mary solvent isotope effect would be associated with this reaction were the role of the methanol merely to solvate the leaving group. On the other hand, if a proton is being transferred in the rate-determining process of leaving group expulsion, a primary isotope effect might be expected.[50] Our result would seem to be in accord with the first hypothesis. However, one has to be very careful with such a conclusion. (1) It is an open question whether such a concurrent protonation of the departing leaving group would necessarily give rise to a primary isotope effect.[51] (2) It has not been proven that methoxide ion catalysis in the reaction of piperidine with 2,4-dinitroanisole is actually due to *general* base catalysis. If it were due to *specific* lyate ion catalysis, as there are good reasons to believe,[52] no primary isotope effect would be expected. The whole problem of base catalysis in nucleophilic aromatic substitutions will be discussed shortly.[52]

Acknowledgment. I wish to thank the Max-Planck Institut für Physikalische Chemie and particularly Professor M. Eigen for the use of the temperature-jump-equipment and for their great hospitality.

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[50] K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

[51] C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 3214 (1961).

[52] C. F. Bernasconi, to be published.

Thermal and Acid-Catalyzed Reactions of Pulegone Oxide

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Abstract: Pyrolysis of neat liquid samples of pulegone oxide (Ia or Ib) at 200° leads to stereoisomeric 2-acetyl-2,5-dimethylcyclohexanones (IIa and IIb) as the major products. This rearrangement is not catalyzed by acids, bases, or radicals and is insensitive to the Pyrex glass used for the reaction vials. Gas phase pyrolysis at 200° produces 2,2,5-trimethylcycloheptane-1,3-dione (IV) by a surface-catalyzed process. Dilute solutions of pulegone oxide in hydrocarbon solvents react slowly at 200° to give IV, whereas in solvents incorporating oxygen atoms, IIa and IIb are the chief rearrangement products. Reaction of Ia and Ib with boron trifluoride etherate results in stereospecific formation of fluorohydrins Va and Vb, which undergo thermal decomposition to give IV. Reaction of Ia and Ib with *p*-toluenesulfonic acid in benzene leads to isomeric, unsaturated ketols believed to be VIa and VIb. The pyrolysis reactions are discussed.

Our past investigations of high-temperature (>200°) reactions of α,β-epoxy ketones[1,2] have disclosed a radical chain decomposition mode and a surface-catalyzed (Pyrex glass) rearrangement paralleling known Lewis acid catalyzed reactions. We now report that pulegone oxide undergoes a solvent-dependent thermal rearrangement, which is not catalyzed by acids or bases, is not a free-radical chain process, and is not a surface reaction. The mechanism of this rearrangement is not yet apparent, but the transformation is similar to the photochemical rearrangement of this epoxy ketone.[2]

A thermal reaction of pulegone oxide was described by Prileschaev[3] over 40 years ago, and, although Pigulevsky and Mironova[4] have confirmed and elaborated this report, both groups used a crystalline modification of the epoxy ketone which has been shown to be a mixture of diastereoisomers.[5] Pigulevsky, *et al.*,[6] have recently modified their interpretation of the pulegone oxide pyrolysis and propose that isomeric α-diketones are the major products. We are unable to find products of this kind in our experiments with the pure isomers Ia and Ib.

Independent work of several research groups[7] has recently established the configurations of the stereoisomeric pulegone oxides Ia and Ib. Pyrolysis of the pure isomers was effected in sealed Pyrex tubes heated in a furnace (details are given in the Experimental Section). This static system allows a greater control of variables than would be possible by passing the sample through a hot tube. Most of the experiments were conducted at 200°, and, by adjusting the ratio of sample size to container volume and the pressure, essentially liquid phase or gas phase reactions could be effected. The random error in experiments of this kind is rather large (*ca.* ±5%); however, despite the poor reproducibility, numerous duplicate experiments by two independent researchers have confirmed the nature of the rearrangements and have established certain general trends. These results and some related acid-catalyzed reactions are reported in the following paragraphs.

When a neat liquid sample of Ia (or Ib) was heated to 200° for several hours (Scheme I), analysis by glpc revealed epimerization to Ib (or Ia) and rearrangement to a mixture of isomers IIa and IIb (Table I). Isomer Ia proved to be less reactive than Ib with respect to both epimerization and rearrangement. Very little

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[1] W. Reusch, C. K. Johnson, and J. A. Manner, *J. Amer. Chem. Soc.*, **88**, 2803 (1966).

