It may be concluded from the data presented that (1) the rate of hydrolysis is affected greatly by the amino acid coupled with lysine; (2) ϵ-peptide bonds are more labile than α-peptide bonds to alkaline hydrolysis; (3) there is only a slight difference between the rates of acid-catalyzed hydrolysis of corresponding α- and ϵ-peptide bonds except those involving dicarboxylic amino acids.

Reactions of the Limonene 1,2-Oxides. I. The Stereospecific Reactions of the (+)-*cis*- and (+)-*trans*-Limonene 1,2-Oxides

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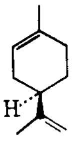
Pure *cis*- and *trans*-limonene 1,2-oxides have been prepared, and certain of their reactions with nucleophilic and with electrophilic reagents have been studied in detail. It has been shown that the Fürst–Plattner rule predicts the predominant products in all cases studied. Studies of the pyrolysis of hydroxyacetates derived from the limonene 1,2-epoxides of known configurations have permitted confirmation of the correct configurations in the carvomenthol series.

The limonene 1,2-oxides, which occur naturally in the essential oils of *Cymbopogon densiflorus*,[2] afford one of the most ideal cases yet investigated for study of the various competing effects which determine the stereochemistry of the opening of the oxirane linkage in substituted monocyclic cyclohexene epoxides.

The stereospecific reactions of cyclohexene epoxides in fused-ring systems, such as steroid epoxides and certain sugar epoxides, have been shown to yield *trans* diaxial products.[3] This rule has been stated for the steroids by Fürst and Plattner[5] and extended to the sugar epoxides by Mills.[6] The case of substituted monocyclic cyclohexene epoxides has not been as thoroughly studied and to assume that *trans* diaxial products will always be the rule would be unwise, since conformational effects in such systems are not always as clear-cut as in the case of fused-ring systems. In resolving this question, three major effects must be considered: (a) conformational effects on the cyclohexene epoxide,[7] (b) the primary steric effect[4] (steric hindrance), and (c) conformational preference of the resultant products.

The effect of bulky[8,9] alkyl groups in anchoring the ring conformation of substituted monocyclic cyclohexene epoxides has been established by their adherence to the Fürst–Plattner rule (*i.e.*, the 4-*t*-butylcyclohexene epoxides[10]), while interconversion of the two possible epoxide conformations has been demonstrated in the anhydroinositols.[11] Angyal has contended that the apparent exceptions to the Fürst–Plattner rule in monocyclic compounds are not due to *equatorial opening,* but rather to the reaction of the epoxide in its alternate conformation with subsequent inversion of the *diaxial* product to the more stable diequatorial conformation. Angyal warned, however, that predictions about the direction of ring opening might not always be reliable, because it would be difficult in some cases to presuppose the conformation in which the epoxide would react.[11]

The epoxidation of alkyl-substituted monocyclic cyclohexenes has been generally assumed to give epoxides which are predominantly *trans* to the alkyl substituents.[12,13] However, from an examination of models of 4-alkylcyclohexenes, it is not apparent that one side is more hindered than the other and thus,



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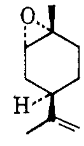

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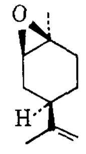

III

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[1] Research Department, R. J. Reynolds Tobacco Co., Winston-Salem, N. C.

[2] Y. R. Naves and A. V. Grampoloff, *Bull. Soc. Chim. France*, 37 (1960).

[3] R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959), and references therein. Occasionally diequatorial products are formed, but these are exceptional cases rather than the rule (see footnote 4).

[4] (a) The term "primary steric effect" as used in this paper may be stated as follows: The incoming reagent in the attack of an epoxide normally attacks the least substituted carbon of the oxirane linkage unless there are marked polar or conjugative effects. [For examples and a more comprehensive discussion see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).] The primary steric effect has been noted to be a dominant factor in the lithium aluminum hydride reduction of 5β,6β-epoxycholestane, the resultant products being largely the diequatorial product, 5-β-cholestanol (two parts) *vs.* 6-β-cholestanol (one part). [See A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957).] The formation of the diaxial 6-β-ol, involves axial attack by the hydride at the tertiary center, and it is known that nucleophilic displacements at tertiary centers occur only with difficulty. (E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y.. 1962, p 290.) A demonstration of the apparent reversal of this effect in monocyclic systems with acidic reagents is dicussed in this paper (see also ref 4b). (b) J. C. Leffingwell and E. E. Royals, *Tetrahedron Letters*, 3829 (1965).

[5] A. Fürst and P. A. Plattner, Abstracts, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., 1951, p 409; see also D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

[6] J. A. Mills, Addendum to article by F. H. Newth and R. F. Homer, *ibid.*, 989 (1953).

[7] The epoxide ring tends to "flatten out" the cyclohexane ring in the same way as an olefinic linkage, causing the cyclohexane ring to assume a half-chair conformation [B. Ottar, *Acta Chem. Scand.*, **1**, 283 (1947)]. It has been assumed that the stable chair conformation of the cyclohexane ring is partially reestablished in the transition state.

[8] The observation that the small hydroxyl group can anchor the ring conformation of epoxycyclohexanols in their reactions with lithium aluminum hydride is presumably the result of the formation of a complex by the hydroxyl with the aluminum hydride. This can, in some cases, lead to anomalous results.[9]

[9] H. B. Henbest and R. A. L. Wilson, *Chem. Ind.* (London), 659 (1956); *J. Chem. Soc.*, 1958 (1957).

[10] J. Sicher, F. Šipoš, and M. Tichý, *Collection Czech. Chem. Commun.*, **26**, 847 (1961).

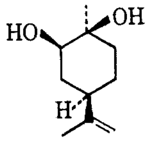
[11] S. J. Angyal, *Chem. Ind.* (London), 1230 (1954); *Quart. Rev.* (London), **11**, 212 (1957); see also R. C. Cookson, *Chem. Ind.* (London), 223, 1512 (1954).

[12] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 293–294, and references therein.

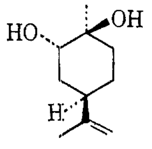
[13] For discussion and leading references on the directing influence of substituents in epoxidation reactions, see H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963).

intuitively, a nearly equal mixture of the two possible epoxides would be expected.[14] In the case of the epoxidation of limonene (I)[15] with organic peracids, a 1:1 mixture of the two epoxides is obtained.[4b]

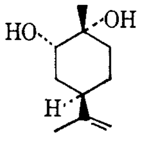
Until recently the only studies on the limonene 1,2-oxides were those involving further epoxidation[15a,c] and those in which the epoxides had been hydrated to produce a limonene 1,2-diol[15,16] different from the limonene 1,2-diol prepared from α-terpineol by permanganate oxidation.[16,17] The stereochemistry of these two glycols was determined by the work of Blumann and Wood[18] and correctly interpreted by Schmidt,[16] who assigned the stereochemistry of the diol derived from the limonene 1,2-oxides as 1-hydroxyneodihydrocarveol (V) and that from α-terpineol as 1-hydroxydihydrocarveol (IV). 1-Hydroxyneodihydrocarveol (V) is the expected diol from both the *cis*- and *trans*-limonene 1,2-oxides if the isopropenyl group anchors the ring conformation and the Fürst-Plattner rule of diaxial opening predominates in the direction of oxirane opening. Recently, Newhall has isolated a third isomer,



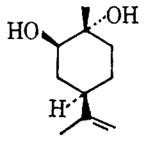
IV



V



VI



VII

which must be 1-hydroxyneoisodihydrocarveol (VII), as a minor hydration product of (+)-*trans*-limonene 1,2-oxide (III).[19,20] The 1-hydroxyisodihydrocarveol (VI) has not been isolated, although in the saturated analogs, the 1-hydroxycarvomenthols, all four isomers have been prepared.[21–23] In view of the general confusion which currently exists in the literature[21,23] as to the nomenclature and configurations of these alcohols, we have tabulated the known isomers of the limonene 1,2-diols (1-hydroxydihydrocarveols) and the 1-hydroxycarvomenthols in Table I and II, correcting inaccuracies when necessary. The configurational assignments of the carvomenthols, whence comes this confusion, have been corrected herein.

TABLE I

1-HYDROXYDIHYDROCARVEOLS

Compd	Mp, °C	$[\alpha]_D$,[a] deg	Ref
(+)-1-Hydroxydihydrocarveol (IV)	71–72	+25	16
(±)-1-Hydroxydihydrocarveol (IV)	63–64	±0	16
(+)-1-Hydroxyneodihydrocarveol (V)[b]	72–73	+55	16
(−)-1-Hydroxyneodihydrocarveol (V)	70–72	−43	16
(±)-1-Hydroxyneodihydrocarveol (V)	60–61	±0	16
(+)-1-Hydroxyneoisodihydrocarveol (VII)	65–66	+28	20

[a] Specific rotations were obtained in acetone solution. [b] The value for this rotation was obtained in this work (see Experimental Section).

