The Acid-Catalyzed Isomerization of α- and *cis*- and *trans*-γ-Methylallyl Alcohols

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Abstract: The rates of the acid-catalyzed isomerization (k_r) of *cis*- and *trans*-crotyl and α-methylallyl alcohols and of the acid-catalyzed loss of optical activity (k_α) of α-methylallyl alcohol in aqueous dioxane have been determined. The observed excess racemization ($k_\alpha/k_r = 5.18$) was interpreted in terms of a carbonium ion mechanism. Evidence has been obtained in the present work that geometrical configuration of the *cis*- and *trans*-butenyl cations was preserved. Furthermore, the geometrically isomerized crotyl alcohols appear to be present only after the presence of α-methylallyl alcohol is detected. The equilibrium constants for the interconversion of the three butenyl alcohols were also measured, and the identification and characterization of five isomeric (*cis* and *trans*) butenyl ethers, including the *meso* and *dl* diastereoisomers of di-α-methylallyl ether, have been reported.

Young and co-workers[1] in 1939 first suggested the possibility that crotyl- and α-methylallyl alcohols could be isomerized in the presence of acid to an equilibrium mixture. The results of a brief investigation demonstrated that allylic isomerization *via* a proposed butenyl carbonium ion had indeed occurred but the equilibration of the butenyl alcohols under homogeneous reaction conditions was never achieved owing to the concurrent side reaction of ether formation.

In recent years, evidence has been accumulated to support the involvement of carbonium ion intermediates in the isomerization reactions of allylic alcohols.[2] Furthermore, where the possibility of geometric isomerism (*cis* and *trans*) exists for allylic cations,[3-5] evidence has been obtained that their respective geometric configurations were preserved during the course of the reaction. The configurational stability of allylic radicals[6] and carbanions[7] has also been recently demonstrated.

In the present investigation, the acid-catalyzed isomerization of α- and *cis*- and *trans*-γ-methylallyl alcohols has been studied under homogeneous reaction conditions by means of vapor phase chromatography. The results of this study are reported and discussed in terms of a carbonium ion mechanism in the present paper.

Results

Allylic Materials. Preparation of the various allylic compounds necessary in the present study are described in the Experimental Section. The methods of the preparation were selected to guarantee structural and geometric purity of the allylic compounds. α-Methylallyl alcohol and *trans*-crotyl alcohol were prepared by lithium aluminum hydride reduction of methyl vinyl ketone and *trans*-crotonaldehyde, respectively, in ether. *cis*-Crotyl alcohol resulted from the semihydrogenation of 2-butyn-1-ol. Purification of the butenyl alcohols was accomplished by preparative vapor phase chromatography (vpc). Analysis by analytical vpc indicated that α-methylallyl alcohol contained no detectable amount of its allylic isomeric alcohols. Similar analyses of *trans*-crotyl alcohol showed no *cis*-crotyl alcohol or α-methylallyl alcohol to be present, and of *cis*-crotyl alcohol revealed that it was not contaminated with α-methylallyl alcohol but contained 0.37% *trans*-crotyl alcohol. The limits of detection by vpc analysis were 0.02% of α-methylallyl alcohol in crotyl alcohol and 0.05% *cis*- or *trans*-crotyl alcohol in α-methylallyl alcohol. Identification and stereochemistry of the butenyl alcohols were established by their infrared and proton nuclear magnetic resonance spectra (nmr).

In the course of the present investigation it became necessary to prepare and characterize the corresponding isomeric (*cis* and *trans*) ethers of the butenyl alcohols. The isomeric dicrotyl ethers (*trans,trans*, *cis,trans*, and *cis,cis*) were prepared by treatment of the sodium alkoxide of crotyl alcohols (*cis* or *trans*) with the respective *cis*- or *trans*-crotyl chlorides in the absence of solvent. Purification of each geometrically isomeric ether was by preparative vpc, while identification of these ethers was made by their infrared and nmr spectra. The method which was employed for the preparation of *cis*- and *trans*-crotyl α-methylallyl ethers and di-α-methylallyl ether was the acid-catalyzed etherification of *trans*-crotyl alcohol. Purification and preparation of these ethers were accomplished in the same manner as described for the dicrotyl ethers.

Analyses by vpc of a specimen of di-α-methylallyl ether indicated that it was a mixture of two components. Separation by preparative vpc and identification of both of the components by their respective infrared and nmr spectra indicated they were most likely *meso* and *dl* isomers of di-α-methylallyl ether. Recently, Traynelis and co-workers[8] have reported the formation of diastereomeric ethers (*meso* and *dl*) of 1-phenyl-1-propanol in varying amounts of dimethyl sulfoxide.

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(2) (a) C. A. Bunton, Y. Pocker, and H. Dahn, *Chem. Ind.* (London), 1516 (1958); (b) H. L. Goering, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **21**, 109 (1956); (c) H. L. Goering and E. F. Silversmith, *J. Am. Chem. Soc.*, **79**, 348 (1957); (d) H. L. Goering and R. E. Dilgren, *ibid.*, **82**, 5744 (1960); (e) H. L. Goering and R. R. Josephson, *ibid.*, **83**, 2585 (1961); (f) H. L. Goering and R. R. Josephson, *ibid.*, **84**, 2779 (1962); (g) H. Kwart and J. Herbig, *ibid.*, **85**, 226 (1963).
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(6) C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).
(7) D. H. Hunter and D. J. Cram, *ibid.*, **86**, 5478 (1964).
(8) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicente, *J. Org. Chem.*, **29**, 123 (1964).

