Table I. Properties of Ether Alcohols and Phenacyl Ethers

	Ether Alcohol, $ROCH_2CHOHPh$				Phenacyl Ether, $ROCH_2COPh$		
R	Yield of distilled product (corrected for purity), %	Melting point, ° C.	n_D^{60}	Purity[a] (GLC), %	Melting point, ° C.	n_D^{60}	Purity[a] (GLC), %
$C_{12}H_{25}$	29	20[b]	1.4727	98	36.7–37.1	1.4769	98
$C_{14}H_{29}$	33	31.3–31.8	1.4710	99^-	45.7–46.3	1.4755	99^+
$C_{16}H_{33}$	30	39.8–40.5	1.4700	99^-	52.1–52.6	1.4739	99
$C_{18}H_{37}$	29	46.6–47.0	1.4688	99	58.1–59.0	1.4728	99^+

[a] Found and theoretical values for OH, C, and H agreed within 0.2, 0.2, and 0.1%, respectively. [b] Freezing point.

Preparation of Ether Alcohols. The reaction of styrene oxide with fatty alcohols is illustrated in the case of tetradecanol. Tetradecanol (214 grams, 1 mole) and 1.07 grams (0.5%) potassium hydroxide were heated to 130°, and 180 grams (1.50 moles) of styrene oxide was added dropwise with stirring over a period of 3 hours. The stirred mixture was kept at 130° to 140° C. for another 3 hours, cooled, neutralized, washed, and distilled through a 13-inch Vigreux column at 0.05 mm. of pressure. After removing 85 grams of tetradecanol, the ether alcohol fraction distilled at 160–68.5° C. (111 grams, yield 33%). The product was redistilled and crystallized from 5 volumes of acetone at –25° to give 1-phenyl-2-tetradecyloxyethanol, m.p. 31.3–31.8° C. corrected, which showed only one component in the vapor phase chromatogram.

Chromic Acid Oxidation. A solution of 0.55 gram (0.0055 mode) of chromium trioxide in 50 ml. of glacial acetic acid was stirred into a solution of 1.125 grams (0.00336 mole) of the pure ether alcohol from tetradecanol at room temperature. After the color changed to green, water and ethyl ether were added. The ether extract was washed with water, aqueous sodium carbonate, and again with water until the washings were neutral. Evaporation of the ether extract gave the keto ether, yield 88%, recrystallized from acetone to give tetradecyl phenacyl ether, m.p. 45.7–46.3°, purity greater than 99% by GLC. The infrared spectrum showed a strong CO peak, characteristic ether absorption, and the absence of hydroxyl or carboxylic acid groups.

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Synthesis and Nuclear Magnetic Resonance Spectra of *cis*- and *trans*-α,β-Dimethylcinnamyl Alcohols and Their Epoxides

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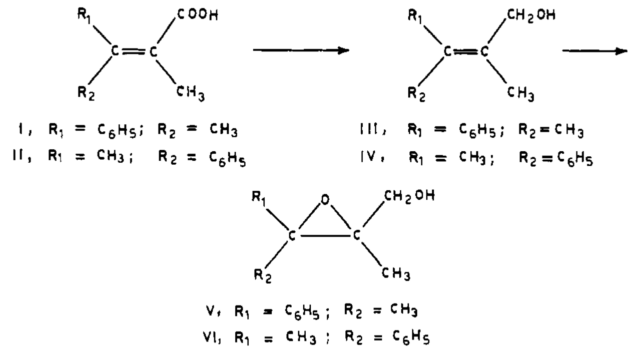
***Cis*- and *trans*-α,β-Dimethylcinnamyl alcohols have been prepared and some inexact data on their preparation and stereochemistry corrected. The alcohols have been transformed with *m*-chloroperoxybenzoic acid into the corresponding epoxides. The NMR spectra of these compounds, which confirm their configurations, are discussed.**

IN CONNECTION with a program for the stereospecific synthesis of compounds of possible pharmacological interest, it was necessary to prepare the title compounds (III, IV, V, and VI). As the literature data about the alcohols are incomplete and in part incorrect, it appeared useful to investigate these compounds in detail.

The alcohols III and IV were obtained by lithium aluminum hydride reduction of *cis*- (I) and *trans*-α,β-dimethylcinnamic acid (II) whose structure and stereochemistry appear to be firmly established in the literature (*1, 2*). The alcohols III and IV were then transformed into *cis*- (V) and *trans*-2-methyl-2,3-epoxy-3-phenylbutanol (VI) with *m*-chloroperoxybenzoic acid.