TABLE II

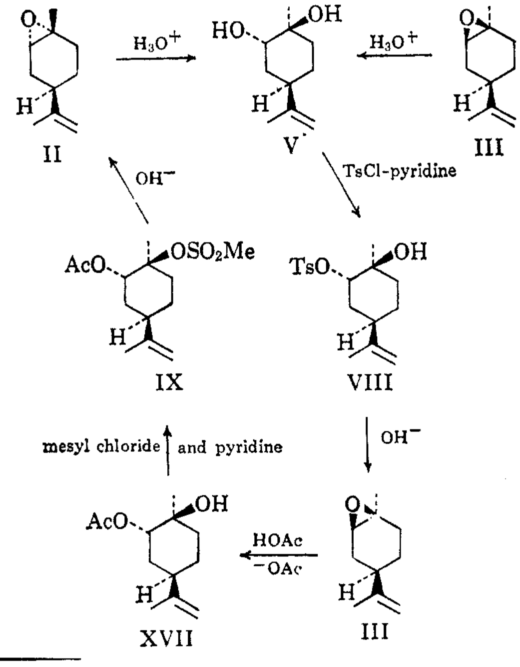
1-HYDROXYCARVOMENTHOLS[a]

Compd	Mp, °C	$[\alpha]_D$, deg	Ref
(+)-1-Hydroxycarvomenthol	76–77	+14	16
(−)-1-Hydroxycarvomenthol	76–77	−12	16
(±)-1-Hydroxycarvomenthol	54–54.5	±0	16, 21
(+)-1-Hydroxyneocarvomenthol[b]	90	+48	16, 23
(±)-1-Hydroxyneocarvomenthol	77–78	±0	16
(±)-1-Hydroxyisocarvomenthol	72.5	±0	21
(+)-1-Hydroxyneoisocarvomenthol	55	+30	22, 23
(±)-1-Hydroxyneoisocarvomenthol	53	±0	21

[a] The configurations for the 1-hydroxycarvomenthols follow that of their unsaturated analogs, the 1-hydroxydihydrocarveols. [b] The value for this rotation was obtained in this work (see Experimental Section).

(+)-*cis*- and (+)-*trans*-Limonene 1,2-Oxides.—(+)-*trans*-Limonene 1,2-oxide (III) was first prepared from the (+)-1-hydroxyneodihydrocarveol (V) obtained from hydration of the mixed epoxides by the action of base on the easily formed (+)-1-hydroxyneodihydrocarveol tosylate (VIII).[24] The (+)-*cis*-limonene 1,2-oxide (II) was prepared in this laboratory by the action of base on (−)-1-mesylneodihydrocarveyl acetate (IX), which may be derived directly from (+)-*trans*-limonene 1,2-oxide by the sequence shown in Chart I. Subsequent to the completion of this work,

CHART I



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[14] B. Rickborn and S.-Y. Lwo [*J. Org. Chem.*, **30**, 2212 (1965)] have shown that 4-alkyl groups exhibit only a very small steric effect on the epoxidation of cyclohexenes; see also ref. 4b.

[15] (a) N. Prileschaev, *Ber.*, **42**, 4814 (1909); (b) H. Meerwein, A. Ogait, W. Prang, and A. Serini, *J. Prakt. Chem.*, **113**, 19 (1926); (c) B. A. Arbuzow and B. M. Mikhailow, *ibid.*, **127**, 92 (1930); (d) H. Schmidt, *Ber.*, **82**, 11 (1949); (e) G. V. Pigulevski and U. I. Khokyryakov, *Chem. Abstr.*, **48**, 153 (1954); (f) E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955); (g) A. Kergomard and M. T. Geneix, *Bull. Soc. Chim. France*, 390 (1958); (h) H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, **33**, 299 (1959); (i) F. P. Greenspan and S. M. Linder, *Chem. Abstr.*, **57**, 4706 (1962); (j) E. E. Royals and J. C. Leffingwell, *J. Am. Chem. Soc.*, **80**, 2067 (1964).

[16] H. Schmidt, *Suomen Kemistilehti*, **B31**, 61 (1958).

[17] A. Ginsberg, *Ber.*, **29**, 1198 (1896); see also H. Schmidt, *ibid.*, **82**, 11 (1949).

[18] A. Blumann and W. R. Wood, *J. Chem. Soc.*, 4420 (1952).

[19] The *trans* isomer refers to the isomer with the 1,4-alkyl groups *trans* to each other. Newhall[20] reverses this nomenclature.

[20] W. F. Newhall, *J. Org. Chem.*, **29**, 185 (1964).

[21] P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, 4384 (1956); A. H. R. Cole and P. R. Jefferies, *ibid.*, 4391 (1956). These authors have reversed the nomenclature of the iso and neoiso isomers on the basis of the incorrect configurational assignments of the carvomenthols [see A. K. Bose, *Experientia*, **8**, 458 (1952)].

[22] W. F. Newhall, *J. Org. Chem.*, **23**, 1274 (1958).

[23] D. Ham, G. Dupont, J. Wiemann, and R. Dulou, *Compt. Rend.*, **249**, 700 (1959). For consistent nomenclature, the following names must be substituted for those assigned by these authors: (+)-*cis*-1-hydroxyneoisocarvomenthol should be (+)-1-hydroxycarvomenthol; (+)-*trans*-1-hydroxyisocarvomenthol should be (+)-1-hydroxyneoisocarvomenthol (see ref 16).

[24] H. Kuczynski and K. Piatkowski, *Roczniki Chem.*, **33**, 311 (1959).

the stereospecific preparation of these epoxides was reported[20] by pyrolysis of the three[25] quaternary ammonium iodide derivatives derived from the amino alcohols obtained from the mixed epoxides (after Sicher, *et al.*[10,26]).

Reactions of the (+)-Limonene 1,2-Oxides with Nucleophilic Reagents.—The first reported reactions of the limonene 1,2- and carvomenthene oxides with nucleophilic reagents, such as ammonia, indicated that the epoxides reacted normally, but the products were frequently assumed to be single compounds.[15e] Evidence for the formation of two amino alcohols from the reactions of the limonene 1,2-oxides and the carvomenthene oxides with ammonia (and amines) was furnished by Newhall.[19,27] The reaction of the limonene 1,2-oxides with ethyl alcohol in the presence of a basic catalyst was shown to afford both 2-ethoxy-1-hydroxy- and 1-ethoxy-2-hydroxy-8-*p*-menthene.[28] Only with the elegant work of Kuczynski and coworkers were all the products correctly identified with regard to both position and stereochemistry.[15h,24,25,28] The preparation of (+)-*trans*-limonene 1,2-oxide[24] made it possible to identify the products formed by each isomeric epoxide.

(+)-*trans*-Limonene 1,2-oxide, treated with dimethylamine, gave exclusively (+)-1-hydroxy-N,N-dimethylneodihydrocarveylamine (X),[25] while a mixture of the epoxides afforded a mixture of (+)-1-hydroxy-N,N-dimethylneodihydrocarveylamine (X), (+)-1-N,N-dimethylaminoneodihydrocarveol (XI), and (−)-1-hydroxy-N,N-dimethylneoisodihydrocarveylamine (XII) in a ratio of 80:50:25[25] (Chart II). The formation of the *two* possible isomers from the (+)-*cis*-limonene 1,2-oxide has been rationalized[25] on the basis of the diaxial opening of the two interconverting epoxide conformations[11] (*vide supra*). This explanation while intuitively plausible is not necessarily correct considering the reluctance with which nucleophilic attack occurs at tertiary centers[4] and the epoxide opening may in fact occur *via* diaxial opening of a "twist" transition state.[4b]

Similar results were obtained in the lithium aluminum hydride reduction of the limonene 1,2-oxides (Chart II).[15h,24,29] The reaction of an equal mixture of (+)-*cis*- and (+)-*trans*-limonene 1,2-oxide (0.31 mole) with lithium aluminum hydride (0.075 mole) in ether has indicated, not unexpectedly, that the *trans* isomer reacts at a faster rate than the *cis* isomer. After refluxing for 36 hr, analysis of the reaction products indicated that 18% of the original *cis*-epoxide did not undergo reaction while all of the *trans* isomer had been reduced (Table III).