Table I. Isomerization[a] of the Butenyl Alcohols in 2.90 M H_2SO_4–Aqueous Dioxane (70:30, v/v) at 50.00°[b]

(I) *trans*-crotyl alcohol $\underset{3.52}{\overset{9.44}{\rightleftharpoons}}$ α-methylallyl alcohol (II)

$\overset{0.20}{\swarrow\!\!\!\nearrow}$ 3.29

(III) *cis*-crotyl alcohol

Substrate	Concn, M	$10k$,[c] sec^{-1}	$10\,k_\alpha$,[d] sec^{-1}	k_α/k
I	0.105	9.44 ± 0.25		
II	0.104	3.72 ± 0.06	19.21 ± 0.5	5.18
III	0.105	3.29 ± 0.29		

[a] Points were taken over the first 12% reaction. [b] ±0.02°. [c] k is the pseudo-integrated first-order rate constant for the rate of disappearance of alcohol. [d] k_α is the integrated first-order polarimetric constant for the loss of optical activity of (+)-α-methylallyl alcohol.

putor. This value recorded in Table I was found to be 5.18 (k_α/k_r) times as fast as the first-order rate constant for the isomerization of α-methylallyl alcohol. In this experiment the loss of optical activity was complete and the calculated polarimetric constants (k_α) were steady over the range the reaction was followed (75–80% completion).

Starting with any of the three butenyl alcohols, a mixture of 66.28 ± 0.13% α-methylallyl alcohol, 24.46 ± 0.12% *trans*-crotyl alcohol, 3.73 ± 0.013% *cis*-crotyl alcohol, and 5.36 ± 0.11% ethers was obtained as reported in Table II. Other workers[9] have reported the equilibration of crotyl alcohol (30%) and α-methylallyl alcohol (70%) in 1% aqueous sulfuric acid at 95° for 5 hr, and obtained similar results in favor of the secondary alcohol. A comparison of the equilib-

Table II. Product Equilibrium Composition from the Isomerization of Each Butenyl Alcohol in 2.90 M H_2SO_4–Aqueous Dioxane (70:30, v/v) at 50.0°[a]

	Mole per cent product composition[b]						Equilibrium constant	
Reactant	*trans*	*cis*	SOH	SOS	SOP	POP	$K\frac{sec\text{-OH}}{cis}$	$K\frac{sec\text{-OH}}{trans}$
SOH	24.51 ± 0.16	3.71 ± 0.03	66.11 ± 0.14	1.03 ± 0.06	3.19 ± 0.12	1.36 ± 0.12	2.69 ± 0.06	17.77 ± 0.19
cis	24.38 ± 0.38	3.75 ± 0.013	66.26 ± 0.30	0.93 ± 0.11	3.06 ± 0.13	1.70 ± 0.13	2.73 ± 0.016	17.64 ± 0.07
trans	24.60 ± 0.13	3.73 ± 0.026	66.28 ± 0.13	1.04 ± 0.06	2.66 ± 0.05	1.46 ± 0.05	2.70 ± 0.013	17.80 ± 0.12
	Average product composition						Average equilibrium constant	
	24.46 ± 0.12	3.73 ± 0.013	66.28 ± 0.13	1.00 ± 0.046	2.87 ± 0.20	1.51 ± 0.13	2.70 ± 0.013	17.74 ± 0.06

[a] Abbreviations: *trans* = *trans*-crotyl alcohol, *cis* = *cis*-crotyl alcohol, S = secondary (α-methylallyl), and P = Primary (crotyl). [b] Ether mole per cent values are expressed in terms of alcohol equivalent mole per cent. Mole per cent product compositions measured at 50 and 76 hr of reaction.

Isomerization. The isomerizations of *cis*- and *trans*-crotyl alcohols and of α-methylallyl alcohol were studied in 70% aqueous dioxane (2.90 M) in sulfuric acid at 50.00°. The resulting mixtures which contained both primary (*cis* and *trans*) and secondary alcohols and ethers were analyzed by vpc as described in the Experimental Section. However, owing to the poor chromatographic peak resolution of the *cis* and *trans* isomers of each individual ether, quantitative measurement was limited to primary–primary, secondary–primary, and secondary–secondary isomeric ether identification.

Good first-order rate constants for the disappearance of each butenyl alcohol were calculated over the first 12% reaction. The initial ether formation was negligible during this time period. A steady material loss was observed throughout each kinetic run (7% at 12% reaction). After 20 half-lives of reaction (equilibrium) 40% of the starting material was unaccounted for, and the reaction solution was dark brown in color. Control experiments showed that solvent decomposition had not occurred. Therefore, the per cent composition of all points was calculated from the material balance found to be present. The results of the pertinent kinetic experiments are summarized in Table I.

