FAVORSKII REARRANGEMENT OF THE PULEGONE EPOXIDES

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Abstract—The pulegone epoxide I, with sodium ethoxide in ethanol, gives as the major product, the 'puleganolic' acid III; similarly epoxide V gives the 'puleganolic' acid VII with the puleganolide IX. The major products obtained from epoxide I, in aqueous ethanol, are a 'normal' hydroxy acid XI together with III, and from epoxide V, a 'normal' hydroxy acid XI together with VII and IX. The results are interpreted on the basis of two stereospecific Favorskii rearrangements, and enable the assignment of configuration to epoxides I and V, as indicated. An 'anomalous' product, $C_{13}H_{14}O_3$, is obtained from both epoxides.

THE crystalline epoxide, m.p. 39–40°, formed from D-(+)-pulegone by the action of alkaline hydrogen peroxide solution,[1] is now known[2,3] to be a mixture comprising approximately equal amounts of the diastereoisomers, I and V. As we had reported[4] previously on the Favorskii rearrangement of the epoxide, m.p. 39–40°, a reinvestigation of this reaction for each of the isomers, I and V, is now described. These stereoisomers have been separated from the original epoxide mixture,[1] by a combination of fractional distillation and recrystallization techniques.[3] The purity of each isomer has been determined by gas chromatography, physical constants being given in the experimental section.

The present studies enable us to assign configuration to each of the pulegone epoxides, I being the epoxide, m.p. 57–57·5°, and V the epoxide, m.p. 54·5–55°. These assignments are the reverse of those proposed[3]* on the basis of NMR spectra, ORD curves, and other data.

The epoxide, m.p. 57–57·5°, that is I, on treatment with sodium ethoxide in ethanol, yields the *trans,trans*-hydroxy acid III (R = H; 62%)† as the major acidic product. The minor product, 3-methylcyclopentanecarboxylic acid (XII, R = H; 3%) has been detected by gas chromatography of its methyl ester. It results from the retroaldol degradation of a 'normal' hydroxy ester (XI, R = Et).[4] The neutral fraction (20%) from the rearrangement of this epoxide which, on gas chromatography shows no evidence of hydroxy esters, yields, on distillation, an 'anomalous' product, $C_{13}H_{14}O_3$ (6%). The remaining material, partly polymeric, has not been investigated.

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* We thank Professor W. Reusch for advising us prior to publication that, as the result of a contemporary investigation, he has also reversed the configurations previously assigned[3] to the epoxides I and V.

† In the designation of configuration, the relationship of the substituents at C_4 and C_2 is given first, and that at C_3 and C_1 second.

[1] W. Treibs, *Ber. Dtsch. Chem. Ges.* **66**, 1483 (1933), and Ref. therein.
[2] E. Klein and G. Ohloff, *Tetrahedron* **19**, 1091 (1963).
[3] W. Reusch and C. K. Johnson, *J. Org. Chem.* **28**, 2557 (1963).
[4] S. A. Achmad and G. W. K. Cavill, *Austral. J. Chem.* **16**, 858 (1963).