Reactions of the (+)-Limonene 1,2-Oxides with Acidic Reagents.[4b]—The initial work on the reactions and isomerizations of the (+)-limonene 1,2-oxides with acidic reagents, other than simple hydration, was done in this laboratory.[15f] The treatment of these epoxides with a solution of sodium acetate in glacial acetic acid led to the formation of the monoacetate of limonene 1,2-diol in good yield. Subsequently, Linder and Greenspan[30] were able to effect the synthesis of impure carvone[31] through pyrolysis of the corresponding diacetate. Kergomard and Geneix[32] nearly simultaneously reported the preparation and pyrolysis of this diacetate. The reported pyrolysis products were

CHART II

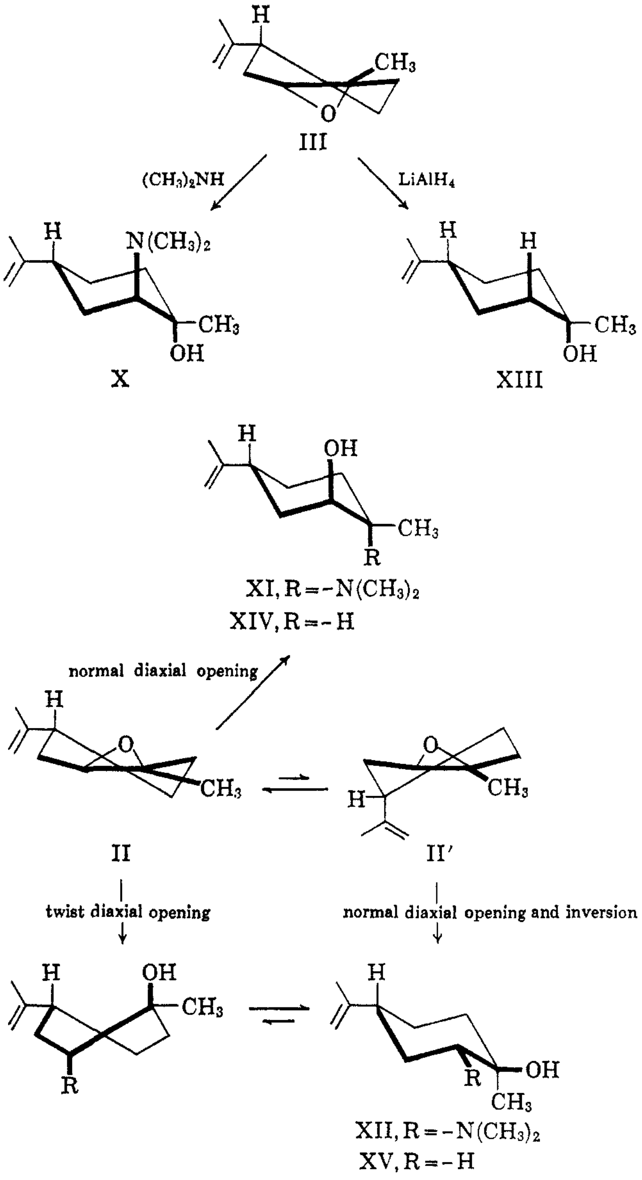

TABLE III

LITHIUM ALUMINUM HYDRIDE REDUCTION OF A 1:1 MIXTURE OF (+)-*cis*- AND (+)-*trans*-LIMONENE 1,2-OXIDE[a]

Product	%[b]	Bp, °C (mm)	$n^{23}D$	$[\alpha]^{23}D$, deg
cis-Limonene 1,2-oxide (II)	9	85–90 (10)	1.4650	+38.50
trans-β-Terpineol (XIII)	48	100 (10)	1.4740	+ 0.02
cis-β-Terpineol (XV)	5	104.5 (10)	1.4763	. . .
Neodihydrocarveol (XIV)	29	107 (8)	1.4784	+29.60
Unidentified products (two)	9	108–111 (9)	. . .	. . .

[a] $[\alpha]^{25}D$ +59.2°. [b] Analysis by vpc.

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(25) H. Kuczynski and A. Zabza, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **9**, 551 (1961); *Roczniki Chem.*, **37**, 773 (1963).

(26) J. Sicher and M. Pánková, *Collection Czech. Chem. Commun.*, **20**, 1409 (1955); M. Svoboda and J. Sicher, *ibid.*, **23**, 1540 (1958).

(27) W. F. Newhall, *J. Org. Chem.*, **24**, 1673 (1959).

(28) A. Kergomard, M. T. Geneix and J. Philbert-Bigou, *Chem. Abstr.*, **54**, 5371 (1959); **55**, 19988 (1959); French Patent, 1,185,651.

(29) G. V. Pigulevski, *J. Gen. Chem. USSR*, **28**, 1471 (1958).

(30) S. M. Linder and F. P. Greenspan, *J. Org. Chem.*, **22**, 949 (1957).

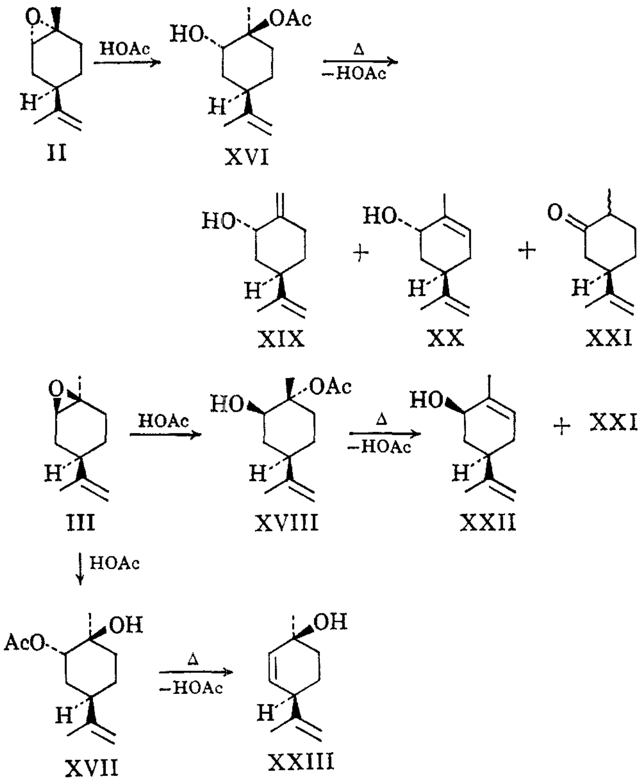
(31) The pyrolysis of 1,2-diacetoxy-8-*p*-menthene would be expected to yield an isocarveyl acetate (2-acetoxy-1,7(8)-*p*-menthadiene) as well as carveyl acetate. Saponification of isocarveyl acetate yields an isocarveol which would give perillyl aldehyde on oxidation[2] as a contaminant in the carvone.

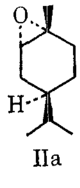
(32) A. Kergomard and M. T. Geneix, *Bull. Soc. Chim. France*, 390 (1958).

dihydrocarvone and *cis*-carveyl acetate.[33] The acid hydrations and isomerizations of the limonene 1,2-oxides will be reported in detail in a subsequent paper.[34]

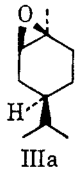
On reinvestigating the action of an acetic acid–sodium acetate solution on the (+)-limonene 1,2-oxides, it was found that (+)-*cis*-limonene 1,2-oxide gave a hydroxyacetate consisting solely of (+)-1-acetoxyneodihydrocarveol (XVI), while (+)-*trans*-limonene 1,2-oxide gave a mixture of (+)-1-hydroxyneodihydrocarveyl acetate (XVII) and 1-acetoxyneoisodihydrocarveol (XVIII) in a ratio of 9:1 (Chart III). A similar product ratio was obtained for the hydroxyacetate mixture from reaction of a sodium acetate buffered solution of acetic acid on the *cis/trans*-(+)-carvomenthene oxides (IIa, IIIa). This direct contrast to the action of nucleophilic reagents on these epoxides has been previously observed in the hydration of the limonene 1,2-oxides[19] (*vide supra*) and the carvomenthene oxides[21,22] in that 1-hydroxyneoisodihydrocarveol (VII) and 1-hydroxyneoisocarvomenthol, respectively, have been isolated as minor components (from the *trans* isomers).

CHART III



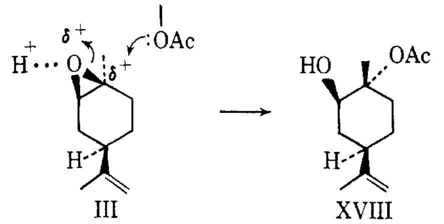


IIa



IIIa

In summary, it is apparent that in both nucleophilic and acidic attack on the limonene 1,2-oxides (and carvomenthene oxides), the Fürst–Plattner rule of diaxial opening predicts the predominant products.[14b] In the case of nucleophilic attack the primary steric effect is observed to some extent for the *cis* isomer, for which diaxial opening involves attack at the tertiary carbon atom (when the isopropenyl group is equatorial). The steric effect is absent in the case of attack by acidic reagents, and is in fact replaced by another effect in the case of *trans*-1,4-dialkylcyclohexene 1,2-epoxides. It is impossible to rationalize the formation of the minor product XVIII from the *trans*-limonene 1,2-oxide (III) (and the saturated analog from IIIa) on the basis of any steric effect. The reaction course for the formation of XVIII is best explained by the formation of a partial positive charge on the tertiary carbon atom, the reaction *approaching* an S_N1 mechanism. In the case of acidic reagents on the *trans*-limonene 1,2-oxide (III) this "abnormal" (effective diequatorial opening) course is minor (*ca.* 10%) compared to the "normal" (diaxial opening) S_N2 reaction (*ca.* 90%).