Optically active (+)-α-methylallyl alcohol (0.092 M) was also subjected to the reaction conditions. The polarimetric rate for the acid-catalyzed loss of optical activity was followed on a Bendex automatic polarimeter at 50.0°. The pseudo-first-order rate constant and its average deviation were obtained by the least-squares method (50 points) using the IBM 7090 computer. This value recorded in Table I was found to be 5.18 (k_α/k_r) times as fast as the first-order rate constant for the isomerization of α-methylallyl alcohol. In this experiment the loss of optical activity was complete and the calculated polarimetric constants (k_α) were steady over the range the reaction was followed (75–80% completion).

rium constants $K\left(\frac{sec\text{-OH}}{trans}\right)$ and $K\left(\frac{sec\text{-OH}}{cis}\right)$ obtained by vpc with those calculated from the kinetic measurements gives an agreement to within 0.75% for the ratio of α-methylallyl alcohol/*trans*-crotyl alcohol and 12.7% for the equilibrium ratio of α-methylallyl alcohol/*cis*-crotyl alcohol.

Careful examination of the initial stages of the acid-catalyzed isomerizations of *cis*- and *trans*-crotyl alcohols indicates the slow development of the geometrically isomerized crotyl alcohol in the product mixture. Furthermore, the geometrically isomerized crotyl alcohols appear to be present only after the presence of α-methylallyl alcohol is detected. However, control experiments show that the limits of detection of either *cis*- or *trans*-crotyl alcohol were 0.05%. Tables III, IV, and V record the calculated and observed values for *cis*- and *trans*-crotyl alcohol present in the reaction mixture starting initially from either *trans*- or *cis*-crotyl alcohol, respectively. These calculated values were obtained assuming all *cis*–*trans* isomerization proceeds through covalent α-methylallyl alcohol. The method of calculation is given in the Experimental Section. The agreement between the observed and calculated values is within the experimental error (0.6% absolute).

Various control experiments were carried out to assist the interpretation of the significance of the results. The extraction procedure was shown to be

(9) G. W. Hearne and D. S. LaFrance, U. S. Patent 2,373,956 (1945); *Chem. Abstr.*, 39, 4081 (1945).

Table III. Conversion[a] of *trans*-Crotyl Alcohol to *cis*-Crotyl Alcohol *via* Covalent α-Methylallyl Alcohol

Time, min	Mole % in total alcohol composition: α-Methylallyl alc	*cis*-Crotyl alc: Obsd	*cis*-Crotyl alc: Calcd
0.0	0.02	...	
3.0	1.59	...	
6.0	3.33	...	
10.0	5.14	...	
15.0	8.45	...	
19.0	10.36	0.047	0.024
25.0	15.41	0.088	0.051

[a] *trans*-Crotyl alcohol (0.105 *M*) run in 70% aqueous dioxane–2.90 *M* H_2SO_4 at 50.00°.

Table IV. Conversion[a] of *cis*-Crotyl Alcohol to *trans*-Crotyl Alcohol *via* Covalent α-Methylallyl Alcohol

Time, min	Mole % in total alcohol composition: α-Methylallyl alc	*trans*-Crotyl alc[b]: Obsd	*trans*-Crotyl alc[b]: Calcd
0.0	0.02	(0.47)	...
6.0	0.76	(0.47)	
12.0	1.74	0.08	0.025
25.0	3.99	0.75	0.14

[a] *cis*-Crotyl alcohol (0.105 *M*) run in 70% aqueous dioxane–2.90 *M* H_2SO_4 at 50.00°. [b] 0.47% *trans*-crotyl alcohol originally present in *cis*-crotyl alcohol.

Table V. Development[a] of *cis*-Crotyl Alcohol from α-Methylallyl Alcohol

Time, min	Mole % in total alcohol composition: *trans*-Crotyl alc	*cis*-Crotyl alc: Obsd	*cis*-Crotyl alc: Calcd
0.0	0.05	...	
8.0	1.47	0.045	0.053
16.0	3.24	0.07	0.17

[a] α-Methylallyl alcohol (0.104 *M*) run in 70% aqueous dioxane–2.90 *M* H_2SO_4 at 50.00°.

essentially 100% complete, and that isomerization of the butenyl alcohols and ethers was negligible. Also, no alcohol or ether isomerization was observed in the absence of acid at 50.00° over a period of 8 half-lives of reaction.

In control experiments on the butenyl ethers, dicrotyl ether and crotyl α-methylallyl ether, it was found that ether cleavage occurred ($\sim 1.8 \times 10^{-7}$ sec^{-1}) under the reaction conditions. The equilibrium composition of the product mixture after 17 half-lives was in each case the same as that observed from the corresponding butenyl alcohols.

Discussion

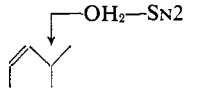
In the present work kinetic studies on optically active α-methylallyl alcohol (70% aqueous dioxane, 50.0°) indicate that loss of optical activity (k_α) was 5.18 times as fast as rearrangement (k_r) to its allylic isomers. Similar results ($k_\alpha > k_r$) were obtained by Goering and co-workers in the acid-catalyzed isomerizations of α-phenylallyl alcohol[10] in aqueous dioxane (k_α/k_r = 2.5) and *cis*- and *trans*-5-methyl-2-cyclohexenol (k_α/k_r = 8.16) in aqueous acetone.[2c] These results were interpreted in terms of a carbonium ion mechanism.