The configuration assigned to the *trans,trans*-hydroxy acid III (R = H) follows from its conversion into the *cis,trans-γ*-lactone IX on treatment with hydrochloric acid in methanol.[4] Treatment of the *trans,trans*-hydroxy ester III (R = Et), the *cis,trans-γ*-lactone IX, or the *cis,cis-γ*-lactone X, with sodium ethoxide in ethanol results, in each case, in the recovery of starting material. No epimerization products were detected.
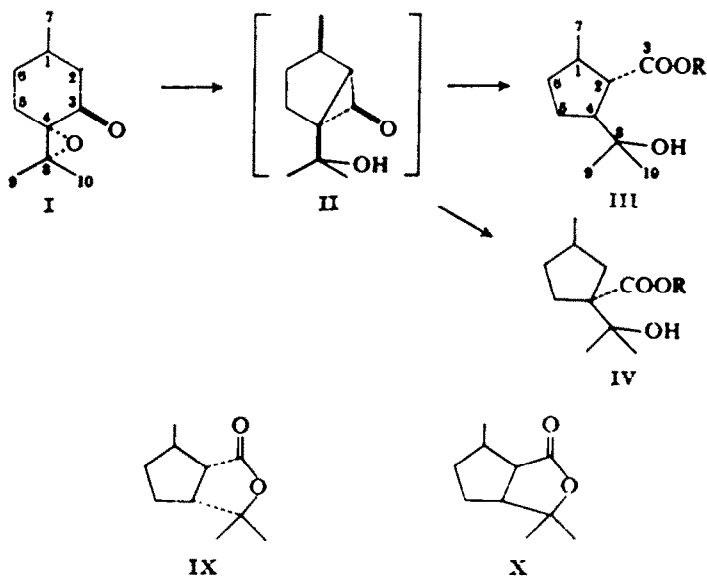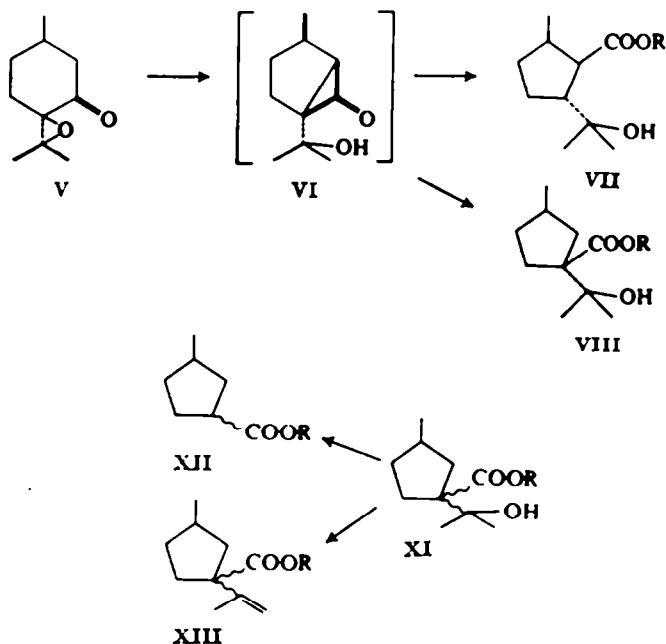

The epoxide I on treatment with sodium hydroxide in aqueous ethanol gives a 'normal' hydroxy acid XI (R = H; 44%) as the major product,[*] together with the *trans,trans*-hydroxy acid III (R = H; 38%). Gas chromatography shows trace amounts of 3-methylcyclopentanecarboxylic acid XII (R = H), and possibly of the dehydration product XIII. A neutral fraction (18%) remained. Epoxide I on treatment with sodium hydroxide in 95% ethanol gives the 'anomalous' product (10%), m.p. and mixed m.p. 113–114°, without associated polymeric material. A 'normal' hydroxy acid XI (R = H; 47%) and the *trans,trans*-hydroxy acid III (R = H; 35%) are the major products of this reaction.

In a comparable series of reactions, the epoxide, m.p. 54·5–55°, that is V, on treatment with sodium ethoxide in ethanol yields the *cis,trans-γ*-lactone IX (46%) and the *trans,cis*-hydroxy acid VII (R = H; 4%). A small amount of the *trans,trans*-hydroxy acid III (R = H, up to 2%), a 'normal' hydroxy acid XI (R = H; 4%) and XII (R = H; 2%) are also present. The neutral fraction (22%) again yields the 'anomalous' product, m.p. and mixed m.p. 113–114°.

The configuration assigned to the *trans,cis*-hydroxy acid VII (R = H) follows from its conversion into the *cis,cis-γ*-lactone X on treatment with hydrochloric acid in methanol.[*] Further, an epimerization of the *trans,cis*-hydroxy ester VII (R = Et) with sodium ethoxide in ethanol gives the *cis,trans-γ*-lactone IX in a 5:1-ratio to the starting material.
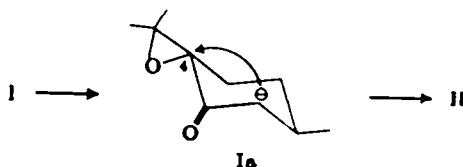
* Cf. Ref. 4.

The epoxide V on treatment with sodium hydroxide in aqueous ethanol yields a 'normal' hydroxy acid XI (R = H; 51%).[*] Further products include the *cis,trans-γ*-lactone IX and the *trans,cis*-hydroxy acid VII (R = H) in a combined yield of 24%. The *trans,trans*-hydroxy acid III (R = H; 9%) is also present, and traces of XII and XIII (R = H) are noted. The neutral fraction (4%) was not resolved.