[2] C. K. Johnson, B. Dominy, and W. Reusch, *ibid.*, **85**, 3894 (1963).

[3] M. N. Prileschaev, *Bull. Soc. Chim. Fr.*, **41**, 687 (1927).

[4] G. V. Pigulevsky and I. K. Mironova, *Zh. Obshch. Khim.*, **27**, 1101 (1957).

[5] W. Reusch and C. K. Johnson, *J. Org. Chem.*, **28**, 2557 (1963).

[6] S. A. Kozhin, S. I. Yakimovich, and G. V. Pigulevsky, *Zh. Obshch. Khim.*, **32**, 2368 (1962).

[7] (a) G. W. K. Cavill and D. H. Hall, *Tetrahedron*, **23**, 1119 (1967); (b) J. Katsuhara, *J. Org. Chem.*, **32**, 797 (1967); (c) W. Reusch and P. Mattison, *Tetrahedron*, **23**, 1953 (1967).

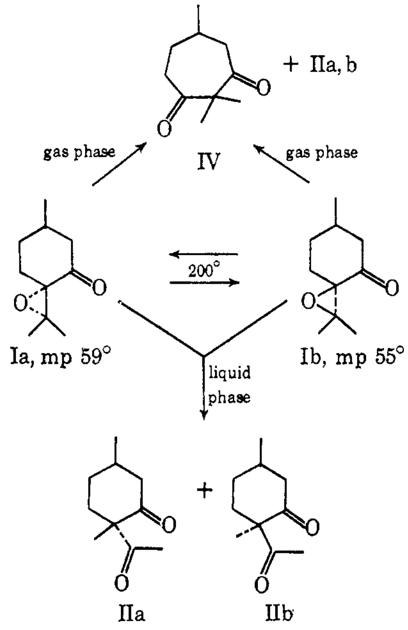
Table I. Liquid Phase Thermal Reactions of Pulegone Oxide at 200°

Run	Isomer	Time, hr	Additives	Reaction,[a] %	Ia/Ib	IIa,[b] %	IIb,[b] %	IIa/IIb	Low boilers, %
1	Ia	4	. . .	15	Large	5	3	1.7	5
2	Ia	6	. . .	29	29	13	7	1.9	7
3	Ia	8	. . .	38	25	18	10	1.8	9
4	Ia	10	. . .	55	13	24	13	1.8	13
5	Ib	2	. . .	55	0.6	20	11	1.8	4
6	Ib	4	. . .	80	1.5	38	19	2.0	7
7	Ib	6	. . .	94	2.3	48	24	2.0	10
8	Ib	2	Air	57	0.5	20	11	1.8	6
9	Ib	4	Air	75	0.9	30	18	1.7	6
10	Ib	4	Pyrex glass[c]	45	0.1	19	11	1.7	9
11	Ib	6	2,6-Lutidine[d]	74	0.8	36	15	2.3	3
12	Ib	6	Dimethylaniline[d]	69	0.4	34	16	2.1	7
13	Ib	5	*t*-Butyl hydroperoxide[d]	51	0.2	20	9	2.2	10
14	Ib	5	Benzoic acid[d]	73	0.6	29	16	1.8	12

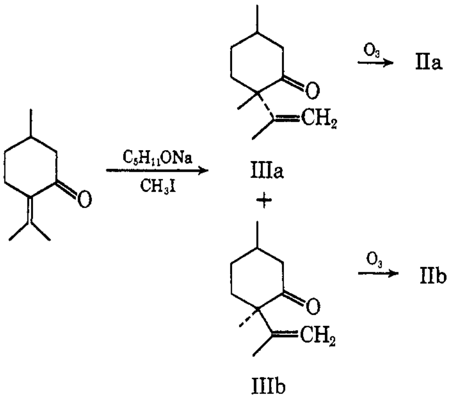
[a] Includes epimerization. [b] Determined by integration of glpc traces. These figures are averages of several runs made at the same time by the same experimentalist. At other times and in other hands Ia has been more reactive than it appears here and Ib slightly less reactive; however, Ib was always more reactive than Ia. [c] Over a 100% increase in surface area. [d] 10% of the amines and 7% of the acid (weight percentage).

high-boiling material was formed; in fact, the reaction is remarkably clean, particularly in the absence of air.