Pyrolysis of the Hydroxyacetates.—The nearly stereospecific reactions of the limonene 1,2- and carvomenthene oxides afford an excellent starting point from which the synthesis of a number of oxygenated terpenes of known configurations may be initiated.

The hydroxy acetate mixture obtained from a mixture of the (+)-*cis*- and (+)-*trans*-limonene 1,2-oxides in 90% yield was subjected to vapor phase pyrolysis at varying temperatures. Between 370 and 396° the 1-acetoxy-2-hydroxy-8-*p*-menthenes (XVI and XVIII) underwent complete acetate pyrolysis while the *trans*-2-acetoxy-1-hydroxy-8-*p*-menthene (1-hydroxyneodihydrocarveyl acetate) (XVII) was recovered unchanged. (+)-1-Acetoxyneodihydrocarveol (XVI) gave a mixture of (+)-1(7)-*p*-menthadien-*trans*-2-ol (*trans*-isocarveol) (XIX), (−)-*trans*-carveol (XX), and the isomeric (+)-dihydrocarvones (XXI), while the small amount of 1-acetoxyneoisodihydrocarveol (XVIII) obtained from the (+)-*trans*-limonene 1,2-oxide (III) gave (−)-*cis*-carveol (XXII) and the isomeric (+)-dihydrocarvones (XXI). The pyrolysis results are presented in Table IV. Similar results were obtained for the hydroxyacetates in the carvomenthene series (Table V). The pyrolysis of (+)-1-hydroxyneodihydrocarveol acetate (XVII) afforded (+)-2,8-*p*-menthadien-*trans*-1-ol (XXIII), while (+)-1-hydroxyneocarvomenthyl acetate gave (−)-2-*p*-menthen-*trans*-1-ol. The pyrolysis products, in all cases, confirmed the structures of the hydroxyacetates derived from the limonene and carvomenthene oxides.

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(33) The *cis*-carveyl acetate obtained[32] corresponds to the isomer generally accepted as *trans* (identified *via* the 3,5-dinitrobenzoate of the corresponding alcohol). G. Farges and A. Kergomard [*Bull. Soc. Chim. France*, 51 (1963)] have postulated the reversal of the accepted configurations of the carveols (and sobrerols) on the basis of a very tenuous conclusion with regard to the observed nuclear magnetic resonance spectra of these alcohols. This reversal of configurations has been rejected on the basis of the intricate stereochemical relationship proofs of the carveols (and sobrerols). For leading references, see J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959); E. E. Royals and J. C. Leffingwell, *ibid.*, **86**, 2067 (1964); *J. Org. Chem.*, **29**, 2098 (1964); S. H. Schroeter and E. L. Eliel, *ibid.*, **30**, 1 (1965).

(34) Also see R. L. Settine, G. L. Parks and G. L. K. Hunter, Abstracts of the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 40c; *J. Org. Chem.*, **29**, 616 (1964).

Table IV

Ratio of Pyrolysis Products from the 1-Acetoxy-2-hydroxy-8-*p*-menthenes[a]

Temp, °C	% of (+)-dihydrocarvone (XXI)[b]	% of (+)-*trans*-isocarveol (XIX)	% of (−)-*trans*-carveol (XX)	% of (−)-*cis*-carveol (XXII)
370	16.7	40.7	38.8	3.8
296	20.4	41.4	35.2	3.0
436[c]	26.6	35.7	34.6	3.1
450[c,d]	26.8	22.1	16.7	2.4

[a] % analysis by vpc. [b] Total of dihydrocarvone and isodihydrocarvone. [c] Neglecting pyrolysis of 2-acetoxy-1-hydroxy-8-*p*-menthene. [d] 31% of mixed hydrocarbons and other low-boiling products present.

Table V

Ratio of Pyrolysis Products from the 1-Acetoxy-2-hydroxy-*p*-menthanes[a]

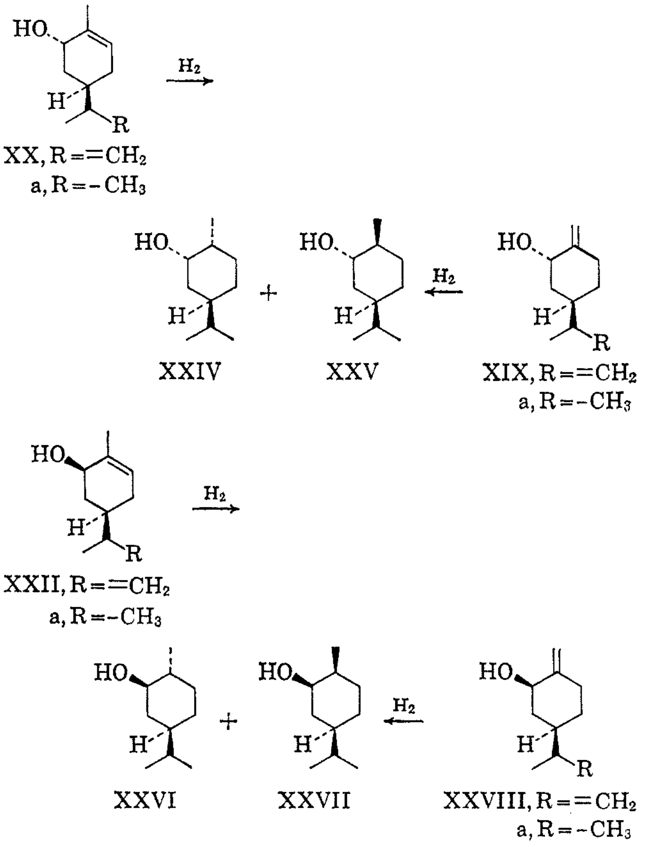
Temp, °C	% of (+)-carvomenthone[b]	% of (+)-*trans*-isocarvotanacetol	% of (−)-*trans*-carvotanacetol	% of (−)-*cis*-carvotanacetol
375[c]	29.6	30.0	36.6	3.8
392[d]	27.7	30.3	38.5	3.5
400[d]	29.4	31.2	36.2	3.2

[a] % analysis by vpc. [b] Total of carvomenthone and isocarvomenthone. [c] Ratio is from hydroxyacetate pyrolyzed, as incomplete pyrolysis occurred. [d] Neglecting pyrolysis of 2-acetoxy-1-hydroxy-*p*-menthane which occurred to a small extent.

A comparison of the products obtained from acetate pyrolysis with those obtained from the pyrolysis of the N oxides of the N,N-dimethylamino alcohols[25] is interesting in that the ratios of the pyrolysis products vary considerably.[35] Only in the acetate pyrolyses were ketonic products observed.

The Configurations of the Carvomenthols.[36]—The (+)-*trans*-isocarveol [1,7(8)-*p*-menthadien-*trans*-2-ol] (XIX) produced in the pyrolysis of XVI was identified as the same isomer previously assigned the *cis* configuration by Naves and Grampoloff[2] on the basis of its hydrogenation to isocarvomenthol. With authentic samples of the carveols, isocarveols, and corresponding carvotanacetols, derived (in part) stereospecifically from epoxides of known configuration, it was possible to undertake a reinvestigation of the questionable assignments[37] of the configurations of iso- and neoisocarvomenthol. Since hydrogenation generally proceeds *cis* to the olefinic linkage and no epimerization of the hydroxyl group has been observed in the hydrogenations in the corresponding menthol series,[38] it was considered that, if each isomer gave only two products on hydrogenation, and no detectable epimerization or rearrangement[39] occurred in any of the cases studied, it would then be possible to assign the structures of the carvomenthols with certainty. The results of this study confirmed the earlier work of Johnston and Read[40] and the configurational assignments of Simonsen and Owen.[41] The *trans*-carveols (XIX, XX) and *trans*-carvotanacetols (XIXa, XXa) gave only neocarvomenthol (XXIV) and isocarvomenthol (XXV) (hydroxyl group *trans* to isopropyl group) while *cis*-carveol (XXII) and the *cis*-carvotanacetols (XXIIa, XXVIIIa)[42] gave only carvomenthol (XXVI) and neoisocarvomenthol (XXVII) (hydroxyl group *cis* to isopropyl; Chart IV). The previous assignments,[37] which reversed the configurations of iso- and neoisocarvomenthol, were based on the isolation of an alcohol as the predominant product from the reaction of nitrous acid with isocarvomenthylamine. However, it is now known that the conformations of isocarvomenthylamine (and isocarvomenthol) are equilibrating and in fact are present in about equal amounts.[43] Thus, it is apparent that the assignment of configurations on the basis of the products resulting from the action of nitrous acid on cyclohexylamines[37,44] is *not valid when the conformations are mobile.* Similar discrepancies arise in the relative esterification rates

Chart IV



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[35] Although both pyrolyses are *cis* eliminations, tertiary N-oxides on cyclohexane rings give predominantly exocyclic olefins whereas tertiary acetate pyrolyses give predominantly endocyclic elimination. This has been explained on the basis of the five-membered transition state for N-oxide pyrolysis *vs.* the six-membered transition state for acetate pyrolysis. A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 361 (1960).

