Tetrahedron, 1967, Vol. 23, pp. 1953 to 1962. Pergamon Press Ltd. Printed in Northern Ireland

THE FAVORSKII REARRANGEMENT OF PULEGONE OXIDE

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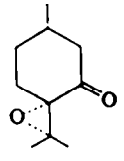
(*Received in USA* 28 *May* 1966; *accepted for publication* 8 *August* 1966)

Abstract—The stereoisomeric pulegone oxides I and II undergo a stereospecific Favorskii rearrangement when treated with sodium methoxide in refluxing glyme. The major products are identified by spectroscopic measurements and by conversion to pulegenic esters (X A,B) and puleganolides (XIII A,B). Abnormal opening of the cyclopropanone intermediates predominates, and the protonation at C-4 proceeds with exclusive retention of configuration. The configurations assigned to I and II in a previous paper[2] must therefore be reversed.

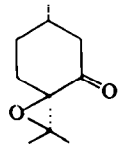
ALTHOUGH an epoxide derivative of pulegone was prepared almost four decades ago,[1] the isolation and characterization of pure diastereoisomeric pulegone oxides was not accomplished until 1963.[2,3] The physical properties of these stereoisomers, reported in our earlier paper,[2] are repeated in Table 1. As part of our previous investigation, interpretations of IR, UV and NMR spectra and ORD led to the assignment of configurations B and A to isomers I and II respectively. However, the recent report[4]

TABLE 1. SOME PROPERTIES OF THE PULEGONE OXIDES

Isomer	m.p.	$\lambda_{max}^{heptane}$ (ε)	$\nu_{max}^{CCl_4}$	$[\alpha]_D^{EtOH}$
I	59°	303 mμ (31)	1727 cm^{-1}	+48·0
II	55°	303 (31)	1728	−19·6



A

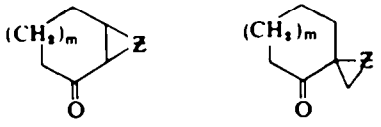


B

of a reversal in the "Octant Rule"[5] as applied to conjugated cyclopropyl ketones and epoxy ketones has seriously weakened this correlation. The data presented[4] convincingly supports the thesis of Octant Rule reversal in compounds of structure III; but examples having spiro configuration (IV) were limited and the argument assumed involvement of near octants, a fact not evident from models. Since the pulegone oxides fall into the latter category, a change in our initial assignment was not required; nevertheless, we though it advisable to resolve any uncertainty by effecting a direct

[1] M. N. Prileschaev, *Bull. Soc. Chim. Fr.* (iv) **41**, 687 (1927).
[2] W. Reusch and C. K. Johnson, *J. Org. Chem.* **28**, 2557 (1963).
[3] E. Kline and G. Ohloff, *Tetrahedron* **19**, 1091 (1963).
[4] C. Djerassi, W. Klyne, G. Ohloff and E. Klein, *Tetrahedron* **21**, 163 (1965).
[5] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

configurational correlation by chemical means. This has now been accomplished by means of a stereospecific Favorskii reaction.



III IV

Z = O, CH_2

The Favorskii rearrangement of α-halo ketones to carboxylic esters is believed to proceed via cyclopropanone intermediates.[6,7] Since stereospecific rearrangement has been observed[8] in nonpolar solvents, the formation of the cyclopropanone ring must in these cases occur by by direct displacement (as in V[9]) without intervention of a mesomeric zwitterion species such as VI. The lack of stereospecificity sometimes observed for reactions in polar solvents has in fact been attributed to the involvement of such zwitterionic intermediates.[10-13] A related characteristic of reactions in polar solvents is the often significant and sometimes predominant formation of solvolysis products (e.g. α-alkoxy ketones), probably as a result of zwitterion stabilization in these solvents.

V VI

At the beginning of this investigation, it was not at all certain that the Favorskii rearrangement would provide a satisfactory means of determining the configurations of the pulegone oxide stereoisomers. Only a few examples of Favorskii rearrangements with α,β-epoxy ketones are known,[12a,14] and Smissman[11] has pointed out that an entirely different mechanism may operate in these substrates. Assuming a similar mechanism, however, the potential complexity of the reaction is illustrated in Chart I. In order to effect a stereospecific transformation of I and II, it was clearly necessary to avoid formation of the zwitterion intermediate VIII. Experience suggested this would be most readily accomplished by employing a nonpolar solvent for the rearrangement, a fact nicely illustrated by the work of House[12a] (Eq. 1).