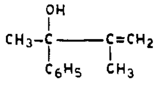


I, $R_1 = C_6H_5$; $R_2 = CH_3$
II, $R_1 = CH_3$; $R_2 = C_6H_5$

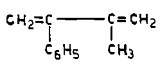
III, $R_1 = C_6H_5$; $R_2 = CH_3$
IV, $R_1 = CH_3$; $R_2 = C_6H_5$

V, $R_1 = C_6H_5$; $R_2 = CH_3$
VI, $R_1 = CH_3$; $R_2 = C_6H_5$

Braude and Evans (*3*) have described the preparation of an α,β-dimethylcinnamyl alcohol by acid-catalyzed rearrangement of 2-phenyl-3-methyl-3-buten-2-ol (VII), 2-methyl-3-phenyl-1,3-butadiene (VIII) being formed concurrently. The configuration of the alcohol was not established, even if a trans configuration (IV) was tentatively proposed on the basis of the ultraviolet spectrum.



VII



VIII

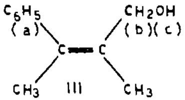
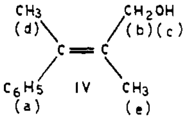
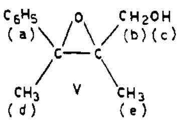
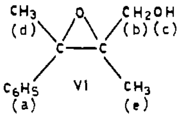
Recently, Canceill, Gabard, and Jacques (*4*) reported the preparation of III through the lithium aluminum hydride reduction of methyl *cis*-α,β-dimethylcinnamate. However, no experimental data were given, as the product was apparently used as an intermediate without isolation and purification.

A reinvestigation of the preparation of Braude and Evans (*3*) has shown that under the exact conditions described by these authors the transformation of VII into IV and VIII is not at all complete, but that a mixture of all three compounds, in which unreacted VII predominates, is formed; they can be separated completely by column chromatography; the α,β-dimethylcinnamyl alcohol which is formed consists of 83% of the cis-isomer III and 17% of the trans-isomer IV. Some of the data for the ultraviolet spectra reported by Braude and Evans (*3*) are different from those observed by the present author, and this may indicate that their compounds were impure.

The two alcohols III and IV have very similar boiling points, refractive indices, and ultraviolet spectra, and show very few differences in their infrared spectra; evidently, in contrast to the supposition by Braude and Evans (*3*), the steric requirements of the methyl and hydroxymethyl groups are not very dissimilar.

The nuclear magnetic resonance spectra of III, IV, V, and VI (Table I), besides showing the complete purity of the products, also confirm their configurations. As for the corresponding acids (2) and esters (1) the α-methyl protons [$CH_3(e)$] of the trans series—i.e., cis to the phenyl—resonate at higher fields than the α-methyl protons of the cis-series. An analogous shift to higher field is shown by the resonance frequency of the CH_2 protons of the hydroxymethyl group [$CH_2(b)$] when it is moved from a trans to a cis position relative to the phenyl group. The $CH_3(e)$ protons in the trans series and the $CH_2(b)$ protons in the cis series are in fact located part of the time directly over the benzene ring, and are therefore subject to increased shielding due to induced ring currents (*5*). Similar effects (*6-8*) have been used for cis-trans structural assignments in compounds sterically similar to these, as for instance the deshielding influence of the carbonyl group on the cis 3-methyl protons in the methyl esters of 3-methyl substituted phenylpentadienoic (*7*) and heptatrienoic (*8*) acids.

Table I. Nuclear Magnetic Resonance Data[a]

	Chemical Shifts, P.P.M.					Coupling Constants, C.P.S.	
Compound	τ_a	τ_b	τ_c	τ_d	τ_e	J_{de}	J_{bd}
	2.92	6.23	8.00	8.07	8.18	1.0	0.7
	2.92	5.83	7.60	8.04	8.39	1.5	0.2–0.3
	2.77[b]	6.83[b]	...	8.41[b]	8.48[b]	...	...
	2.76[b]	6.20[b]	7.90[b]	8.35[b]	8.99[b]	...	...