[36] E. E. Royals and J. C. Leffingwell, *J. Am. Chem. Soc.*, **86**, 2067 (1964); Y. R. Naves, *Helv. Chim. Acta*, **47**, 308, 1617 (1964); D. K. Shumway and D. J. Barnhurst, *J. Org. Chem.*, **29**, 2320 (1964); S. H. Schroeter and E. L. Eliel, *ibid.*, **30**, 1 (1965); Z. Chabudzinski and H. Kuczynski, *Bull. Acad. Polon. Sci.*, **12**, 91 (1964); Z. Chabudzinski, H. Kuczynski, and J. Kuduk, *ibid.*, **12**, 603 (1964); W. Hückel and P. Heinzelmann, *Ann.*, **687**, 82 (1965); G. S. Sidhu and M. Swaleh, *Indian J. Chem.*, **2**, 421 (1964). With the exception of the authors named last, everyone quoted now agrees with the conclusion presented herein.

[37] A. K. Bose, *Experientia*, **8**, 458 (1952); for reviews, see H. D. Orloff, *Chem. Rev.*, **54**, 347 (1954); T. S. Halsall, *Ann. Rept. Progr. Chem. Soc.* (London) **49**, 179 (1952).

[38] D. Malcolm and J. Read, *J. Chem. Soc.*, 1037 (1939); see also A. K. Macbeth and J. S. Shannon, *ibid.*, 2852 (1952).

[39] M. C. Dart and H. B. Henbest, *ibid.*, 3563 (1960).

[40] R. G. Johnston and J. Read, *ibid.*, 1138 (1935).

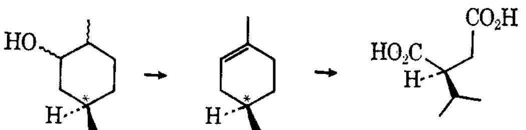
[41] J. Simonsen and L. N. Owen, "The Terpenes," Vol. III, 2nd ed, Cambridge University Press, Cambridge, 1951, pp 515–516.

[42] (a) R. L. Kenney and G. A. Fisher, *J. Org. Chem.*, **28**, 3509 (1963); (b) A. Blumann, E. W. Della, C. A. Henrick, J. Hodgkin, and P. R. Jefferies, *Australian J. Chem.*, **15**, 290 (1962).

[43] (a) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5483 (1959); see also *ibid.*, **81**, 5493 (1959). (b) S. H. Schroeter and E. L. Eliel, *ibid.*, **86**, 2066 (1964).

[44] J. A. Mills, *J. Chem. Soc.*, 260 (1953); A. K. Bose, *Experientia*, **9**, 256 (1953).

when dealing with mobile systems.[45] Essentially these same conclusions have also been reached on the basis of recent independent spectral and chemical evidence[36] although a decade has passed since the initial reports of the discrepancies in the configurational assignments were reported.[37] The recent review of the subject of the configurations of the carvomenthols and related compounds by Schroeter and Eliel[36] should well serve as a guide for correcting any inaccuracies which grew out of the incorrect configurational assignments of Bose.[37] The absolute configurations of the carvomenthols have been assigned as follows on the basis of the known absolute configurations of (+)-limonene [and (+)-carvomenthene, XXVI]:[15j] D-(−)-carvomenthol (1*S*,2*R*,4*R*) (XXVI), D-(+)-neocarvomenthol (1*S*,2*S*,4*R*) (XXIV), D-(+)-isocarvomenthol (1*R*,2*S*,4*R*) (XXV), and D-(+)-neoisocarvomenthol (1*R*,2*R*,4*R*) (XXVII). These four carvomenthols were assigned to the D- series by taking the 4-carbon atom of the *p*-menthane system as the reference carbon and relating these center of asymmetry to D-(+)-isopropylsuccinic acid (XXVa).[15j]



XXVa

A very powerful, and often overlooked tool in configurational and conformational assignments in the monocyclic terpene series is the accuracy with which Brewster's method of calculating molecular rotations[43a] may be applied to cases such as are dealt with here. Besides confirming the configurations of the carvomenthols as assigned above, Brewster's rule predicts that the carvotanacetol, $[\alpha]\mathrm{D}$ +100°, obtained by Ponndorf reduction of (+)-carvotanacetone,[46a] and different from the *cis*-carvotanacetol (XXIIa), $[\alpha]\mathrm{D}$ +56.5°,[47] is in fact an impure sample. This impure carvotanacetol was postulated to afford a sharp melting 1:1 mixture of the *cis*- and *trans*-*p*-nitrobenzoates.[48] This was confirmed in this work by the isolation of (−)-*trans*-carvotanacetol (XXa), $[\alpha]\mathrm{D}$ −164°, which gave a different 3,5-dinitrobenzoate than that reported for the (+)-carvotanacetol previously isolated.[46]

Experimental Section

The commercial peracid (+)-limonene 1,2 oxide used was obtained from FMC Corp., $n^{20}\mathrm{D}$ 1.4697, $[\alpha]^{27}\mathrm{D}$ +63.33° (neat), and fractionally distilled over a 3-ft spinning-band column to remove the small percentage of (+)-limonene: bp 70° (20 mm), $[\alpha]^{28}\mathrm{D}$ +94.06° (neat). The main fraction consisted of a 1:1 mixture of (+)-*cis*- and (+)-*trans*-limonene 1,2-oxides:[49] bp 92–94° (20 mm), $[\alpha]^{25}\mathrm{D}$ +59.20° (neat), $n^{25}\mathrm{D}$ 1.4654. The values for the starting material indicated that some racemic material was present and that all optical rotation values reported are somewhat lower than for optically pure materials.[20]

All melting points and boiling points are uncorrected. Melting points were taken in capillary tubes on a Mel-Temp melting point apparatus.

Analyses were done by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

Vapor phase chromatography (vpc) analyses were carried out on a Wilkens Aerograph Master Model A-100 using a 10-ft Carbowax 20M column (on firebrick) with helium as the carrier gas.

(+)-*cis*- and (+)-*trans*-Limonene 1,2-Oxide.—The mixture of (+)-limonene 1,2-oxides (150 g), $[\alpha]^{25}\mathrm{D}$ +59.20°, was fractionated over a 3-ft metal helix packed Todd column with an automatic fraction cutter at atmospheric pressure under nitrogen. Cuts (35) were arbitrarily taken, the distillation being followed by the observed optical rotation and refractive index of each cut. Cut 10, bp 197° (1 atm), $[\alpha]^{25}\mathrm{D}$ +50.80° (neat), $n^{25}\mathrm{D}$ 1.4640, was impure (+)-*cis*-limonene 1,2-oxide (II). Cut 35, bp 198° (1 atm), $[\alpha]^{25}\mathrm{D}$ +75.34° (neat), $n^{25}\mathrm{D}$ 1.4665, was predominantly (+)-*trans*-limonene 1,2-oxide (III). The infrared spectrum of the *cis*-epoxide (II) showed a band at 10.5 μ which was nearly absent in the *trans*-epoxide (III) fraction. Of the total charge, 110 g distilled over the range 196–198° (1 atm); 40 g was left as a dark, resinous pot residue which had the distinct spearmint odor of carvone.

(+)-1-Hydroxyneodihydrocarveol (V).—Commercial grade limonene 1,2-oxide (500 g) was stirred at ice-bath temperature in 6% sulfuric acid (2500 ml) for 5 hr. The solution was filtered; the crude diol hydrate was dissolved in hot chloroform, separated from the water of hydration, and crystallized to give 375 g (67%) of material: mp 70–70.5°, $[\alpha]^{25}\mathrm{D}$ +55° (acetone) (lit.[16] mp 72–73°, $[\alpha]\mathrm{D}$ +48°).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.13; H, 10.75.

Hydrogenation of V over PtO_2 in ethyl acetate afforded (+)-1-hydroxyneocarvomenthol, mp 88°, $[\alpha]^{25}\mathrm{D}$ +48° (acetone), on recrystallization from benzene–petroleum ether (bp 70–110°) (lit.[23] mp 90°, $[\alpha]\mathrm{D}$ +46°).