[6] A. S. Kende, *Org. Reactions* **11**, 261 (1960).
[7] N. Turro and W. Hammond, *J. Amer. Chem. Soc.* **87**, 3258 (1965).
[8] G. Stork and I. Borowitz, *J. Amer. Chem. Soc.* **82**, 4307 (1960).
[9] A previous suggestion by House and Thompson[10] (and more recently by Smissman *et al.*[11]) that in conformationally rigid α-halocyclohexanones an equatorial orientation of X is necessary for rearrangement, should be reconsidered in view of the recent work by H. O. House and G. A. Frank, *J. Org. Chem.* **30**, 2948 (1965).
[10] H. O. House and H. W. Thompson, *J. Org. Chem.* **28**, 164 (1963).
[11] E. Smissman, T. Lemke and O. Kristiansen, *J. Amer. Chem. Soc.* **88**, 334 (1966).
[12a] H. O. House and W. Gilmore, *J. Amer. Chem. Soc.* **83**, 3972 (1961);
[b] H. O. House and W. Gilmore, *Ibid.* 3980 (1961).
[13] R. Deghenghi, G. Schilling and G. Papineau-Couture, *Canad. J. Chem.* **44**, 789 (1966).
[14] W. Treibs, *Ber. Dtsch. Chem. Ges.* **66**, 610, 1483 (1933) and earlier papers.

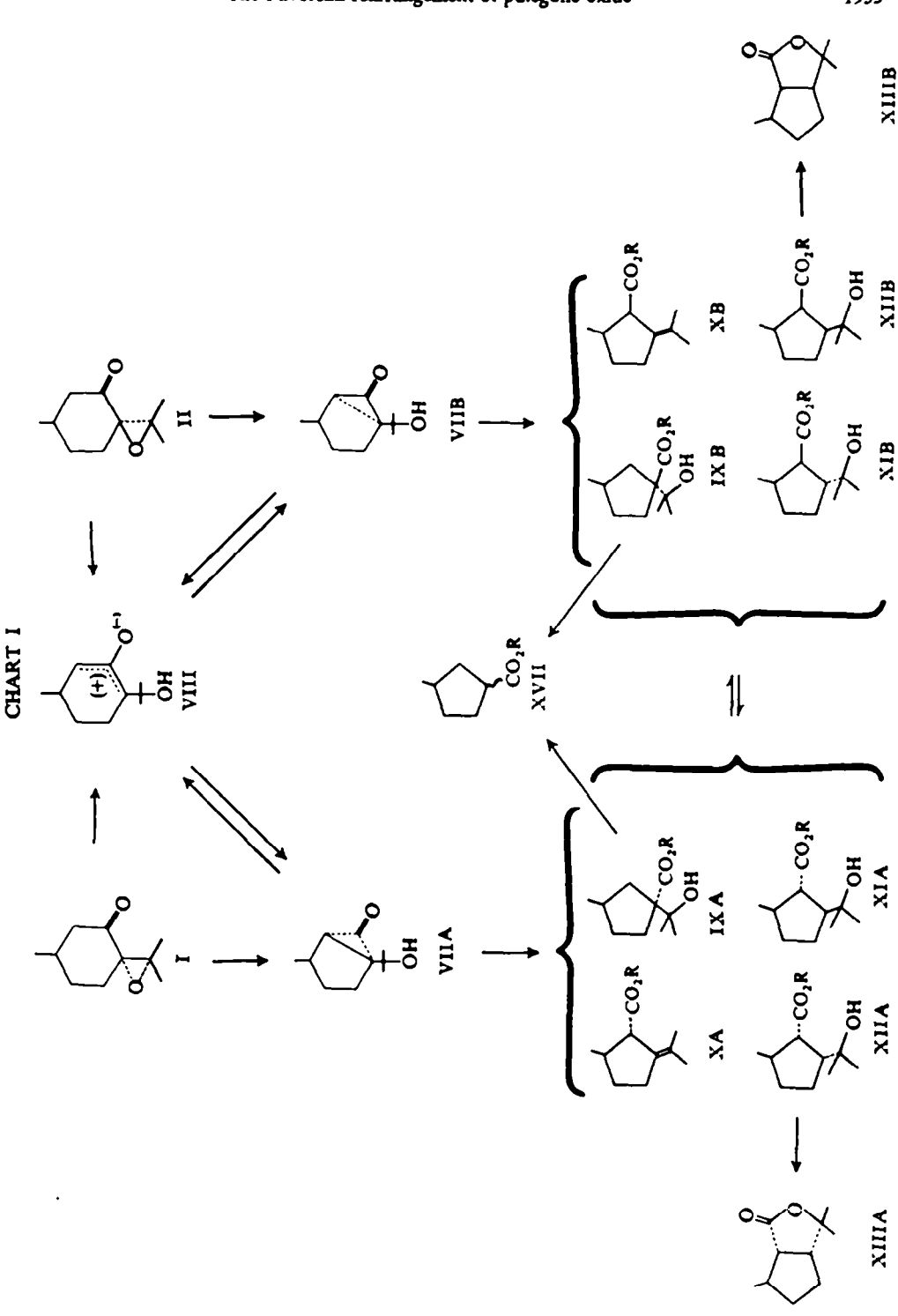
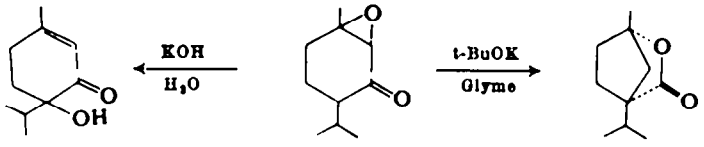
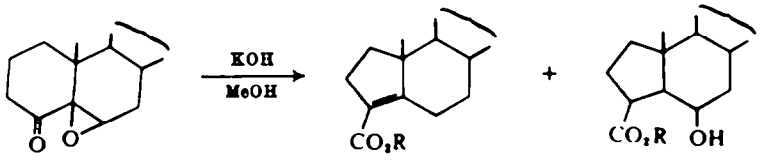