The products isolated from the above rearrangements are summarized in Table 1. Under comparable reaction conditions, the major products obtained from epoxide I correspond in structure to those obtained from epoxide V. However the corresponding products, from each isomer, show significant stereochemical differences which are interpreted on the basis of two predominantly stereospecific Favorskii rearrangements.[5–8]

Thus, the major product obtained on rearrangement of I with sodium ethoxide in ethanol, the *trans,trans*-hydroxy acid III (R = H), would have resulted from the cyclopropanone intermediate II. Such a stereospecific Favorskii transformation[†] requires that the cyclopropanone II be formed with direct displacement of the epoxide oxygen by the enolate ion (i.e. Ia), and consequently with inversion at C_4, viz:

[*] Cf. Ref. 4.   [†] Cf. Ref. 8.

[5] For a comprehensive review see: A. S. Kende, *Org. React.* 11, 261 (1960).
[6] G. Stork and I. Borowitz, *J. Amer. Chem. Soc.* 82, 4307 (1960).
[7] H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.* 83, 3972, 3980 (1961); H. O. House and H. W. Thompson, *J. Org. Chem.* 28, 164 (1963).
[8] E. E. Smissman, T. L. Lemke and O. Kristiansen, *J. Amer. Chem. Soc.* 88, 334 (1966).

The solvent, ethanol distilled over sodium would contain ~0·5% water, and hence fission of the cyclopropanone II would occur by a nucleophilic attack of either the ethoxide, or hydroxide, ion.* It has been suggested[6] that the 'normal' opening of a cyclopropanone, such as II, should result in the formation of a secondary carbanion (e.g. XIa) rather than a tertiary carbanion (e.g. IIIa). That is, a 'normal' hydroxy acid IX (R = H) rather than a 'puleganolic' acid III (R = H) should be the predominant product. Presently, the rearrangement of pulegone epoxide I, in ethanol, has given the *trans,trans*-hydroxy acid III (R = H) as the major product, whence the 'abnormal' opening of the cyclopropanone II may be ascribed to the inductive effect of the OH group of the carbinol substituent at C_4.

TABLE 1. FAVORSKII AND OTHER REARRANGEMENT PRODUCTS

Compound	Reagents	III	VII	IX	XI	XII	Neutrals*
Epoxide (I)	NaOEt/EtOH	62			trace	3	20%[b]
Epoxide (V)		2	4	46	4	2	22
Epoxide (I)	NaOEt/EtOH/H_2O	38			44	trace	18%
Epoxide (V)		9	24		51	trace	4

* Neutrals are calculated as $C_{19}H_{34}O_3$.
[b] Percentages relate to isolated products, the proportions of the hydroxy esters are estimated from gas chromatographic data.

IIIa   VIIa   XIa

XIVa   XIVb   XIVc   etc.
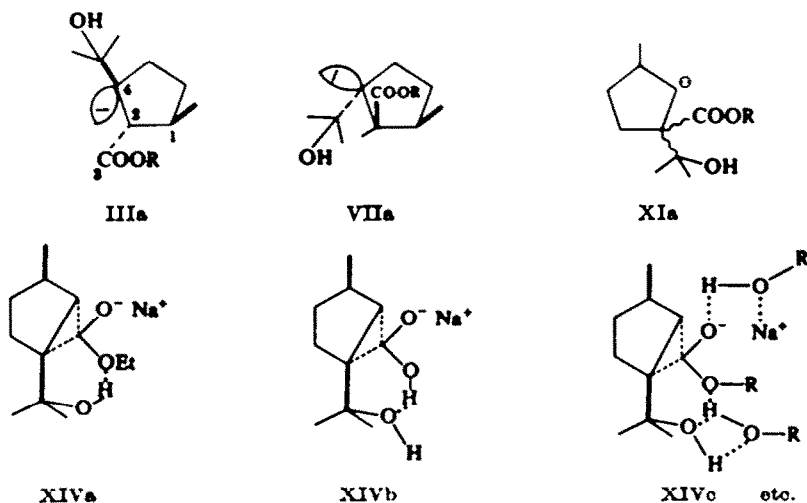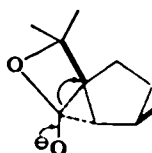
Further, the retention of configuration observed at C_4 in the *trans,trans*-hydroxy acid III (R = H), reflects a rapid protonation, formally represented as that of the carbanion IIIa. This rapid step could involve abstraction of a proton from the solvent (ethanol), from the dimethylcarbinol, appropriately positioned by intramolecular hydrogen bonding (e.g. XIVa); additionally, it could involve abstraction of a proton from the cyclopropanol (e.g. XIVb), if nucleophilic attack on the cyclopropanone II