(+)-1-Hydroxyneodihydrocarveyl Tosylate (VIII).—(+)-1-Hydroxyneodihydrocarveol (V) (41.3 g) was added to a solution of *p*-toluenesulfonyl chloride (49.8 g) in dry pyridine (100 ml). The flask was sealed and stirred at 25° for 48 hr. This was poured into ice–hydrochloric acid solution and ether extracted (4 75-ml portions); the extracts were washed with cold dilute hydrochloric acid, followed by a saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure leaving 43.0 g (55%) of (+)-1-hydroxyneodihydrocarveyl tosylate (VIII). Distillation of 8.0 g in a modified Hickman still gave 7.0 g of material: $n^{24}\mathrm{D}$ 1.4944; $[\alpha]^{24}\mathrm{D}$ +51.05° (neat); $\lambda_{\max}^{CCl_4}$ 3.21, 3.37, 6.08, 6.89, 6.94, 7.25, 8.11, 8.40, 9.18, 9.64, 10.05, 10.45, 10.98, 11.19 μ.

(+)-*trans*-Limonene 1,2-Oxide (III)[24].—To a solution of 13.5 g of potassium hydroxide in methanol (100 ml) was added 37.0 g of (VIII), and the reaction mixture was stirred at room temperature for 30 min. The solution immediatedly became milky in appearance. The solution was poured into water and extracted with ether; the extracts washed with water and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the oil was distilled to yield 16.6 g (96%) of (+)-*trans*-limonene 1,2-oxide (III): bp 78.5–80.5° (10 mm), $[\alpha]^{24}\mathrm{D}$ +83.22° (neat), $n^{24}\mathrm{D}$ 1.4657 (lit.[20] $[\alpha]\mathrm{D}$ +92.7°). The infrared spectrum was identical with that reported[20] (notable in the total absence of a band at 10.5 μ).

Reaction of (+)-*trans*-Limonene 1,2-Oxide with Glacial Acetic Acid–Sodium Acetate.—Compound III (500 mg) was added to a solution of 1.5 g of sodium acetate in 10 ml of glacial acetic acid and stirred at room temperature for 48 hr; then the solution was diluted with water (300 ml), neutralized with solid sodium bicarbonate and extracted with 7 30-ml portions of ethyl acetate; and the extracts were dried over anhydrous sodium sulfate and hy-

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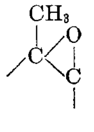
(45) E. L. Eliel, *Experientia*, **9**, 91 (1953).

(46) (a) J. Read and G. Swann, *J. Chem. Soc.*, 239 (1937); (b) S. H. Schroeter [*Ann.*, **674**, 118 (1964)] and A. Blumann, *et al.*,[42b] have recently isolated the highly rotating *trans*-carvotanacetol also.

(47) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(48) J. A. Mills, *ibid.*, 4976 (1952).

(49) Two other methods were employed to determine the epoxide percentages in the original mixture of (+)-limonene 1,2-oxides, $[\alpha]^{25}\mathrm{D}$ +59.2°. The nmr spectrum of the mixed epoxides shows two methyl peaks at τ 8.84 (center) corresponding to the



methyl of the two epoxides. The area ratio of the two peaks was 50.5:49.5. By employing the equation % of *trans* epoxide = ($[\alpha]\mathrm{D}^{\text{mixture}}$ − $[\alpha]\mathrm{D}^{cis}$)/($[\alpha]\mathrm{D}^{trans}$ − $[\alpha]\mathrm{D}^{cis}$) 100 and using reported density values[20] for the epoxides a ratio of 49% (III) and 51% (II) was obtained. The three methods agree as to a 1:1 ratio. Commercial limonene 1,2-oxide has previously been reported to consist of a 1:1 mixture as indicated by direct vpc analysis.[4b,20]

drogenated (PtO_2) at 60 psi. The catalyst was removed by filtration; the solvent was removed *in vacuo* yielding a mixture of carvomenthene hydroxyacetates (monoacetates of the 1-hydroxycarvomenthols) (400 mg), $n^{25}\mathrm{D}$ 1.4596, which were analyzed by vpc. Analysis indicated the hydroxyacetates to be 90% 1-hydroxyneocarvomenthyl acetate and 10% 1-acetoxyneoisocarvomenthol. An authentic sample of 1-hydroxyneocarvomenthyl acetate was added to identify the major peak. This indicated that the initial hydroxyacetates were 90% 1-hydroxyneodihydrocarveyl acetate (XVII) and 10% 1-acetoxyneoisodihydrocarveol (XVIII).

Reaction of (+)-*cis*- and (+)-*trans*-Limonene 1,2-Oxide with Glacial Acetic Acid–Sodium Acetate.—The peracid (+)-limonene 1,2-oxides (76.0 g), $[\alpha]^{25}\mathrm{D}$ +59.20°, were added to a solution of 41.0 g of sodium acetate in 500 g of glacial acetic acid with stirring. The reaction temperature rose to 37° but the flask was cooled to 27°; the reaction was stirred 68 hr. The solution was diluted with 2 l. of water and extracted with 7 75-ml portions of ether, and the extracts were neutralized with a saturated sodium bicarbonate solution. The solvent was removed under reduced pressure and the viscous oil was distilled to give 96.0 g (90.5%) of material: bp 132–138° (7 mm), $n^{25}\mathrm{D}$ 1.4742, $[\alpha]^{25}\mathrm{D}$ +53.60° (neat). Hydrogenation (PtO_2–ethyl acetate) of a small portion and analysis by vpc indicated the original hydroxyacetate mixture to be 46.4% 1-hydroxyneodihydrocarveyl acetate (XVII), 5.1% 1-acetoxyneoisodihydrocarveol (XVIII), and 48.5% of 1-acetoxyneodihydrocarveol (XVI). From these percentages it follows that the original epoxide mixture consisted of 51.5% (+)-*trans*-, and 48.5% (+)-*cis*-limonene 1,2-oxide.[49]

Pyrolysis of Mixed Limonene Hydroxyacetates (Monoacetates of 1-Hydroxydihydrocarveols) (Typical Procedure).—Mixed limonene hydroxyacetates (99 g), bp 114° (3 mm), $n^{25}\mathrm{D}$ 1.4750, $[\alpha]^{25}\mathrm{D}$ +56.80°, prepared as above from the peracid (+)-limonene 1,2-oxides, were pyrolyzed at 370°. The ester was dropped into the pyrolysis column at a rate of 1 drop/27 sec. The crude pyrolysate was taken up in ether and washed with a saturated sodium bicarbonate solution until neutral, then with water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the pyrolysate was distilled over a simple cold finger to give two fractions: (1) bp 85–126° (6–8 mm) (32 g) and (2) bp 126–130° (6 mm) (35 g).

Analysis of fraction (1) by vpc indicated five components (see Table IV). Fractionation over a 3-ft spinning-band column yielded the first two components as a single fraction: bp 85–87° (8 mm), $n^{25}\mathrm{D}$ 1.4714, $[\alpha]^{25}\mathrm{D}$ +21.80° (neat), identified as a mixture of isodihydrocarvone and dihydrocarvone (XXI) by the semicarbazone, mp 189°, and 2,4-DNP, mp 147–149° (lit.[50] semicarbazone, mp 189–191°; $[\alpha]\mathrm{D}$ −17.75° for (−) isomers). The infrared spectrum and vpc retention times were identical with that of an authentic sample.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.77; H, 10.92.

The third component, bp 102° (10 mm), $n^{25.5}\mathrm{D}$ 1.4925, $[\alpha]^{25}\mathrm{D}$ +82.00° (neat), gave a 3,5-dinitrobenzoate, mp 69–69.5°. The physical constants and infrared spectrum indicated that this was the *cis*-1(7),8-*p*-menthadien-2-ol (*cis*-isocarveol) isolated by Naves and Grampoloff[2] (lit.[2] $[\alpha]\mathrm{D}$ 94.3°, $n^{20}\mathrm{D}$ 1.4955, 3,5-dinitrobenzoate, mp 69–69.5°) (really the *trans* isomer, XIX).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.67; H, 10.86.

Hydrogenation of this alcohol (1.0 g, PtO_2–ethyl acetate (0.1:25) (g/ml), 60 psi) gave a mixture (1.0 g) of 24.5% neocarvomenthol (XXIV) and 75.5% isocarvomenthol (XXV) as analyzed by vpc using authentic samples as standards.[51] The hydrogenation products were distilled in a modified Hickman still to give the mixture of carvomenthols, $n^{25}\mathrm{D}$ 1.4630, $[\alpha]^{25}\mathrm{D}$ +21.06° (neat). This mixture afforded a 3,5-dinitrobenzoate, mp 111°, corresponding to that of (+)-isocarvomenthol (lit.[51] mp 111° for (−) isomer). In view of the preparation of this (+)-isocarveol from (+)-1-acetoxyneodihydrocarveol (XVI), and the correct configurations of the carvomenthols, the unsaturated alcohol was assigned the *trans* configuration, (+) 1(7),8-*p*-menthadien-*trans*-2-ol (*trans*-isocarveol, XIX).[52]

The fourth component, bp 106° (10 mm), $n^{25}\mathrm{D}$ 1.4934, $[\alpha]^{25}\mathrm{D}$ −181.80° (neat), was identified as (−)-*trans*-carveol (XX) (lit.[51] $n^{25}\mathrm{D}$ 1.4942, $[\alpha]^{25}\mathrm{D}$ +213° for (+) isomer) as indicated by the 3,5-dinitrobenzoate, mp 111° (lit.[50] mp 111.5°).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.96; H, 10.80.