CHART 1
I
II
VIIA
VIIB
VIII
XVII
XA
XB
IXA
IXB
XIA
XIB
XIIA
XIIB
XIIIA
XIIIB
CO2R
OH



88% 73% (1)

By analogy with other Favorskii rearrangements,[6] base catalyzed opening of cyclopropanones VIIA and VIIB would be expected to occur at the least substituted α-carbon atom, yielding IX_A and IX_B respectively. It is, however, the products from "abnormal" cyclopropanone cleavage that will be of value in the correlation of configuration. The pulegenic acids (X_A and X_B) and the puleganolides ($XIII_A$ and $XIII_B$) have been isolated and unambiguously characterized by Wolinsky.[15,16] Thus, if the rearrangement of I and II leads stereospecifically to products that are readily converted to puleganolides or pulegenic acid derivatives the correlation will be successful. There were in fact reasons for believing that "abnormal" opening would predominate in these reactions. We had previously observed[17] that cholestane-4-one-5β, 6β-oxide (XIV) gave a mixture of XV and XVI (R = H and Me) when treated with methanolic potassium hydroxide. The stereochemistry of XVI was not rigorously demonstrated, and in the absence of similar experiments with the corresponding α-epoxide no conclusions concerning the stereospecificity of this reaction could be



XIV XV XVI (2)

made. In 1963 it was reported[18] that a mixture of pulegone oxide stereoisomers reacted in refluxing ethanolic sodium ethoxide to give a 3:1 mixture of $XIII_A$ and XI_A in an overall yield of 20%. It was not possible to interpret this result unambiguously, and the rearrangement may have been stereoselective rather than stereospecific.