The observed excess racemization of (+)-α-methylallyl alcohol can also be accounted for by a carbonium ion mechanism (eq 1). The polarimetric rate constant would then be a measure of the rate of production of the carbonium ion intermediate which is common to both racemization (k_{rac}) and rearrangement (k_r) processes. Assuming that only the carbonium ion mechanism is operating, the fraction of carbonium ions ($(k_\alpha - k_r)/k_r$) which racemize and return to starting material under the present conditions is 0.806, *i.e.*, the carbonium ion intermediates racemize 4.18 times faster than they give rearranged products. The present data could not be

$$R{-}OH_2^+ \underset{}{\overset{k_{rac}}{\rightleftharpoons}} R^+ + H_2O \overset{k_r}{\rightleftharpoons} \text{products} \qquad (1)$$

explained on the basis of an SN2 and/or SNi mechanism since both require that $k_\alpha = k_r$.

On the other hand, the simultaneous operation of SN2 and SN2′ mechanisms (I) could possibly also account for the observed excess racemization in the allylic system.



$k_\alpha = 2k_{SN_2} + k_{SN_2'}$
$k_{SN_2'} = k_r$

In order to obtain a value of 5.18 for k_α/k_r by mechanism I, the ratio of $k_{SN_2}/k_{SN_2'}$ would have to be 2.09; this corresponds to a bimolecular rate constant for racemization of approximately $7.4 \times 10^{-5}/h_0$ l. $mole^{-1}$ sec^{-1}.

Bunton and co-workers[11] found the ratio of racemization to exchange for active *sec*-butyl alcohol to be about 2 in aqueous sulfuric acid at 99.8°. This result corresponds to an SN2 displacement mechanism for racemization. Thus, a rough measure of the bimolecular rate ($k_{SN_2}^{Sat}$) of active *sec*-butyl alcohol under the present reaction conditions ($H_0 = -1.00$) can be calculated from the measured dependence of the racemization rates on h_0. Correcting for temperature effects, the bimolecular attack (k_{SN_2}) on *sec*-butyl alcohol was calculated to be approximately $4 \times 10^{-8}/h_0$ l. $mole^{-1}$ sec^{-1} at 50.0°; or in other words, the relative reactivity of α-methylallyl alcohol to *sec*-butyl alcohol ($k_{SN_2}^{allylic}/k_{SN_2}^{Sat}$) is 2000 at 50.0. The measured relative reactivities[12] in the SN2 displacements reactions of allylic to saturated halides at 50.0 is of the order of 20 to 70. This higher relative reactivity ($k_{SN_2}^{allylic}/k_{SN_2}^{Sat}$) for α-methylallyl alcohol under the present conditions as compared to the bimolecular reactivity of the allylic halides suggests that the preferred mechanism of the isomerization reaction is more SN1 character than bimolecular. In addition, the rates of rearrangement of α-methylallyl alcohol, like that of other allylic alcohols, would be expected to parallel the acidity function h_0 at high acid concentrations. This h_0 dependence has been interpreted in terms of a carbonium ion mechanism[13,14] rather than a bimolecular process. Thus, it would appear that the bimolecular mechanism I is not favored under the present reaction conditions.

(10) H. L. Goering and R. E. Dilgren, *J. Am. Chem. Soc.*, 82, 5744 (1960).

(11) (a) C. A. Bunton, A. Konasiewcz and D. R. Llewellyn, *J. Chem. Soc.*, 604 (1955); (b) C. A. Bunton and D. R. Llewellyn, *ibid.*, 3402 (1957).

(12) R. H. DeWolfe and W. G. Young, "The Alkenes," Interscience Publishers, Inc., New York, N. Y., 1965, p. 681.

(13) E. A. Braude, *Quart. Rev.* (London), 4, 4049 (1950).

(14) F. A. Long and M. A. Paul, *Chem. Rev.*, 57, 935 (1957).

In the Results section of this paper, evidence was presented that the interconversion of *cis*- and *trans*-crotyl alcohol starting from either primary alcohol (*cis* or *trans*) took place through covalent α-methylallyl alcohol. The acid-catalyzed isomerization of α-methylallyl alcohol, as already discussed, gives rise to two (*cis* and *trans*) butenyl carbonium ions, depending on the conformation from which the secondary alcohol ionizes. For the data to be consistent with what is observed the *cis*- and *trans*-butenyl cations would collapse to their respective products without undergoing *cis–trans* isomerization within the butenyl cation. In other words, the data indicate that the retention of geometric configuration in the cationic intermediate is preserved in the acid-catalyzed isomerizations of *cis*- and *trans*-crotyl alcohols. This result also agrees with similar reports on the geometric stability of the allylic *cis*- and *trans*-butenyl cations which have appeared in the literature.[3,4] The observed retention of configuration of the butenyl cations is certainly in accord with theoretical expectations,[3] and under the present reaction conditions it represents a case where the leaving group is uncharged which should give rise to a longer lived allylic cation. The fact that configuration is preserved apparently indicates that anionic charge interaction with the allylic cation has little effect on its stability.