Compound (XX) gave 63% neocarvomenthol (XXIV) and 37% isocarvomenthol (XXV) on hydrogenation (PtO_2–ethyl acetate) as indicated by vpc analysis.

The fifth component, bp 108° (10 mm), was identified as a slightly impure sample of *cis*-carveol (XXII) by comparison of its infrared spectrum and vpc retention time with an authentic sample.

Pyrolyses at 396, 436, and 450° were carried out in a similar manner and are tabulated in Table IV.

The second fraction from the crude distillation, bp 126–130° (6 mm), was (+)-1-hydroxyneodihydrocarveyl acetate (XVII). Redistillation gave a pure fraction: bp 143° (10 mm), $n^{25}\mathrm{D}$ 1.4728, $[\alpha]^{25}\mathrm{D}$ +73.50° (neat). This hydroxyacetate formed a 3,5-dinitrobenzoate, mp 161–162°.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.63; H, 9.56.

Pyrolysis of (+)-1-hydroxyneodihydrocarveyl acetate (XVII) (34.0 g), as above, at 455° yielded 21 g (86%) of crude (+)-2,8-*p*-menthadien-*trans*-1-ol (XXIII): bp 90–101° (10 mm), $n^{25}\mathrm{D}$ 1.4838, $[\alpha]^{25}\mathrm{D}$ +41.62° (neat). Fractionation through a 3-ft spinning-band column gave the main cut: bp 81–83° (7 mm), $n^{26}\mathrm{D}$ 1.4826, $[\alpha]^{26}\mathrm{D}$ +46.70° (neat). The infrared spectrum was identical with that reported.[2]

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.06; H, 10.75.

Hydrogenation of (XXIII) (PtO_2–ethyl acetate) gave *p*-menthan-*trans*-1-ol which was purified by distillation in a modified Hickman still: $n^{24}\mathrm{D}$ 1.4564, $[\alpha]^{24}\mathrm{D}$ +0.83° (neat) (lit.[2] $n^{20}\mathrm{D}$ 1.4600 $[\alpha]^{20}\mathrm{D}$ +0.02°). The *p*-menthan-*trans*-1-ol gave a 3,5-dinitrobenzoate, mp 82–83° (lit.[2] mp 83–83.5°), and an infrared spectrum identical with that reported.[2] Analysis by vpc indicated this alcohol to be better than 95% pure.

(+)-*cis*-Limonene 1,2-Oxide (II).—(+)-1-Hydroxyneodihydrocarveyl acetate (XVII) (21.2 g) was added to a solution of 12.0 g of methanesulfonyl chloride in 45 ml of dry pyridine at 15° and the reaction vessel was sealed. The temperature was allowed to rise to 25°, and the solution was stirred for 58 hr. The reaction mixture was worked up as for (+)-1-hydroxyneodihydrocarveyl tosylate (VIII) to yield crude (−)-1-mesylneodihydrocarveyl acetate (IV) (24.5 g), $n^{23}\mathrm{D}$ 1.4787, $[\alpha]^{23}\mathrm{D}$ −7.38° (neat). The crude mesylacetate (20.0 g) was added to a solution of 12.0 g of potassium hydroxide in 100 ml of 75% methanol and stirred for 48 hr at room temperature. The reaction mixture was poured into 700 ml of water, and extracted with 4 50-ml portions of ether, washed with 2 50-ml portions of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield an oil containing some crystalline material. Addition of 50 ml of pentane caused a mass of crystals to precipitate which were filtered off. The crystals (2.10 g), mp 55–57°, were recrystallized from benzene–pentane to give (+)-1-hydroxyneodihydrocarveol (V), mp 68–69°, identical with an authentic sample. No melting point depression occurred on admixture, and the infrared spectra were identical. The pentane was removed from the filtrate under reduced pressure, and the oil was distilled through a 5-in. Vigreux column to give (+)-*cis*-limonene 1,2-oxide (II) (3.10 g): bp 96–98° (26 mm), $n^{23.5}\mathrm{D}$ 1.4683, $[\alpha]^{23.5}\mathrm{D}$ +36.0° (neat), and a mixture of (+)-*trans*-isocarveol (XIX) and (−)-*trans*-carveol (XX) (4.00 g), bp 96–115° (10 mm), $n^{23.5}\mathrm{D}$ 1.4894, $[\alpha]^{23.5}\mathrm{D}$ −61.0° (neat). The limonene 1,2-oxide and carveols were identified by vpc and their infrared spectra compared to the peracid limonene 1,2-oxides and authentic samples of the carveols. The infrared spectrum of (II) was identical with that published[20] subsequent to the completion of this work [notably, a band at 10.5 μ which is absent for the *trans* isomer (III)]. (+)-*cis*-Limonene 1,2-oxide (II) (1.0 g) was hydrated in 1% sulfuric acid (10 ml) to yield (+)-1-hydroxyneodihydro-

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(50) E. Guenther and D. Althausen, "The Essential Oils," Vol. II, D. Van Nostrand Co., Inc., Princeton, N. J., 1949.

(51) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IIB, Elsevier Publishing Co., The Netherlands, 1953. The authentic samples of the carvomenthols used as standards in vpc analyses were characterized by their 3,5-dinitrobenzoates; (−)-carvomenthol, mp 107°; (+)-neocarvomenthol, mp 129°; (+)-neoisocarvomenthol, mp 69°; (+)-isocarvomenthol, mp 111°. The authors wish to thank Dr. J. T. Gresham for furnishing three of the above samples.

(52) S. Schroeter [Mulheim-Ruhr, Dissertation, Gottingen (1962)] has been reported to have correctly assigned this alcohol the *trans* configuration [E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963); footnote 24]; see also G. O. Schenck, K. Gollnick, G. Buchwald, S. H. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).

carveol dihydrate, which, upon loss of water of hydration and recrystallization from benzene–pentane, gave (+)-1-hydroxyneodihydrocarveol (V), mp 70–71°, $[\alpha]^{25}\mathrm{D}$ +53° (acetone).

Reaction of (+)-*cis*-Limonene 1,2-Oxide with Glacial Acetic Acid–Sodium Acetate.—(+)-*cis*-Limonene 1,2-oxide (II) (600 mg), treated like (+)-*trans*-limonene 1,2-oxide (III) above, gave a hydroxyacetate on hydrogenation (PtO_2–ethyl acetate) that was better than 95% pure (*via* vpc) and was identified as 1-acetoxyneocarvomenthol, which indicated the limonene hydroxyacetate to be 1-acetoxyneodihydrocarveol (XVI). Identification was made by comparison with an authentic sample previously identified by its pyrolysis products.

(+)-*cis*- and (+)-*trans*-Carvomenthene Oxides (*p*-Menthane 1,2-Oxides).—The peracid (+)-limonene 1,2-oxides, 15.2 g (0.10 mole), bp 92–94° (20 mm), $n^{25}\mathrm{D}$ 1.4654, $[\alpha]^{25}\mathrm{D}$ +59.20° (neat), was hydrogenated [PtO_2–ethyl acetate (0.5:250) (g/ml), 60 psi] until 0.10 mole of hydrogen had been absorbed. The catalyst was removed by filtration, the solvent removed under reduced pressure and the product distilled to give a nearly quantitative yield of epoxide, bp 72–75° (10 mm), $n^{25}\mathrm{D}$ 1.5404, $[\alpha]^{25}\mathrm{D}$ +51.46° (neat). This corresponded to an approximately 1:1 ratio of the (+)-*cis*- and (+)-*trans*-carvomenthene oxides, since the ratio of the limonene 1,2-oxides was known.[49]

Reaction of the (+)-Carvomenthene Oxides with Glacial Acetic Acid–Sodium Acetate.—A 1:1 mixture of the (+)-carvomenthene oxides (77.0 g), prepared as above, was added to a solution of sodium acetate (41.0 g) in glacial acetic acid (350 ml) and stirred at room temperature for 68 hr. The reaction was then worked up as for the mixed limonene hydroxy acetates (*vide supra*). Distillation afforded 91.2 g (86%) of mixed hydroxyacetates: bp 120–136° (7 mm) mainly 133–135° (7 mm), $n^{25}\mathrm{D}$ 1.4629, $[\alpha]^{25}\mathrm{D}$ +56.80° (neat). Analysis by vpc showed the hydroxyacetate mixture to consist of 46.5% 1-hydroxyneocarvomenthyl acetate, 5.3% 1-acetoxyneoisocarvomenthol, and 48.2% 1-acetoxyneocarvomenthol. As this was essentially the same ratio as was obtained by hydrogenation of the mixed limonene hydroxyacetates, a second method of preparation was afforded.