The above observations were encouraging but it was recognized that even if "abnormal" cyclopropanone opening predominated in the rearrangement of the pulegone oxides, a complex array of products could still result. Thus, the electrophilic protonation at the α-carbon atom may occur with retention of configuration (giving XI_A and XI_B) or inversion (giving XII_A and XII_B) or both. Furthermore, if the acids or esters initially formed in the rearrangement are epimerized, any stereospecificity inherent in the reaction could very well be lost.

Favorskii rearrangement of the pulegone oxide stereoisomers (I and II) was effected by refluxing a 1,2-dimethoxyethane (glyme) solution of each isomer with ca. four equivalents of sodium methoxide. The solvent contained approximately 0·3% water which caused the Favorskii products to form as the acids rather than the

[15] J. Wolinsky, H. Wolf and T. Gibson, *J. Org. Chem.* **28**, 274 (1963).
[16] J. Wolinsky, T. Gibson, D. Chan and H. Wolf, *Tetrahedron* **21**, 1247 (1965).
[17] Ronald LeMahieu, Ph.D. thesis, Michigan State University, 1963.
[18] S. Achmad and G. Cavill, *Austr. J. Chem.* **16**, 858 (1963).

more readily epimerized methyl esters. These acids were easily separated from a small amount of neutral material and represented a 70 to 85% conversion of the epoxy ketone. The mixture of esters produced by treating the crude acidic product with diazomethane was analyzed by VPC. Pure samples of the various components were collected and identified by IR and NMR spectroscopy. The results of these experiments are presented in Table 2.

TABLE 2. ACIDIC PRODUCTS FROM FAVORSKII REARRANGEMENT OF I AND II

Pulegone Oxide Isomer	% Yield*					
	X_A	XI_A	$XIII_A$	X_B	XI_B	XVII
I	29	50	—	—	—	21
II	12	—	21	11	33	15

* Obtained by VPC analysis.

The rearrangement of isomer I is remarkably stereospecific, and although the products from isomer II have suffered some epimerization of the carboxylate groups, the stereospecificity in this reaction is clearly evident. Methyl *trans*-pulegenate (X_A, R = CH_3) and *trans, trans*-hydroxy ester XI_A (R = Me) were both converted to *cis, trans*-puleganolide ($XIII_A$) by refluxing with a methanol–hydrochloric acid mixture. The spectra of X_A (R = CH_3) and $XIII_A$ were identical with those of authentic samples.[19] In parallel reactions X_B (R = Me) and XI_B (R = Me) were converted to the *cis, cis*-puleganolide ($XIII_B$). Although the stereoisomeric puleganolides ($XIII_A$ and B) are poorly resolved by our VPC procedures, the IR and NMR spectra have strong characteristic absorptions that permit easy identification and analysis.

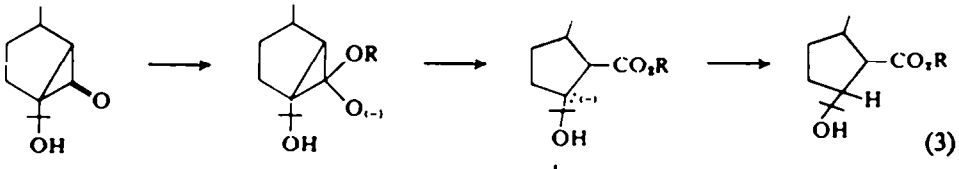
The absence of hydroxy acids XII_A and XII_B and of *cis, cis*-puleganolide ($XIII_B$) among the products of these reactions is striking. In order to rule out the possibility that facile epimerization of these compounds had occurred during the lengthy reflux with base, a 4:1 mixture of $XIII_A$ and $XIII_B$ was subjected to identical treatment and was recovered unchanged after similar work up. Furthermore, when the Favorskii rearrangement of II was carried out for a much shorter reaction period (1 hr *vs.* 19 hr) the only significant change in the products was recovery of ca. 40% of the epoxy ketone. No attempt was made to separate or rigorously identify the 3-methylcyclopentylcarboxylic acid mixture (XVII A and B) obtained from both pulegone oxide isomers. This material is undoubtedly formed from the "normal" Favorskii products (IXA and B) by retroaldol fragmentation, as originally suggested.[18] The Favorskii rearrangement of both I and II also yielded a small amount (ca. 10%) of a neutral material which did not absorb in the carbonyl region of the IR. We have not investigated this mixture, since Prof. Cavill has notified us that a study of these neutral products is now in progress.