The greater proportion of α-methylallyl alcohol over the primary isomers (*cis* and *trans*) at equilibrium demonstrates its greater thermodynamic stability. Equilibrium mixtures of the butenyl bromides,[15] chlorides,[16] and acetates[12] favor the primary isomer over the secondary isomer by factors of about 3 to 1. This predominance of α-methylallyl alcohol over the primary isomers can be explained by considering two important structural factors common to both alcohols, the positions of the double bond and alcohol functional group. For example, the differences in the heats of combustion between 1-butene and either *cis*- or *trans*-2-butene reveal that the primary isomers (internal double bond) are favored by 1.6 and 2.6 kcal/mole, respectively, over the secondary isomer.[17] It is clear that the alcohol functional group would rather be attached to a secondary carbon than to a primary carbon atom. This is seen in the greater relative thermodynamic stability of isopropyl alcohol over *n*-propyl alcohol by 6 kcal/mole as measured by their differences in heats of combustion in the gas phase.[18] Comparison of these two structural considerations would seem to suggest that the tendency of the alcohol functional group to occupy the secondary position is a more important factor in determining the equilibrium product than the position of the double bond. If this is the case, then α-methylallyl alcohol would be expected to be favored at equilibrium.

Experimental Section

The Butenyl Alcohols. α-Methylallyl and *trans*-crotyl alcohols were derived by the lithium aluminum hydride reduction of the corresponding carbonyl compounds using standard techniques. *cis*-Crotyl alcohol was made by the standard method involving the semihydrogenation of 2-butyn-1-ol in methanol with the catalyst described by Lindlar.[19] The butenyl alcohols were purified by preparative scale vpc on a 20-ft ($^3/_8$ in. o.d.) aluminum column for the Auto-Prep packed with 15% (w/w) β,β'-thiodipropionitrile on 80–100 mesh Chromosorb W at 90°. The infrared and nmr spectra of each butenyl alcohol were identical with that of authentic material.

The Butenyl Chlorides. α-Methylallyl and *trans*-crotyl chlorides were kindly supplied by C. Seil. Analysis by vpc of the α-methylallyl chloride indicated that the material was contaminated with small traces of *trans*- (0.2%) and *cis*-crotyl chlorides (0.1%). *trans*-Crotyl chloride was contaminated with 0.7% α-methylallyl chloride and 0.9% *cis*-crotyl chloride. Analyses were carried out on a Perkin-Elmer 800 gas chromatograph using a 10-ft. ($^1/_8$ in. o.d.) aluminum column packed with 10% (w/w) β,β'-thiodipropionitrile on 80–100 mesh Chromosorb W at 70°.

cis-Crotyl chloride was prepared by the previously described method of Young, Sharman, and Winstein.[3] No further purification was carried out.

***trans,trans*-Dicrotyl Ether.** Sodium hydride (6.67 g, 0.148 mole) was added slowly to a magnetically stirred, ice–salt–water cooled solution of excess *trans*-crotyl alcohol (22.4 g, 0.28 mole). An evolution of hydrogen immediately occurred from the yellow reaction mixture. After stirring the reaction mixture overnight, *trans*-crotyl chloride (14.0 g, 0.154 mole) was added to the mixture and stirred overnight. A low-pressure flash distillation was performed from the precipitated sodium chloride, and the resulting colorless product was fractionated carefully through an efficient column. Purification of a fraction boiling between 150 and 153° by preparative vpc on the Auto-Prep with a column packed with 15% (w/w) β,β'-thiodipropionitrile on 80–100 mesh Chromosorb W at 90° yielded *trans,trans*-dicrotyl ether (95% pure).

The infrared spectrum showed absorption bands at 1670 (C=C), 1160–1060 (C–O, stretch), and 987–948 cm^{-1} (C=C, out-of-plane deformation).

The proton nmr spectrum showed the expected crotyl pattern: τ 8.30 (doublet split into a triplet, J = 4.8 cps, J = 2.5 cps, J = 1.2 cps), 6.20 (unsymmetrical septet), and 4.48 (complex multiplet). The proton signals integrated to 6:4:4, respectively.

***cis,trans*-Dicrotyl Ether.** This compound was synthesized in the same manner as *trans,trans*-dicrotyl ether using *cis*-crotyl alcohol and *trans*-crotyl chloride as starting materials.

The infrared spectrum showed absorption bands at 1670 and 1620 (C=C, stretch), 1150–1060 (C—O, stretch), 720–690 (=CH, out-of-plane deformation), and 985–950 cm^{-1} (C=C, out-of-plane deformation).

The proton nmr spectrum in carbon tetrachloride showed hydrogens at τ 8.34 (two doublets, J = 4.8 and 5.2 cps), 6.16 (multiplet), and 4.40 (multiplet), in the ratio of 6:4:4.

***cis,cis*-Dicrotyl Ether.** This compound was synthesized in the same manner as *trans,trans*-dicrotyl ether using *cis*-crotyl alcohol and *cis*-crotyl chloride as starting materials.

The infrared spectrum showed absorption bands at 1640 (C=C, stretch), 1150–1050 (C—P, stretch, and 685 cm^{-1} (=CH, out-of-plane deformation).

The proton nmr spectrum in carbon tetrachloride showed hydrogens at 8.36 (doublet, J = 5.2 cpc), 6.07 (doublet, J = 4.0 cps), and 4.40 (multiplet) in the ratio of 6:4:4.