Pyrolysis of Mixed Carvomenthene Hydroxyacetates.—A mixed carvomenthene hydroxyacetate fraction (240 g), bp 140–141° (10 mm), $n^{23}\mathrm{D}$ 1.4613, $[\alpha]^{23}\mathrm{D}$ +57.80° (neat), prepared by hydrogenation of a limonene hydroxyacetate fraction, was pyrolyzed at 392° and worked up as above. The pyrolysate was distilled to give two fractions: (1) bp 87–130° (6–7 mm) (86 g), and (2) bp 132–135° (8 mm) (98 g). Analysis of the first cut by vpc indicated the presence of at least five components (see Table V). Fractional distillation of the first fraction over a 3-ft spinning-band column yielded a cut, bp 57–70° (4 mm), which was subsequently shown by vpc to be a small amount of impure 2-*p*-menthen-*trans*-1-ol. The first major component, bp 72° (4 mm), $n^{23}\mathrm{D}$ 1.4596, $[\alpha]^{23}\mathrm{D}$ +14.60° (neat), corresponded to a mixture of carvomenthone and isocarvomenthone.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.78. Found: C, 77.29; H, 11.56.

This component was identified by vpc and its infrared spectrum compared with an authentic sample. The ketone formed a semicarbazone, mp 176–177°.

The third component, bp 98–100° (10 mm), $n^{25}\mathrm{D}$ 1.4765, $[\alpha]^{25}\mathrm{D}$ +62.91° (neat), was identified as (+)-1(7)-*p*-menthen-*trans*-2-ol [(+)-*trans*-isocarvotanacetol, XIXa], 3,5-dinitrobenzoate mp 80.5–81.5°. Its infrared spectrum was identical with that reported.[53]

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.78. Found: C, 77.22; H, 11.94.

A catalytic reduction (PtO_2–ethyl acetate) of a sample gave 25% neocarvomenthol (XXIV) and 75% isocarvomenthol (XXV), as indicated by vpc using authentic samples as standards.

The fourth component, bp 101–102° (10 mm), $n^{23.5}\mathrm{D}$ 1.4772 $[\alpha]^{23.5}\mathrm{D}$ −164.50° (neat), corresponded to (−)-*trans*-carvotanacetol (XXa) and formed a 3,5-dinitrobenzoate: mp 115° (lit.[42,46a] $n^{25}\mathrm{D}$ 1.4757, $[\alpha]\mathrm{D}$ −113.9°, 3,5-dinitrobenzoate mp 109–111°); infrared spectrum, $\lambda_{\max}^{\text{film}}$ 3.01, 3.41, 6.82, 6.95, 7.22, 7.32, 7.65, 7.90, 8.55, 8.65, 9.15, 9.54, 9.68, 10.38, 10.67, 11.02, 11.54, 12.39 μ.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.78. Found: C, 77.86; H, 11.98.

Hydrogenation (PtO_2–ethyl acetate) gave 64% neocarvomenthol (XXIV) and 36% isocarvomenthol (XXV) as indicated by vpc using authentic sampes as standards

The fifth component of the pyrolysate was assigned as *cis*-carvotanacetol (XXIIa) by analogy with the pyrolysis of the limonene hydroxyacetates, although it was not isolated. Similar pyrolyses of the 1-acetoxycarvomenthols at 375 and 400° are tabulated in Table V.

The second cut from the crude distillation of the pyrolysate, bp 132–135° (8 mm), $n^{25}\mathrm{D}$ 1.4608, $[\alpha]^{25}\mathrm{D}$ +70.90° (neat), corresponded to (+)-1-hydroxyneocarvomenthyl acetate, homogeneous by vpc analysis. This hydroxyacetate gave a 3,5-dinitrobenzoate, mp 155–155.5°. It was noted that for both the limonene and carvomenthene hydroxyacetates, when the infrared spectra were taken neat, two carbonyl bands appeared at 5.74 and 5.79 μ, whereas in CCl_4 solution only a single band at 5.75 μ occurred.

(+)-1-Hydroxyneocarvomenthyl Acetate.—(+)-1-Hydroxyneodihydrocarveyl acetate (XVII) (2 g), bp 143° (10 mm), $n^{25}\mathrm{D}$ 1.4750, $[\alpha]^{25}\mathrm{D}$ +73.50° (neat), hydrogenated (PtO_2–ethyl acetate) as above yielded a crude hydroxyacetate which was distilled in a modified Hickman still to give a nearly quantitative yield of (+)-1-hydroxyneocarvomenthyl acetate, $n^{26}\mathrm{D}$ 1.4583, $[\alpha]^{26}\mathrm{D}$ +81.0° (neat).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.72; H, 10.48.

Pyrolysis of (+)-1-Hydroxyneocarvomenthyl Acetate.—(+)-1-Hydroxyneocarvomenthyl acetate (19.0 g) was pyrolyzed at 450° and worked up as above, leaving 11.3 g (84%) of crude (−)-2-*p*-menthen-*trans*-1-ol. Distillation in a modified Hickman still afforded material, $n^{25}\mathrm{D}$ 1.4764, $[\alpha]^{25}\mathrm{D}$ −13.02° (neat) (lit.[42] $[\alpha]\mathrm{D}$ −12.0°).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.01; H, 11.60.

Hydrogenation (2.5 g, PtO_2–ethyl acetate) gave *p*-menthan-*trans*-1-ol (2.2 g) after distillation in a modified Hickman still, $n^{23}\mathrm{D}$ 1.4555, $[\alpha]^{23}\mathrm{D}$ +2.30° (neat). Analysis by vpc indicated this sample contained about 5% impurity. A 3,5-dinitrobenzoate, mp 83° (lit.[2] mp 83–83.5°), was formed.

(−)-*cis*-Carveol (XXII).—(−)-Carvone (45.0 g), $n^{25}\mathrm{D}$ 1.4967, $[\alpha]^{25}\mathrm{D}$ −58.47° (neat), was reduced with lithium aluminum hydride according to Reitsema[54] to give 40.5 g (89%) crude (−)-carveol, $n^{23}\mathrm{D}$ 1.4940, $[\alpha]^{25}\mathrm{D}$ −32.40° (neat), which was distilled to give (−)-carveol (39.9 g), $n^{25}\mathrm{D}$ 1.4955, $[\alpha]^{25}\mathrm{D}$ −32.74° (neat), shown by vpc analysis to be 94.4% (−)-*cis*-carveol and 5.6% (−)-*trans*-carveol. Hydrogenation of pure *cis*-carveol (PtO_2–ethyl acetate) gave 49% carvomenthol (XXVI) and 51% neoisocarvomenthol (XXVII).

Lithium Aluminum Hydride Reduction of a 1:1 Mixture of the Limonene 1,2-Oxides.—The peracid limonene 1,2-oxides (*cis–trans* isomers, 47.0 g), $n^{25}\mathrm{D}$ 1.4654, $[\alpha]^{25}\mathrm{D}$ +59.20° (neat), were dropped into a solution of lithium aluminum hydride (3.10 g) in ether (130 g) and refluxed for 36 hr. Water was then added dropwise until a flocculent white precipitate formed which was filtered off and washed with ether. The solvent was removed from the filtrate; the crude reaction product(s) was analyzed by vpc (Table III) prior to distillation through a 3-ft spinning-band column. The first component, bp 90° (10 mm), $n^{23}\mathrm{D}$ 1.4650, $[\alpha]^{23}\mathrm{D}$ +38.50° (neat), was identified as (+)-*cis*-limonene 1,2-oxide (II) *via* vpc and its infrared spectrum compared with that of an authentic sample. The second component, bp 100° (10 mm), $n^{23}\mathrm{D}$ 1.4740, $[\alpha]^{23}\mathrm{D}$ +0.02° (neat, supercooled), mp 31°, was *trans*-β-terpineol (XIII) (lit.[15h] mp 32°).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.57; H, 12.09.

The third component was *cis*-β-terpineol (XV), bp 104.5° (10 mm), $n^{23}\mathrm{D}$ 1.4763 [lit.[15h] bp 78° (1.5 mm), $n^{20}\mathrm{D}$ 1.4793]. The fourth component, bp 107° (8 mm), $n^{23}\mathrm{D}$ 1.4784, $[\alpha]^{23}\mathrm{D}$ +29.60° (neat), was (+)-neodihydrocarveol (XIV) (lit.[55] $[\alpha]\mathrm{D}$ −32.5° for (−) isomer); hydrogenation (PtO_2–ethyl acetate gave only neocarvomenthol (XXIV). Analysis was by vpc using an authentic sample as a standard. Two other unidentified products were present in the minor fraction, bp 108–111° (9 mm). The total distillate amounted to 36.3 g (76%).

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