DISCUSSION

Two unusual aspects of these Favorskii rearrangements deserve elaboration. The first is the predominate "abnormal" opening of the cyclopropane intermediates,

[19] Kindly provided by Prof. J. Wolinsky.

which finds analogy in the rearrangements of α,β-dihaloketones.[6] For example, pulegone dibromide is converted to a mixture of *trans*- and *cis*-pulegenic acids by heating with aqueous alkali.[15,20,21] Two explanations for this mode of reaction readily come to mind. Either the inductive effect of the electronegative β-substituent is strong enough to reverse the predilection for cleavage at the less substituted α-carbon (Eq. 3), or a concerted cyclopropane opening—elimination process (Eq. 4) provides an energetically favored alternate reaction path. It is not possible to choose between these mechanisms on the basis of the α,β-dihaloketone reactions, since only elimination products are obtained. However, in the epoxy ketone work reported here only a small portion of the substrate undergoes β-oxygen elimination; consequently, we favor the former rationale for the abnormal opening.



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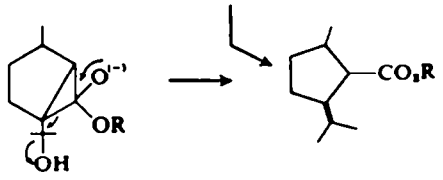
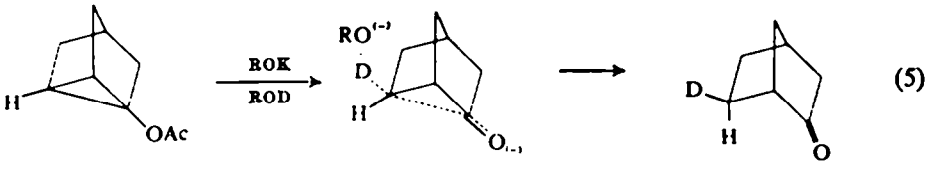


(4)

The second noteworthy feature in these rearrangements is the exclusive retention of configuration during electrophilic protonation at C-4. Although this stands in striking contrast to the predominant inversion of configuration observed[22] in the base catalyzed opening of 1-nortricyclanol to norcamphor (Eq. 5), it agrees well with the principles of carbanion substitution disclosed by the comprehensive studies of Cram.[23]



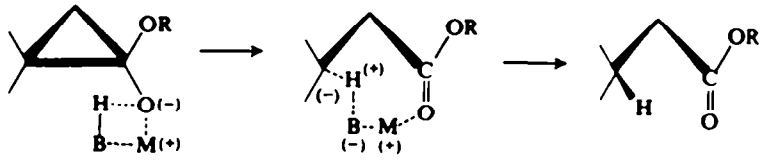
(5)

XVIII

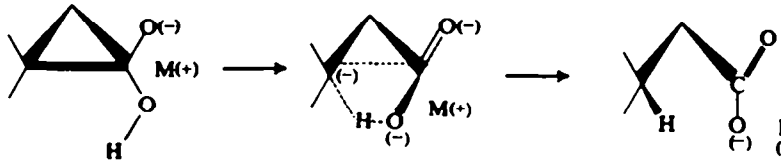
According to the latter work, the stereochemical course of cleavage reactions in which a carbon-carbon bond is broken heterolytically depends on the solvent employed and the cation accompanying the base. In solvents of low dielectric constant and with alkali metal cations a high degree of retention of configuration was observed. The stereochemistry was relatively insensitive to the concentration and pK_a of the electrophilic reagent and the structure of the leaving group. When solvents having high

[20] O. Wallach, *Liebig's Ann.* **414**, 233 (1918).
[21] J. Wolinsky and D. Chan, *J. Org. Chem.* **30**, 41 (1965).
[22] A. Nickon, J. Hammons, J. Lambert and R. Williams, *J. Amer. Chem. Soc.* **85**, 3713 (1963).
[23] D. J. Cram, *Fundamentals of Carbanion Chemistry* p. 144. Academic Press, New York (1965).