***cis*- and *trans*-Crotyl α-Methylallyl Ethers.** These compounds were prepared by the acid-catalyzed etherification of *trans*-crotyl alcohol.

To a 2-l. round-bottomed, three-necked flask, fitted with a reflux condenser and Hershberg stirrer, and containing a 4 *M* solution (800 ml) of sulfuric acid cooled by an ice–salt water bath, was added 193 g (2.68 moles) of *trans*-crotyl alcohol. The mixture was stirred for 24 hr at 50°, by which time a dark red ether layer had separated from the orange aqueous layer. The separated ether layer had separated from the orange aqueous layer. The separated ether layer then was neutralized with anhydrous potassium carbonate and stirred overnight. Distillation of the ether layer through an efficient column gave a fraction boiling between 131 and 134.5°. Purification of this fraction by preparative vpc with a 15-ft 30% β,β'-thiodipropionitrile on 80–100 Chromosorb W column gave a sample consisting of 97.0% *trans*-crotyl α-methylallyl ether, 2.5% *cis*-crotyl α-methylallyl ether, and 0.5% α-methylallyl alcohol.

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(16) D. C. Dittmer and A. F. Marcantonio, *J. Org. Chem.*, **29**, 3473 (1964).
(17) F. D. Rossini and K. S. Pitzer, "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons," Government Printing Office, Washington, D. C., 1947.
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An infrared sample of *cis*-crotyl α-methylallyl ether was obtained by repeated preparative scale vpc of the above ether fraction. The infrared spectrum showed absorption bands at 1190–1050 (C—O, stretch), 990, 910, and 1820 (=CH, out-of-planede formation), 980–945 (C=C, out-of-plane deformation), and 720–630 cm (=CH, out-of-plane deformation).

The infrared spectrum of *trans*-crotyl α-methylallyl ether showed absorption bands at 1190–1050 (C—O, stretch), 980–945 (C=C, out-of-plane deformation), 990, 910, and 1820 (=CH, out-of-plane deformation), 1660 and 1625 cm (C=C, stretch). The proton nmr spectrum showed hydrogens at τ 8.81 (doublet, J = 6.5 cps), 8.31 (doublet split into a triplet, J = 4.8 cps, J = 2.8 cps, J = 1.2 cps), 6.23 (multiplet), and 4.95 and 4.40 (multiplet) in the ratio of 3:3:3:5.

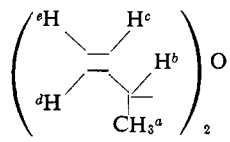
Di-α-methylallyl Ether. The preparation of this compound was carried out in the same manner as previously described for the synthesis of *cis*- and *trans*-crotyl α-methylallyl ethers.

Fractions boiling between 78 and 90°, 100 and 107°, and 107 and 108° were found by vpc analysis to contain mixtures of di-α-methylallyl ethers (two peaks) and α-methylallyl alcohol. Separation and purification of the di-α-methylallyl ethers (two peaks) from these fractions by preparative scale vpc on a 7-ft (3/4 in. o.d.) column packed with 30% (w/w) 3-nitro-3-methylpimelonitrile on firebrick at 70° indicated the presence of diastereomers (*meso* and *dl*) of di-α-methylallyl ether. The infrared and nmr spectral data from these ether specimens are summarized in Table VI.

Table VI. Diastereomers of Di-α-methylallyl Ether

Data	Diastereomer 1	Diastereomer 2
Vpc[a] retention times, min	2.7 (NMPN) 4.0 (UCON)	3.1 (NMPN) 4.7 (UCON)
Infrared, cm^{-1}	3040 1625 1180–1140 990 and 910 (1820)	3040 1625 1200–1040 990 and 910 (1820)
Nmr,[c] τ (peak description)	8.84 (doublet) 6.23 (quintuplet) 4.55 and 4.25 (quadruplet, two sets) 5.15 (multiplet)	8.85 (doublet) 6.17 (quintuplet) 4.50 and 4.24 (quadruplet two sets) 5.05 (multiplet)
C and H analyses[d]		
Calcd	C, 76.26; H, 11.18	C, 76.26, H, 11.18
Found	C, 76.16; H, 11.48	C, 76.06; H, 11.10

[a] Retention times were measured from the air peak on a Perkin-Elmer 154: (NMPN) 4-m, column (1/4 in. o.d.) 20% 3-methyl-3-nitro-pimelonitrile on 60–80 mesh firebrick at 95° (preheater 120°) (Ucon) 4-m column (1/4 in. o.d.) 20% Ucon-550 HB on 60–80 mesh firebrick at 102° (preheater 148°) ph. [b] Infrared spectra of 1 and 2 differ slightly in the region of 1200–1100 cm^{-1} (C—O stretch). [c] The coupling constants for di-α-methylallyl ether



are J_{ab} = 6.5 cps, J_{bc} = 6.5 cps, J_{cd} = 17.5 cps, J_{ce} = 10.0 cps. These spectra were determined in carbon tetrachloride with tetramethylsilane as an internal standard. Both spectra integrated to 14 protons (6:2:2:4).

Rates of Isomerization. Reaction solutions were prepared by dissolving weighed samples of each butenyl alcohol (0.105 M) in 70% aqueous dioxane solution,[20] 2.90 M in sulfuric acid.

