determinations; the standard deviations × 10^3 are reported in parentheses for f_i and R_{ij}. [b] Mean absolute D/H value.

Table 3. Site-Specific Deuterium Distribution in 2-Phenylethyl Acetates (2)

	mole fraction of deuterium[a] and absolute D/H value[a]				internal isotopic ratios[a]			
sample	f_1 (D/H)$_1$	f_2 (D/H)$_2$	f_3 (D/H)$_3$	(D/H)[b] m	R_{13}	R_{23}	R_{21}	R_{41}
8	0.459 (7)	0.114 (6)	0.167 (9)		5.51 (380)	1.37 (120)	1.24 (70)	4.59 (300)
	140.2	86.9	127.7	127.4				
9	0.450 (11)	0.112 (8)	0.167 (9)		5.42 (360)	1.35 (140)	1.24 (110)	4.83 (370)
	130.9	81.4	121.0	121.1				
10	0.465 (9)	0.105 (7)	0.175(8)		5.33 (330)	1.21 (110)	1.14 (90)	4.83 (450)
	140.1	79.5	131.7	125.5				
11	0.490 (13)	0.099 (7)	0.159 (10)		6.20 (540)	1.25 (130)	1.02 (90)	5.07 (370)
	145.9	73.6	118.0	123.9				
12	0.439 (4)	0.174(4)	0.150 (6)		5.88 (290)	2.33 (150)	1.98 (40)	2.73 (110)
	163.4	161.9	139.0	154.9				
13	0.423 (8)	0.161 (7)	0.156 (6)		5.45 (250)	2.07 (110)	1.90 (110)	3.24 (190)
	149.3	141.8	137.1	146.9				

[a] The values of the mole fractions (f_i), internal isotopic ratios (R_{ij}), and absolute D/H values are averaged over 10 determinations; the standard deviations $\times 10^3$ are reported in parentheses for f_i and R_{ij}. [b] Mean absolute D/H value.

nylethanols which, as reported above, are strongly deuterium depleted at site 2 compared with compounds of synthetic origin.

In Tables 2 and 3 some internal isotopic ratios are also reported for the examined 2-phenylethanols and 2-phenylethyl acetates, which obviously must reflect the variations of the molar fractions discussed above. In fact, natural and synthetic 2-phenylethanols show strong differences of the values of R_{23} (ca. 1.2 and 2.2, respectively) and R_{21} (ca. 1.2 and 1.8, respectively). In some cases such internal isotopic ratios are more useful than the molar ratios to discriminate between samples. For instance, in the case of sample 7 which was synthesized starting from the natural phenylalanine, the value of R_{21} unequivocally indicates that some abiological steps occurred in the process.

Analogously the natural and synthetic 2-phenylethyl acetates show strong differences of the values of R_{23} (ca. 1.3 and 2.2, respectively), R_{21} (ca. 1.1 and 1.9, respectively), and R_{41} (ca. 4.9 and 2.9, respectively), making it a simple matter to differentiate between them. During many attempts to build up a graphical representation for an easy discrimination between the natural or the synthetic origin of samples of 2-phenylethanols and 2-phenylethyl acetates, the best results were obtained by plotting the internal isotope ratios R_{23} against R_{21}; in this plot the natural and synthetic samples appear confined in two well-defined distinct regions (Figure 3).

The absolute isotopic ratios D/H for 2-phenylethanols (Table 2) do not add further information to that extracted from the molar fractions. The natural samples 5 and 6 show a very low proportion of deuterium at the hydroxymethylene group (61 and 67, respectively), while the deuterium portions of synthetic samples 1 and 2 are much higher (92 and 100, respectively). The mean D/H values reported in Table 2 for each sample do not show significant differences, suggesting that the total deuterium content determined via mass spectrometry is not useful in this case to discriminate between samples. Similarly, the absolute deuterium content at the acetoxymethylene group for 2-phenylethyl acetates (Table 3) is higher for the synthetic samples 12 and 13 (162 and 142, respectively) than for the natural samples 8–11 (73–87). However, in this case the mean D/H value is different for natural (ca. 125) and synthetic (ca. 150) samples, thus allowing the discrimination between them via isotopic mass measurements.

Seen together, these results show the utility of natural abundance ^{2}H NMR studies in determining the origin of the C_6-C_2 moiety of the important flavor components **1** and **2**, the isotopic content at the hydroxy- or acetoxymethylene group being particularly diagnostic for the determination of authenticity.

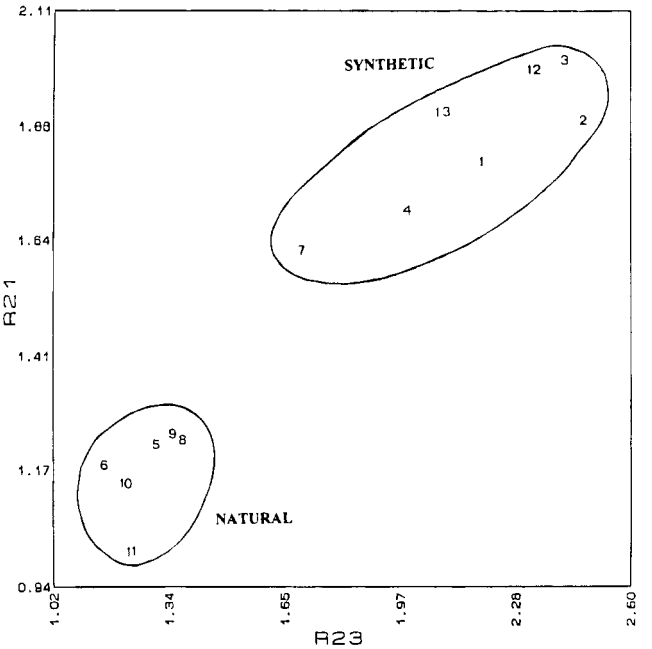


Figure 3. Graphical representation of the internal isotopic ratios R_{21} vs R_{23} showing distinct regions for the natural and synthetic 2-phenylethanols and 2-phenylethyl acetates.

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