dielectric constants and pK_as were employed (e.g. DMSO), complete racemization occurred in almost every case. Similar results attended the use of quaternary ammonium bases in low dielectric constant solvents. Finally, proton donating solvents having high dielectric constants gave moderate inversion of configuration. Since our reaction conditions clearly fall into the first classification, the retention of configuration at C-4 appears reasonable. The mechanism presented in Eq. 6 is based on Cram's suggestions. Alternatively, an intramolecular protonation as in Eq. 7[24] may play an



(6)



(7)

important role. An explanation for the opposite stereochemical course observed in cyclopropanol opening[22,25] remains to be found. At first we believed the answer lay in the acidic solvents (ROH) used by Nickon and DePuy. Thus, inversion of configuration requires that a proton donating species be available at the back side of the carbon atom experiencing electrophilic substitution (e.g. XVIII). The relatively small amounts of Brønsted acids present in our experiments would tend to be oriented at the front of the cyclopropane system (as in Eq. 6), and consequently retention of configuration would result. However, Prof. G. W. K. Cavill has carried out similar rearrangements of I and II using ethanol as a solvent, and finds retention of configuration to be predominant.[26] The suggestion that inversion transition states (e.g. XVIII) are preferred when sufficient acid is available is thus untenable.

The chief difference between Prof. Cavill's results and ours appears to be the absence of pulegenic acid derivatives among his products. This fact is nicely explained by considering the relative concentrations of protons donors in the two studies. The Australian group worked with a proton rich system in which carbanionic intermediates could not long survive. On the other hand, the low concentration of acids employed in our work has prevented the solvation necessary for internal stereospecific protonation (Eqs. 6 and 7) from being achieved in all cases. Some of the cyclopropanone intermediates must therefore suffer heterolysis to a carbanionic species which, in the absence of a proton source, can only collapse to hydroxide ion and a pulegenic acid derivative.

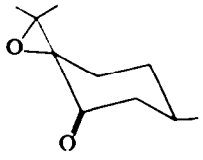
The stereospecific Favorskii rearrangement reported here requires that our initial assignment of configurations B and A to isomers I and II respectively must be reversed.

[24] The OH group of the dimethylcarbinol side chain could also provide an internal proton source. In this case the transfer may proceed by both retention and inversion of configuration at C-4; however, hydrogen bonding to an oxygen function at C-3 would favor retention.

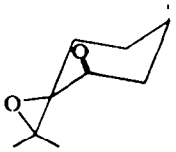
[25] C. H. DePuy and F. Breitbeil, *J. Amer. Chem. Soc.* **85**, 2176 (1963).

[26] We thank Prof. Cavill for communicating his findings to us prior to publication.

This leaves us with the problem of how to best interpret the data from which the previous assignment was made. A detailed conformational analysis of these isomers will be presented in a future paper, and for the present discussion it is sufficient to point out that conformations Ia and IIa adequately account for the properties of I and II. In this interpretation the octant rule is applied in the normal fashion.



Ia



IIa

EXPERIMENTAL

VPC analyses were made with an Aerograph A-90-P instrument. IR spectra were determined with a Perkin-Elmer 237B spectrophotometer. NMR spectra were determined with a Varian associates A-60 high resolution spectrometer, using TMS as an internal standard.

Reagents. Pulegone oxide isomers I and II were prepared according to the procedure in our earlier paper[9] and exhibited properties identical to those reported therein.

Dimethoxyethane (glyme) was obtained from Aldrich Chemical Co. The amount of water present in this solvent was determined by reaction with NaH, the H_2 evolved being measured by a gas buret. Values from 0·25 to 0·30% were obtained.

Commercial MeONa (Matheson, Coleman and Bell) was used.

Favorskii reaction of pulegone oxide I

A. A soln of I (300 mg, 1·8 mmoles) and MeONa (435 mg, 8·0 mmoles) in glyme (30 ml) was refluxed for 19 hr. After cooling, the mixture was taken up in ether and extracted 3 times with 10% NaOHaq. The combined aqueous portions were acidified with HClaq (pH < 1), and then extracted with ether. The combined ether extracts, after being washed, dried and evaporated, yielded 210 mg of an oily acidic material.