Aliquots of the reaction mixture were dispensed into Pyrex test tubes. The charged test tubes were sealed and placed in a constant temperature (50.00 ± 0.01°) bath. After initial temperature equilibration (2 min) one reaction ampoule was quenched in a Dry Ice–acetone bath to give a zero-time point. At appropriate time intervals the remaining ampoules were removed and quenched.

An aliquot (5.0238 ml) of each reaction mixture was delivered into 20 ml of cold saturated potassium carbonate solution and 0.09608 ml of an ethyl ether solution of *n*-butyl alcohol (internal standard). After shaking the mixture in the separatory funnel for 30 sec, the resulting white emulsion was transferred to a 50-ml conical centrifuge tube. After centrifugation was completed, the top organic layer of the three-phased mixture was separated from the aqueous layer and the precipitated solid potassium carbonate.

Analyses of the organic layer were then performed by vpc.

Control experiments were performed in order to determine the efficiency of the work-up procedure. For example, a mixture of the following composition (given in mole per cent) was weighed into the reaction solvent: 30.40% *trans*-crotyl alcohol, 27.30% *cis*-crotyl alcohol, 19.25% α-methylallyl alcohol, and 23.05% *trans*-crotyl α-methylallyl ether. The mixture was then subjected to the standard work-up and analyzed by vpc using *n*-butyl alcohol as an internal standard. The results of the analyses were: 30.62% *trans*-crotyl alcohol, 27.13% *cis*-crotyl alcohol, 19.25% α-methylallyl alcohol, and 23.00% *trans*-crotyl α-methylallyl ether. These data indicate that no measurable amount of isomerization occurred during the work-up procedure and that the extraction (dioxane) was essentially 100% efficient.

The average integrated first-order constant for each rate of rearrangement of the butenyl alcohols was calculated by the equation

$$k = \frac{2.303 \log C_0/C_t}{t}$$

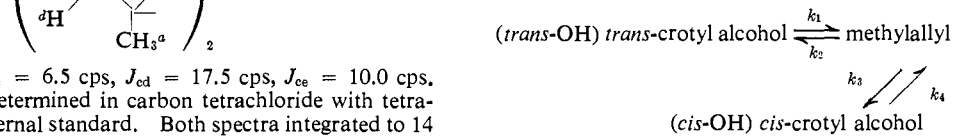
where C_0 is the concentration of the butenyl alcoho' at t_0, and C_t is the concentration of the unreacted butenyl alcohol at time t.

Polarimetric Rate of Optically Active α-Methylallyl Alcohol. A sample of optically active α-methylallyl alcohol prepared by Oliver[21] was used for the determination of the rate of loss of optical activity of α-methylallyl alcohol. Vpc analysis indicated that the sample was 98% pure; infrared and nmr spectra of the optically active sample agreed with an authentic sample of α-methylallyl alcohol. A rotation of α^{25} +14.78° (neat, l = 0.5 dm) was observed on a Hilger polarimeter.

A reaction solution, 0.091 M optically active α-methylallyl alcohol in 70% aqueous dioxane–2.90 M sulfuric acid, was sealed in a 1-cm cell and placed into a 50.0° thermostated holder. The loss of optical activity was followed by means of a Bendix Ericsson ETL NPL automatic-type polarimeter 143 A equipped with a Leeds and Northrup 1-mv speedomax b recorder. Values (given in degrees) interpolated from the chart were computed on a 7090 computor using a Fortran II program for integrated first-order rate constants.

Estimation of *cis–trans* Isomerization *via* α-Methylallyl Alcohol. The following relationships were used to calculate the values for *cis–trans* isomerization given in Tables III, IV, and V.

Assume the following kinetic scheme for the conversion of *trans*-crotyl alcohol to *cis*-crotyl alcohol.



For example, if we use the experimentally determined integrated first-order rate constants (k_1 and k_3) and the average concentration ($\bar{C}_{sec\text{-}OH}$) of α-methylallyl alcohol at time t when the back reactions (k_2 and k_4) are unimportant, the expected conversion of *trans*-crotyl alcohol *via* α-methylallyl alcohol to *cis*-crotyl alcohol can be estimated by the following relationship

$$\frac{k_3\bar{C}_{sec\text{-}OH}}{k_1\bar{C}_{trans\text{-}OH}}(sec\text{-}OH)_t = (cis\text{-}OH)_t$$

where $k_3\bar{C}_{sec\text{-}OH}/k_1\bar{C}_{trans\text{-}OH}$ is the fraction of *cis*-crotyl alcohol produced from α-methylallyl alcohol starting from *trans*-crotyl

(20) The reaction solvent was prepared by diluting a weighed sample of sulfuric acid (Baker and Adamson, 94.17%) with 70% aqueous dioxane (v/v). The 70% aqueous dioxane was prepared by mixing 7 volumes of anhydrous dioxane (L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p 284) with 3 volumes of distilled water. Aliquots of the reaction solvent were titrated with standard base to determine the sulfuric acid concentration; the volumes of the reaction solvent were measured at 25°.