* Subsequent hydrolysis of the ethyl esters results in the isolation of the hydroxy acids (or γ-lactones).

has been by hydroxide rather than ethoxide ion. Protonation by the solvent is likely to occur with retention at C_4 as protons from the solvent, hydrogen-bonded to the α-oriented oxygen-containing groups, are readily available (e.g. XIVc). On the other hand, the β-face is relatively hindered to an intermolecular approach by the solvent. In the absence of additional experimental evidence, a detailed mechanism for fission of the cyclopropanone II *via* a cyclopropanol type intermediate has not been proposed.* The anionic species obtained from the opening of the cyclopropanol is formally represented as IIIa; however, it is not intended to exclude mechanisms of a more concerted type (for example, XIVd). Structures XIVa–c illustrate further the availability of protons for retention of configuration at C_4 in the course of the rearrangement.
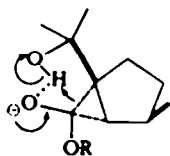
XIVd   XIVe

An intramolecular fission of the cyclopropanone II with retention of configuration at C_4, as in XIVe, would also account for the formation of the *trans,trans*-hydroxy acid III (R = H) from I. Intermolecular fission of the cyclopropanone (see XIVd) by ethoxide, or hydroxide, ion appears the more likely path.

Comparably, the rearrangement of epoxide V would be expected to give the *trans,cis*-hydroxy acid VII (R = H) as the major product. In fact, the major product is the *cis,trans*-γ-lactone IX, the *trans,cis*-hydroxy acid VII being a minor constituent (see Table 1). But the *trans,cis*-hydroxy ester VII (R = Et) is readily converted into the *cis,trans*-γ-lactone IX by the action of sodium ethoxide in ethanol, so that the Favorskii rearrangement, *via* the cyclopropanone VI, would have given essentially the *trans,cis*-isomer VII.† Isolation of the *cis,trans*-γ-lactone IX also implicates ethoxide, rather than hydroxide, ion in the nucleophilic attack on the cyclopropanone VI, as the ester VII (R = Et) readily undergoes epimerization.

The major products, VII and IX, are of the 'puleganolic' type. The predominant retention of configuration at C_4 again reflects a rapid protonation formally represented as that of the carbanion VIIa. The solvent, the OH group of the dimethylcarbinol (cf. XIVa) and/or the OH group of the cyclopropanol (cf. XIVb) are likely proton donors. Should the solvent be the proton donor, then an intermolecular approach to C_4 from the less hindered α-side (see VIIa) by ethanol would be possible, *in addition* to the steps already considered. The additional protonation step would result in partial inversion at C_4. The small amount of *trans,trans*-hydroxy acid III (R = H), invariably found among the products from V, could have resulted from such an inversion, together with an epimerization of the carboxylate group at C_2.

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* Cf. Ref. 9.

† It is now known[10] that the *trans,cis*-hydroxy acid VII is the major product from the reaction of sodium methoxide in dimethoxyethane on V.

⁹ D. J. Cram, *Pure and Appl. Chem.* 7, 155 (1963).

¹⁰ W. Reusch and P. Mattison, personal communication.

The isolation of a 'normal' hydroxy acid XI (R = H) as the major product from the rearrangement of each epoxide with sodium hydroxide in aqueous ethanol, distinguishes these reactions from those with ethoxide in ethanol (see Table 1). However, the additional acidic products obtained, in each case, are those already noted from the respective, and predominantly stereospecific, rearrangements in ethanol. That is, the *trans,trans*-hydroxy acid III (R = H) is also obtained from epoxide I, and the mixture of the *cis,trans*-γ-lactone IX and the *trans,cis*-hydroxy acid VII (R = H) from epoxide V.