The original organic layer was washed, dried and evaporated, yielding 115 mg of a light oil. Analysis of this material by VPC (4% QF-1 on 60/80 Chromosorb G at 140°) disclosed that the major component was glyme (ca. 80%); the remaining neutral products (retention times 3·3 and 4·4 min) exhibited OH absorption but no CO absorption in the IR.

The crude acid products were methylated with diazomethane, and analysis (VPC same conditions) showed 3 components having retention times of 1·3, 2·5 and 6·5 min. These were identified as XVII, XA and XIA (R = Me) (integrated areas 3:4:7 respectively) by a combination of spectroscopic and chemical evidence.

(1) The IR spectrum of XVII showed CO absorption at 1730 cm^{-1}, but no OH bands. Only end absorption was observed in the UV. The NMR spectrum exhibited a pair of doublets at τ 9·03 and 8·97 (J ≈ 7 c/s, area 3), a singlet at τ 6·41 (area 3) and broad absorption from τ 7·0 to 8·9 (area 8·5).

(2) The IR spectrum of XA (R = Me) was identical with that of an authentic sample of methyl *trans*-pulegenate.[10] The NMR spectrum exhibited a doublet at τ 8·99 (J = 7 c/s, area 3), a pair of Me singlets centered at τ 8·40 and separated by 5 c/s (area 6), a singlet at τ 6·42 (area 3) and broad absorption from τ 7·0 to 8·3 (area 6).

(3) The IR spectrum of XIA (R = Me) showed OH absorption at 3500 cm^{-1} and CO absorption at 1730 cm^{-1}. The NMR spectrum exhibited a doublet at τ 8·98 (J = 6 c/s, area 3), a singlet at τ 8·90 (area 6), a singlet at τ 6·37 (area 3) and broad absorption from τ 7·5 to 8·8.

(4) *Conversion of* XA *to* XIIIA. A soln of XA (R = Me) (60 mg) in 2 ml MeOH containing 0·5 ml conc. HCl was refluxed for 7 hr. The reaction mixture was dissolved in ether, washed, dried and concentrated. The oily residue (40 mg) was analyzed by VPC (5% FFAP on 60/80 Chromosorb G at 150°); the most readily eluted component was unreacted XA (19%), a minor unidentified material

(7%) followed and the major product (74%), which was the last to appear, was identified as *cis, trans*-XIIIA. The IR and NMR spectra of the XIIIA isolated here were identical with those reported by Wolinsky.[19]

(5) *Conversion of* XIA *to* XIIIA. A soln of XIA (R = Me) (65 mg) in 3 ml MeOH containing conc. HCl (1 ml) was refluxed for 5 hr and worked up by the previous procedure. The oil thus obtained (52 mg) was analyzed by VPC and proved to be a mixture of XA (27%), XIIIA (30%), unreacted XIA (22%) and an unidentified component (22%) exhibiting absorption at 1730 cm^{-1} in the IR. This compound may be a γ,δ-unsaturated isomer of XA.

B. A soln of I (100 mg) and MeONa (145 mg) in glyme (10 ml) was refluxed 19 hr followed by a work-up procedure similar to that used above. The acidic product (75 mg) was dissolved in 2 ml MeOH containing 0·8 ml conc. HCl, and this soln was refluxed 1 hr followed by the usual work-up. The resulting oil (52 mg) was analyzed by VPC and IR spectroscopy and proved to be 90% XIIIA.

Favorskii reaction of pulegone oxide II

A. A soln of II (600 mg, 319 mmoles) and MeONa (870 mg) in glyme (60 ml) was refluxed for 19 hr and subjected to the same work-up procedure employed with isomer I. The neutral product (41 mg) showed 3 components on VPC analysis, and IR spectra of these disclosed no CO absorption. Analysis of the acidic product mixture (501 mg), after methylation with diazomethane, demonstrated the presence of 5 components: XVII (15%), an equimolar mixture of XA and XB (R = Me) which was not resolved by the VPC technique used here (23%), XI_B (R = Me) (33%), XIIIA (22%) and an unidentified component (8%). The proof for these structures rested on spectroscopic and chemical correlations.