(21) K. L. Oliver and W. G. Young, *J. Am. Chem. Soc.*, **81**, 5811 (1959).

alcohol while $(sec\text{-OH})_t$ is the concentration of α-methylallyl alcohol at time t. Similarly, the conversion of *cis*-crotyl alcohol to *trans*-crotyl alcohol *via* α-methylallyl alcohol can be calculated by using the relationship

$$\frac{k_2\bar{C}_{sec\text{-OH}}}{k_4\bar{C}_{sec\text{-OH}}}(sec\text{-OH})_t = (trans\text{-OH})_t$$

Vapor Phase Chromatography. The instrument employed in this work was a Perkin-Elmer Model 800 gas chromatograph epuipped with a differential flame ionization detector. Analyses of the reaction mixtures were carried out on two separate vpc columns: a 20-ft copper column (1/8 in. o.d.) packed with 10% (w/w) β,β'-thiodipropionitrile (TDPN) on 80–100 mesh Chromosorb W; and a 10-ft copper column (1/8 in. o.d.) packed with 10% (w/w) Ucon 550HB on 80–100 mesh Chromosorb W. A suggested antitailing agent, ATPET-80 (0.1% by weight), was added to the above column packings.

α-Methylallyl alcohol and crotyl α-methylallyl ethers were analyzed on the (TDPN) vpc column operated at 70° column temperature/160° preheator, 23 cc/min nitrogen carrier gas flow, and 15 psi of hydrogen gas for detector response. While the (Ucon) column operated at 70° column temperature/160° preheator, 23 cc/min nitrogen carrier gas flow provided data for the per cent composition of the reaction mixture with respect to *cis*- and *trans*-crotyl alcohol, di-α-methylallyl ethers, and the dicrotyl ethers. Under these operating conditions, the geometric isomers (*cis* and *trans*) of the butenyl ethers could not be satisfactorily resolved for quantitative measurements. Consequently, all ether measurements are reported without regard for isomeric composition.

Calibration factors were determined for each butenyl compound using *n*-butyl alcohol as an internal standard. Peak areas were integrated with a Disc Chart integrator Model 203 connected to the recorder of the Perkin-Elmer 800 gas chromatograph. Individual peak areas were corrected for base-line drift by employing a drift corrector part no. 1295 with each individual area measurement.

Control experiments performed with mixtures of known compositions indicated that the analyses are accurate to ±0.6%. In some cases the accuracy is considerably greater.

H_0 Measurement for the Reaction Solvent. The determination of H_0 for the reaction solvent (70% aqueous dioxane, 2.90 *M* in sulfuric acid) was carried out as described by Braude.[22] The indicator base used in the determination of H_0 was *o*-nitroaniline ($pk_\beta = -0.29$; λ_{max} 415 μ (ϵ 3050), $A = 0.22$).

Instruments. All infrared spectra were taken on a Beckman I.R. 5-A. Nmr spectra were determined on a Varian Model A-60 nmr spectrometer.

(22) E. H. Braude, *J. Chem. Soc.*, 1971 (1948).

The Structure of the Cactus Sterol Macdougallin (14α-Methyl-Δ^8-cholestene-3β,6α-diol). A Novel Link in Sterol Biogenesis[1,2]

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Contribution from the Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois, and the Department of Chemistry, Stanford University, Stanford, California. *Received October 16, 1965*

Abstract: The nonsaponifiable fraction of the ethanolic extract of *Peniocereus macdougallii* has been found to contain β-amyrin, lophenol, peniocerol, a mixture of sterols presumed to be cholesterol, campesterol, and β-sitosterol, and a new sterol named macdougallin. Degradative experiments are described which establish the structure of macdougallin as 14α-methyl-Δ^8-cholestene-3β,6α-diol. Its biogenetic significance as the first naturally occurring 14α-methyl sterol is discussed.

During the systematic investigation of a number of cactus species for the presence of alkaloids and triterpenoids,[4] it was observed that certain species contained appreciable neutral fractions. Investigation of the neutral constituents of *Lophocereus schottii* resulted in the identification of lophenol[5] (4α-methyl-Δ^7-cholesten-3β-ol) (I) which was of particular interest since it appeared to be an intermediate in the biological conversion of lanosterol to cholesterol.[6] This was confirmed by its independent isolation from rat skin and feces,[7] and the reports of its *in vitro* conversion to cholesterol by tissue homogenates.[8,9] In the hope of finding further intermediates that might shed some light on the biosynthetic processes involved in the demethylation of lanosterol, several other species of cactus were examined. Particular attention was given to the genera *Peniocereus* and *Wilcoxia*, which both possess relatively large, tuberous roots, an unusual feature among the *Cactaceae*. This study has resulted in the isolation and identification of several unusual sterols, among them peniocerol[10] (II, $R_1 = R_2 = R_3 = H$) and viperidinone[11] (III) from *Peniocereus fosteria-*

(1) Supported by the U. S. Atomic Energy Commission and by Grant GM-06840 from the National Institutes of Health.

(2) For a preliminary report of the structure of macdougallin see C. Djerassi, J. C. Knight, and D. I. Wilkinson, *J. Am. Chem. Soc.*, **85**, 835 (1963).

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(4) For a review see C. Djerassi in "Festschrift Arthur Stoll," Birkhäuser Verlag, Basel, Switzerland, 1957, pp 330–352.

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