[a] Spectra were determined on ca. 6% solutions in carbon tetrachloride for III and IV and in deuteriochloroform for V and VI on a Varian DA-60 I spectrometer using tetramethylsilane as an internal standard. Chemical shifts were measured directly from spectra determined at a sweep width of 500 c.p.s. The recorder J values were measured using a sweep width of 100 c.p.s. [b] Singlet.

The signals of two methyl groups [$CH_3(d)$ and $CH_3(e)$] of III and IV appear as quartets with J = 1.0 and 1.5 c.p.s., respectively; the values of these long-range coupling constants are in good agreement with the fact that homoallylic coupling constants lie in the range 0 to 1.6 c.p.s., and with the observation that the magnitude of the transoid homoallylic coupling constant is usually larger by 0.3 to 0.5 c.p.s. than that of the cisoid one for identical substitution on the double bond (*9*). The quartets that have been attributed to the β-methyl groups [$CH_3(d)$] of these compounds (III and IV), particularly in the case of III, consist of broad lines; as has been shown with double resonance experiments, involving the alternative irradiation of $CH_3(d)$ and $CH_2(b)$ protons, this is due to a further long-range coupling existing between $CH_3(d)$ and $CH_2(b)$; also, in this case, the homoallylic coupling constant for the trans isomer (J = 0.2 to 0.3 c.p.s.) is smaller than that of the cis isomer (J = 0.7 c.p.s.).

The attribution of the signals of the methyl protons has been based on the fact that the values of the β-methyl [$CH_3(d)$] resonances remain almost constant in passing from the cis to the trans form: in such a passage the position of the β-methyl [$CH_3(d)$] relative to the phenyl and therefore to the local magnetic field generated by the ring current should not undergo an appreciable change.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were carried out in the microanalytical laboratory of this institute. Ultraviolet spectra were recorded in 95% ethanol on a Beckman DU spectrophotometer. Infrared spectra were taken as neat films or as Nujol mulls on a Perkin-Elmer Infracord Model 137 spectrophotometer. All comparisons between compounds were made on the basis of IR spectra.

***cis*- (I) and *trans*-α,β-Dimethylcinnamic Acid (II)** were prepared according to the procedure of Jackman and Lown (*1*) from ethyl 2-methyl-3-phenyl-3-hydroxybutyrate (*10*); I had m.p. 111-12° C. [lit. (*1*) m.p. 112-13° C.] and II had m.p. 109-10° C. [lit. (*1*) m.p. 109-10° C.]. The cis-acid (I) underwent complete cyclization in concentrated sulfuric acid to 2,3-dimethylindenone, m.p. 78-9° C. [lit. (*11*) m.p. 80° C.].

cis-α,β-Dimethylcinnamyl Alcohol (III). To a stirred suspension of 3.0 grams (0.08 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether cooled at 0° C. was added drop-wise a solution of 12.0 grams (0.068 mole) of I in 300 ml. of anhydrous ether, at such a rate as to keep the temperature below 0° C. After the mixture was stirred for 3 hours at 0° C., it was then allowed to warm slowly to room temperature; after 12 hours the reaction mixture was cooled below 5° C. and hydrolyzed with 30 ml. of water and 150 ml. of 10% sulfuric acid. The ether layer was washed successively with water, 10% sodium carbonate and water, dried over magnesium sulfate, and evaporated to dryness to give 5.4 grams of crude III. From the alkaline washings, evaporated under reduced pressure to a small volume and acidified, 5.2 grams of unchanged acid I was recovered. Distillation yields 4.85 grams of pure III, b.p. 90–1° C./1 mm., n_D^{21} 1.5502, λ_{OH} 2.99 μ (neat); λ_{max} 233 mμ (ε 6850). Anal. calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.41; H, 8.78.

The *p*-nitrobenzoate of III was prepared by heating for 1 hour at 100° C. a solution of 1 mmole of III and 1.1 mmoles of *p*-nitrobenzoyl chloride in 5 ml. of pyridine; it crystallized from ethanol as light yellow plates, m.p. 72–3° C. Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.44; H, 5.56; N, 4.49.

***trans*-α,β-Dimethylcinnamyl Alcohol (IV).** Compound II (12 grams, 0.068 mole), reduced with 3.0 grams (0.08 mole) of lithium aluminum hydride under the conditions used for the reduction of cis isomer III, gave 6.3 grams of crude IV, 4.2 grams of II being recovered unchanged. Distillation of the crude product yielded 5.7 grams of IV, b.p. 88° C./0.9 mm., n_D^{20} 1.5504; λ_{OH} 2.99 μ (neat); λ_{max} 234 mμ (ε 6850). Anal. calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.39; H, 8.75.