(1) The mixture of XA and XB (R = Me) exhibited an IR spectrum consistent with a mixture of *cis*- and *trans*-methylpulegenates. The NMR spectrum showed a pair of doublets at τ 9·03 and 8·98 (J = 6·5 c/s) (area 3·2), a broad singlet at τ 8·37 (area 6·1), a pair of singlets centered at τ 6·41 and separated by 1 c/s (area 3), and a broad absorption from τ 8·3 to 6·7.

(2) The IR spectrum of XIB (R = Me) showed OH absorption at 3500 cm^{-1} and CO absorption at 1730 cm^{-1}. The NMR spectrum exhibited a doublet at τ 9·12 (J = 6·5 c/s) (area 3), a singlet at τ 8·98 (area 6), a singlet at τ 6·37 (area 3) and broad absorption from τ 8·4 to 7·1.

(3) The IR and NMR spectra of XIIIA from this reaction were identical to corresponding spectra of authentic *cis, trans*-puleganolide.[19]

(4) *Conversion of* XA *and* XB *to* XIIIA *and* XIIIB. A 50 mg sample of the XA + XB mixture was dissolved in 2 ml MeOH containing 0·8 ml conc. HCl and refluxed for 5 hr. The usual work-up gave 20 mg of an oil which VPC analysis showed to consist of at least 4 components. These were identified as starting material (21%), XIIIA (40%), XIIIB (33%) and an unidentified material (6%). The stereoisomeric puleganolides XIIIA and XIIIB were characterized by VPC retention time and IR spectra.

(5) *Conversion of* XIB *to* XB *and* XIIIB. A soln of 48 mg XIB (R = Me) in 3 ml MeOH containing 1 ml conc. HCl was refluxed for 5 hr and subjected to the usual work-up procedure. At least 3 components were disclosed by VPC analysis of the crude product (37 mg). The first to be eluted (32%) was identified as XB by comparison with authentic methyl *cis*-pulegenate.[19] The next component (15%) was not identified. The major component (53%) proved to be XIIIB by comparison of its IR spectrum with that of authentic *cis, cis*-puleganolide.[19]

B. A soln of II (600 mg) and MeONa (870 mg) in 60 ml glyme was refluxed for 1 hr and worked up by the procedure used for the previous Favorskii reactions. The neutral product (219 mg) was analyzed by VPC and proved to be largely (90%) recovered II. The remaining neutral material was homogeneous to VPC and exhibited an IR spectrum similar to that found for a mixture of XA and XB.

The acidic product (283 mg) was treated with diazomethane and analyzed by VPC. The major products were XVII (19%), XA + XB (30%), XIB (20%) and XIIIA (21%). Identification was based on VPC retention times and IR spectra.

Treatment of XIB *with base*

A 47 mg sample of XIB (R = Me) was mixed with 20 ml of 10% NaOHaq, heated with vigorous stirring to 60°, and allowed to stand for 14 hr. Acidification to pH < 1 followed by ether extraction yielded 39 mg crude product. This was treated with diazomethane and analyzed by VPC and IR spectroscopy. Only recovered XIB was observed.

Treatment of XIIIA *and* XIIIB *with base*

A soln of XIIIA (50 mg), XIIIB (15 mg) and MeONa (87 mg) in 6 ml glyme was refluxed for 19 hr. A work-up similar to that used previously gave 48 mg crude material (both neutral and acidic) which was treated with diazomethane (no apparent reaction) and analyzed by VPC. Only recovered starting material was detected.

Note added in proof—A recently reported study by P. Wharton and T. Blair, *J. Org. Chem.* **31**, 2480 (1966), has shown that endo- and exo-7-hydroxy-1,6-dimethyl[4.1.0]bicycloheptane undergoes base catalyzed ring opening (potassium t-butoxide in t-butyl alcohol) with >90% retention of configuration.

Acknowledgements—A National Institutes of Health predoctoral fellowship to Mr. Mattison helped support this work. The senior author (W. R.) wishes to thank the Chemistry Department of Stanford University for its hospitality during the 1965–1966 academic year.