The structure of the 'normal' hydroxy acid XI (R = H) has been established.[4] Gas chromatography of the hydroxy esters XI (R = Me) shows a single peak under a variety of conditions (Table 2). However, the 'normal' hydroxy ester from epoxide I has $[\alpha]_D$ −12°, and that from epoxide V has $[\alpha]_D$ −23°. The NMR spectra of those hydroxy esters show similar peaks assigned to the protons of the methyl substituent at C_1 (centered at δ 0·98, 3H), of the gemdimethyl moiety (δ 1·2, 6H), and of the methyl ester (δ 3·71 and δ 3·74 respectively, 3H). Each ester exhibits an individual, ill-defined, set of signals in the range δ 1·4–2·5. Thus the hydroxy esters, from I and V, are considered to be individual products, corresponding to the hydroxy acids IV and VIII (R = H), or *vice versa*. A stereospecific synthesis of IV and VIII is intended.

The present studies, and those of Reusch and Mattison,[10] establish through the isolation and characterization of the 'puleganolic' acids, that the rearrangements of epoxide I, and of epoxide V, in ethanol or in dimethoxyethane, involve the cyclopropanone intermediates, II and VI, respectively. The rearrangement of each epoxide in aqueous ethanol differs from the above reactions in that the major products are the 'normal' rather than the 'puleganolic' hydroxy acids. Nevertheless, these rearrangements, as shown by the stereochemistry of the associated 'puleganolic' products (Table 1), would again involve the stereospecific intermediates, II and VI, respectively. Hence, it is now proposed that epoxide I which yields the *trans,trans*-hydroxy acid III (R = H), would also yield the 'normal' hydroxy acid IV, and that epoxide V which gives the *trans,cis*-hydroxy acid VII (R = H) together with the *cis,trans*-γ-lactone IX, would also give the 'normal' hydroxy acid VIII. That is, IV and VIII would be derived *via* the cyclopropanone intermediates, II and VI, respectively. Whilst IV could be obtained by a direct displacement at C_4, in Ib, such a mechanism does not accommodate the formation of the associated 'puleganolic' acid III (R = H). The cyclopropanone mechanism which accommodates both products III and IV is preferred. A similar argument would apply in the case of VIII.
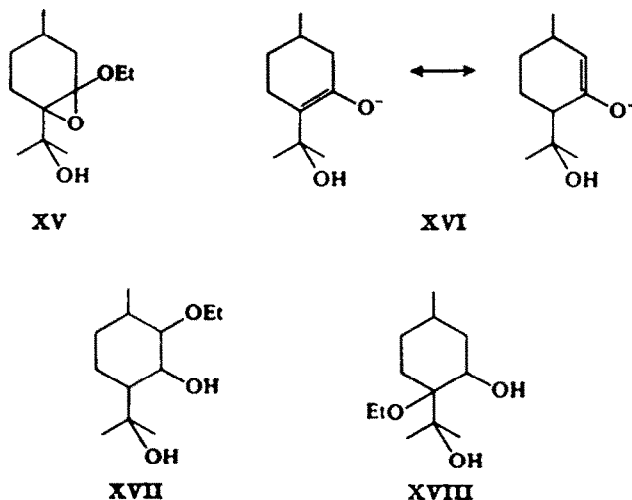

Ib
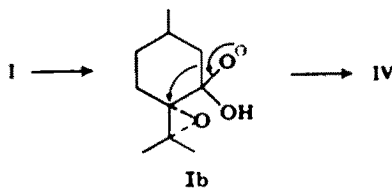
Quite recently it has been suggested[9] that the Favorskii rearrangement of 3-*e*-bromo-*trans*-2-decalone, and of 2-*e*-bromo-9-methyl-*trans*-3-decalone, occurs via a cyclopropanone intermediate in both polar and non-polar solvents, namely, ethanol and dimethoxyethane. Our findings on the Favorskii rearrangement of the pulegone epoxides in ethanol, and in aqueous ethanol, lend additional support to the proposal

that a dipolar or zwitterion intermediate is not necessarily involved in such rearrangements in polar media.