The *p*-nitrobenzoate of IV was prepared as described above for the same derivative of III; light yellow blades (from ethanol), m.p. 60–1° C. Anal. calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.46; H, 5.42; N, 4.56.

2-Phenyl-3-methyl-3-buten-2-ol (VII) was prepared by the method of Braude and Evans (*3*) from acetophenone and isopropenil-lithium; b.p. 67–8° C./1 mm., n_D^{27} 1.5288; λ_{OH} 2.9, $\lambda_{=\mathrm{CH_2}}$ 11.0 μ (neat); λ_{max} 247 (ε 230), 252 (250), 257.5 (250), 264 mμ (190); [lit. (*3*) b.p. 58° C./0.1 mm.; n_D^{22} 1.5300; λ_{max} 244 mμ (ε 500, ethanol)]. The author s values seem to be in better accordance with the fact that in general simple monoalkyl benzenes exhibit several maxima of low intensity (ε 10 to 300) between 240 and 280 mμ: similar absorptions are shown, for example, by benzyl alcohol and allylbenzene (*12*). Anal. calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.40; H, 8.71.

Acid-Catalyzed Rearrangement of VII (*3*). A solution of 3.0 grams of VII in 100 ml. of 0.005*M* hydrogen chloride in 60% aqueous acetone was refluxed for 12 hours and then neutralized with potassium carbonate. After evaporation in vacuo at room temperature of the acetone, the product was extracted with ether, the ether layer dried over magnesium sulfate and evaporated to give a residue (2.8 grams), which was chromatographed over 130 grams of neutral Al_2O_3 (act. II): 1300 ml. of hexane, 4000 ml. of 9 to 1 hexane-benzene, 1600 ml. of 4 to 1 hexane-benzene, 1500 ml. of 7 to 3 hexane-benzene, 1500 ml. of 3 to 2 hexane-benzene, 700 ml. of benzene and 500 ml. of ether eluted in succession 0.18 grams of VIII, 1.40 grams of unchanged VII, and 0.80 gram of III containing 17% of IV. The composition of this mixture was estimated from the NMR spectrum, by integrating the areas of the peaks at 6.23 τ for III and at 5.83 τ for IV.

2-Methyl-3-phenyl-1,3-butadiene (VIII). A solution of 3.0 grams of VII in 100 ml. of 0.18*M* hydrogen chloride in 60% aqueous acetone was refluxed for 45 hours and then treated as described above. Distillation of the residue (2.5 grams) gave 2.0 grams of VIII, b.p. 93–4° C./20 mm., n_D^{29} 1.5356; $\lambda_{=\mathrm{CH_2}}$ 11.1 μ (neat); λ_{max} 217 mμ (ε 12,100) [lit. (*3*) b.p. 39–41° C./0.1 mm., n_D^{22} 1.5380; λ_{max} 223 mμ (ε 10,000, ethanol)]. Anal. calcd. for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.53; H, 8.42.

***cis*-2-Methyl-2,3-epoxy-3-phenylbutanol (V).** A solution of 2.35 grams (14.5 mmole) of III in 300 ml. of chloroform was cooled at 0° C. and treated with a solution of 3.70 grams (16 mmole) of 75% *m*-chloroperoxybenzoic acid in 70 ml. of chloroform. After 1 hour at 0° C. and 20 hours at room temperature the solution was washed with 10% sodium carbonate and water, and evaporated in vacuo to give 1.90 grams of V, which crystallized from petroleum ether (b.p. 30° to 50° C.) in blades, m.p. 44–5° C.; λ_{OH} 2.87 μ (Nujol). Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13 H, 7.92. Found: C, 74.01; H, 7.86.

***trans*-2-Methyl-2,3-epoxy-3-phenylbutanol (VI).** A solution of 1.30 grams (8 mmoles) of IV in 20 ml. of chloroform treated, as described above for the preparation of V, with a solution of 2.0 grams (8.8 mmoles) of 75% *m*-chloroperoxybenzoic acid in 40 ml. of chloroform, produced 1.15 grams of crude VI, which was distilled to give 0.70 grams of the pure product, b.p. 85–6° C./0.1 mm., n_D^{22} 1.5224; λ_{OH} 2.93 μ (neat). Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.05; H, 7.87.

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