It remains to consider the structure of the 'anomalous' product, $C_{12}H_{24}O_3$, m.p. 113–114°, obtained from both epoxides. Structure XV, tentatively suggested for this compound,[4] is now excluded on the basis of additional elemental analyses, and the mass spectrum. A peak corresponding to a parent ion, m/e 216 is not observed, but the spectrum shows a base peak, m/e 198, and a further peak, m/e 201, which correspond to the loss of a molecule of water, and of a methyl group, respectively from the parent ion. The IR spectrum is transparent in the carbonyl region, but shows a strong OH absorption (ν_{max} 3410 cm^{-1}). The compound has one OEt group and the two active hydrogens are presumably those of the two OH groups. The compound does not appear to react with sodium periodate at room temperature. It is not readily dehydrated.

As the same product has been isolated from each of the epoxides I and V, it is reasonable to seek a common precursor: the dipolar ion XVI is a logical choice.[*] This intermediate, as the result of a nucleophilic substitution[7] and reduction of the carbonyl group,[11] with sodium ethoxide in ethanol, could yield the ethoxydiols XVII and XVIII. The 'anomalous' product may be represented by one of these structures, further studies are in progress.

XV   XVI

XVII   XVIII

EXPERIMENTAL

* Cf. Ref. 7.

[11] cf. C. S. Barnes and A. Palmer, *Austral. J. Chem.* 10, 334 (1957).

Pulegone epoxides I *and* V

A mixture of the epoxides (20 g), m.p. 39–41°, was obtained[1a] on treatment of D-(+)-pulegone†
(30 g), $[\alpha]_D$ +24·1°, with H_2O_2 (100 ml, 30%) in 4N NaOH (26 ml). The epoxides I and V were
separated from the mixture by repeated fractional distillation, and recrystallization.[3] Epoxide I was
obtained as colourless prisms, m.p. 57–57·5°, from light petroleum. (Found: C, 71·1; H, 9·5.
Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·6%), $[\alpha]_D$ +42·5° (MeOH), +43·8° (c, 8·14 in chf). Epoxide V
was obtained as fine needles, m.p. 54·5–55°, also from light petroleum. (Found: C, 71·1; H, 9·8%),
$[\alpha]_D$ −16·3° (c, 10·5 in chf). Reusch and Johnson[5] report $[\alpha]_D$ +48·0° (EtOH) for the epoxide,
m.p. 59°, and $[\alpha]_D$ −19·6° (EtOH) for the epoxide, m.p. 55°. On gas chromatography (butanediol
succinate, 130°, 60 ml/min), epoxide I has a retention time of 17 min 45 sec, and epoxide V of
11 min 40 sec. The NMR spectrum of each epoxide is in agreement with that previously reported.[6]
The rearrangement products of I and V are reported below.

Gas chromatography. Products were separated by gas chromatography: (i) A Perkin–Elmer
Fractometer 154D was used with He as carrier gas. Preparative separations were achieved on glass
columns (2 m × 10 mm), using 20% silicone oil (SE30), or 20% LAC-2R-446 on "Celite" (50–60
mesh). (ii) A Perkin–Elmer 800 gas chromatograph was used with N as carrier gas. Separations
were achieved (Table 2) on aluminium columns (2 m × 6 mm) with 5% stationary phase on
"Chromosorb G" (80–100 mesh). Retention times correspond to ±5 sec in an absolute time of
about ~15 min.

TABLE 2. GAS CHROMATOGRAPHIC DATA

Compounds	Retention Times					
	Silicone (SE30)		Apiezon L		Butanediol succinate	
'Normal' hydroxy esters (XI, R = Me)	11 min 30 sec		10 min 55 sec		10 min 45 sec	
cis,trans-γ-Lactone (IX)	11	20	12	45	20	45
cis,cis-γ-Lactone (X)	11	55	14	20	21	05
'Puleganolic' ester (III)	12	35	11	55	17	30
'Puleganolic' ester (VII)	13	40	14	05	20	35

Reaction of epoxide I *with sodium ethoxide in ethanol*

(a) Pulegone epoxide, m.p. 57–57·5°, (I, 50 mg) was treated with a solution of EtONa in EtOH
(1 ml).‡ The mixture was heated under reflux (5 hr). On cooling, and after evaporation of the bulk
of the solvent, water (2 ml) was added. The mixture was then extracted with ether (3 × 2 ml).
The ethereal layer, after drying and removal of solvent, gave a neutral fraction (10 mg, 20%). Gas
chromatography of the neutral fraction showed no 'normal' or 'puleganolic' type esters. This
fraction finally gave the 'anomalous' product, m.p. and mixed m.p. 113–114° (see below).

The original aqueous layer was acidified with HCl, extracted with ether (6 × 2 ml), and the
ethereal layer dried and treated with freshly prepared diazomethane. The methylated product,
purified by distillation, is essentially the *trans,trans*-hydroxy ester III (R = Me), (37 mg, 62%).
(Found: C, 65·7; H, 10·2. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·0%).§ Gas chromatography
(Apiezon L, and butanediol succinate) gave a major peak corresponding to that of an authentic
specimen,[4] (Table 2), methyl 3-methylcyclopentanecarboxylate (XII, ~3%) was also identified.

(b) In another experiment, pulegone epoxide I (1·4 g) gave a neutral fraction, partly polymeric
(0·79 g).‖ On distillation, and subsequent recrystallization, this neutral fraction yielded the
'anomalous' product (97 mg), as colourless needles, m.p. 113–114°, from light petroleum. $[\alpha]_D^{27}$

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* Cf. Ref. 4.
† Supplied by Keith Harris and Co. Ltd., Sydney.
‡ Reagent prepared from sodium (0·15 g) in EtOH (5 ml, freshly distilled over Na).
§ Cf. Ref. 4.
‖ The amount of the neutral fraction varies considerably from run to run, and often contains
much polymeric material. Little variation is noted in the proportions of individual Favorskii products
in the acidic fraction.

+44·7° (*c*, 2·44 in chf). (Found: C, 66·6; H, 11·1; OC$_3$H$_5$, 18·0; active H. 0·89. C$_{13}$H$_{24}$O$_3$ requires: C, 66·6; H, 11·2; 1 × OC$_3$H$_5$, 20·9; 2 × active H, 0·92%.) Mixed m.p. with the 'anomalous' product, m.p. 106° from the epoxide mixture,[4] was undepressed.

Reaction of epoxide I with sodium hydroxide in aqueous ethanol

Pulegone epoxide I (100 mg) in EtOH (0·7 ml) was heated under reflux (5 hr) with 4N NaOH (0·3 ml). After removal of the solvent, water (1 ml) was added, and the mixture extracted with ether. The ethereal layer, worked-up as above, gave a neutral fraction (18 mg). The original aqueous layer was acidified (HCl), and extracted with ether. This ethereal soln, after treatment with an excess of diazomethane, gave a mixture of esters (97 mg) which were separated by gas chromatography. The 'normal' hydroxy ester (possibly IV, 44%), further purified by distillation, has [α]$_D$ −12° (*c*, 1·9 in chf). Its retention times on three columns (Apiezon L, butanediol succinate, and SE30) correspond to those of the 'normal' hydroxy ester XI[4] (Table 2). The *trans,trans*-hydroxy ester III, (38%) was also present and, in addition, gas chromatography indicated trace quantities of XII and possibly XIII.

Reaction of epoxide V with sodium ethoxide in ethanol

Pulegone epoxide, m.p. 54·5–55°, V (0·5 g) in EtOH (4 ml) was treated with EtONa soln, prepared from Na (0·3 g) in EtOH (5 ml, freshly distilled from Na), and the soln heated under reflux (5 hr). After cooling and removal of the bulk of the solvent, the mixture was diluted with water (10 ml) and extracted with ether (3 × 4 ml). The ethereal layer, worked up as above, gave a crystalline product (0·14 g, 22%) after distillation. On recrystallization from light petroleum it had m.p. and mixed m.p. 113–114°, with a specimen from epoxide I. [α]$_D$ +46·6° (*c*, 2·17 in chf). (Found: C, 66·8; 66·5; H, 11·3, 10·9; OC$_3$H$_5$, 18·0; active H, 0·93. Calc. for C$_{13}$H$_{24}$O$_3$: C, 66·6; H, 11·2; 1 × OC$_3$H$_5$, 20·9; 2 × active H 0·92%.) Gas chromatography of the crude neutral fraction showed no 'normal' or 'puleganolic' type esters.

The aqueous layer was acidified (HCl), and extracted with ether (6 × 4 ml) and the ethereal layer then dried and treated with freshly distilled diazomethane. The solvent was removed, and the product distilled to give a lactone-hydroxy ester mixture (0·36 g). The mixture contains 2% of the *trans,trans*-hydroxy ester III, and approximately 2% of methyl 3-methylcyclopentanecarboxylate, as shown on gas chromatography (butanediol succinate). The *trans,trans*-hydroxy ester III was then separated by preparative gas chromatography (LAC-2R-446, 160°, 250 ml/min). Its IR spectrum and retention times (Apiezon L, butanediol succinate and SE30 columns) correspond to those of an authentic specimen.[4] The remaining product, on gas chromatography (SE30), was shown to consist of the *cis,trans-γ*-lactone IX (80%) and the *trans,cis*-hydroxy ester VII (20%). This mixture was separated by preparative gas chromatography (SE30). The *cis,trans-γ*-lactone IX was identified by comparison of its IR spectrum and retention times (Table 2) with those of an authentic specimen.[*] The *trans,cis*-hydroxy ester VII was characterized by the reactions reported below. (Found: C, 65·9; H, 10·5. C$_{11}$H$_{20}$O$_3$ requires: C, 66·0; H, 10·0%.)

Reaction of the epoxide V with sodium hydroxide in aqueous ethanol

Pulegone epoxide V (500 mg) in EtOH (4 ml) was added to 4N NaOH (3 ml) and the mixture heated under reflux (5 hr). The reaction was worked-up as above, giving a neutral product (20 mg, 4%). The methyl ester fraction (470 mg) was shown by gas chromatography (Table 2) to contain a 'normal' hydroxy ester (possibly VIII, 51%) [α]$_D$ −23° (*c*, 1·9 in chf). The *trans,cis*-hydroxy ester VII and the *cis, trans-γ*-lactone IX were obtained in a combined yield of 24%,[†] with the *trans,trans*-hydroxy ester III, (9%). Again, the products were characterized by gas chromatography, and by comparison of IR spectra.

Reactions of the trans,cis-hydroxy ester VII

(a) The *trans, cis*-hydroxy ester VII, (R — Et, 50 mg) was heated under reflux (5 hr) with EtONa in EtOH (1 ml, 0·48N). After cooling, the solvent was evaporated, water (0·5 ml) added and the

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* Cf. Ref. 4.

† The fraction contains approx. 20% of the *trans,cis*-ester (VII).

mixture extracted with ether. The ethereal layer, after drying and removal of solvent, gave a neutral polymeric fraction (10 mg, 20%). The aqueous layer was acidified (HCl), and extracted with ether. This ethereal extract was treated with NaHCO₃aq, whence the *cis,trans-γ*-lactone (20 mg) remained in the ethereal layer. The aqueous layer was re-acidified (HCl), re-extracted with ether, dried and then treated with excess of a diazomethane soln. Evaporation of the solvent gave an ester fraction (7 mg), shown by gas chromatography (Table 2), to contain the *cis,trans-γ*-lactone IX (20%) and the *trans,cis*-ester VII, (80%). The overall ratio of the *cis,trans-γ*-lactone IX to the *trans,cis*-hydroxy ester VII is 5:1. Under similar conditions, the *trans,trans*-hydroxy ester III was not epimerized.

(b) The ester VII, (20 mg) was refluxed (8 hr) with MeOH (0·1 ml) and 10N HCl (35 µl). The solvent was evaporated and water (0·5 ml) added. The mixture was then extracted with ether (6 × 0·5 ml), washed and dried. Removal of the solvent gave the *cis, cis-γ*-lactone X, (10 mg, 60%). Its IR spectrum and retention times (Apiezon L, Butanediol succinate and SE30 columns) correspond to those of an authentic specimen, prepared from *cis*-pulegenic acid.* No other products were identified.

Attempted epimerization of the cis,cis- and cis,trans-γ-lactones

Attempted epimerization of the *cis,cis-γ*-lactone X, (200 mg) with EtONa in EtOH (0·5 ml, 1N) led to the recovery of the *cis,cis-γ*-lactone X, (172 mg, 86%), m.p. 48–49° from light petroleum. Wallach[11] reports m.p. 50–51°. No *trans, trans*-hydroxy ester III was detected on gas chromatography. Similarly, an attempted epimerization of the *cis,trans-γ*-lactone IX, (50 mg) resulted in the recovery of starting material (37 mg, 74%). No additional 'puleganolic' products were detected by gas chromatography.

* Cf. Ref. 4.

[11] O. Wallach, *Liebigs Ann.* **392**, 49 (1912).