Scheme I



The identification of IIa and IIb as the major products from the pyrolysis of pulegone oxide was accomplished by a combination of physical measurements and chemical transformations. Thus, both isomers exhibited carbonyl absorption at 1705 cm^{-1}, formed crystalline carbonyl derivatives, and gave a positive iodoform test. The molecular ion at m/e 168 in the mass spectrum showed an isotope peak at m/e 169, the abundance of which indicated a $C_{10}H_{16}O_2$ composition for each isomer. Also the base peak (m/e 126) was the same for both isomers and suggested loss of ketene from a β-diketone by a McLafferty-type fragmentation.[8] The nmr spectrum of IIa displayed methyl resonance peaks at τ 9.01 (doublet, J = 6 cps), 8.77, and 7.98. Similar peaks were observed at τ 9.00 (doublet, J = 6 cps), 8.85, and 8.02 in the spectrum of IIb. Treatment of both IIa and IIb by refluxing methanolic sodium hydroxide (5%) gave 2,5-dimethylcyclohexanone and acetic acid. In addition, IIb (but not IIa) gave a keto acid believed to be 3,6-dimethyl-7-keto-octanoic acid. Conclusive evidence for the structures and configurations assigned here to IIa and IIb was obtained by synthesis from the isomeric 4-methylisopulegones (IIIa and IIIb). Direct methylation of (+)-pulegone leads in good yield to a mixture of IIIa and IIIb (eq 1),[9] the levorotatory isomer (IIIa) predominating over the dextrorotatory IIIb by roughly 4:1. The configurations of these isomers rest on degradation of IIIa to (+)-2-methyl-2-isopropylsuccinic acid,[10] the absolute configuration of which is known by X-ray diffraction analysis.[11] Finally, ozonolysis converted IIIa and IIIb into IIa and IIb, respectively (eq 1), completing the proof of configuration for the latter isomers.



(1)

Remarkably, the gas phase pyrolysis of pulegone oxide yielded a new rearrangement isomer (IV) as the major product (Table II). Starting with either Ia or Ib very little epimerization was observed at 200°. Rearrangement to IV was more rapid from isomer Ib than Ia, and the reaction of both isomers was accelerated by an increase of the surface area in contact with the sample (entries 3 and 5, Table II). The glpc analysis of

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(8) J. H. Bowie, D. H. Williams, S. O. Lawesson, and G. Schroll, *J. Org. Chem.*, **31**, 1384 (1966).

(9) (a) G. A. R. Kon and J. H. Nutland, *J. Chem. Soc.*, 3101 (1926); (b) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, **83**, 4433 (1961).

(10) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *ibid.*, **82**, 3476 (1960).

(11) M. R. Cox, H. P. Koch, W. B. Whalley, H. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

Table II. Gas Phase Thermal Reactions of Pulegone Oxide at 200°

Run	Isomer	Additives	Reaction,[a] %	Time, hr	Ia/Ib	IIa, %	IIb, %	IV, %
1	Ia	. . .	30	4.5	Large	. .	Trace	30
2	Ia	Air	23	4.5	Large	. .	Trace	23
3	Ia	Pyrex glass[b]	59	4.5	Large	. .	Trace	59
4	Ib	. . .	75	4	Small	5	17	53
5	Ib	Pyrex glass[b]	99	4	Small	10	24	66
6	Ib	. . .	90	12	Small	12	12	66

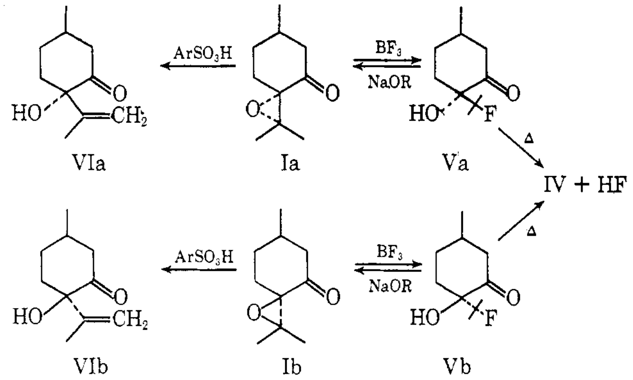
[a] Determined by integration of glpc traces. Samples of known composition were used to check the accuracy of these determinations. In many experiments internal standards were employed. These figures are averages of two to five simultaneous runs. Epimerization occurs to only a very small degree. [b] Lengths of Pyrex tubing are added to increase the surface area by *ca.* 100%.

these reactions was complicated by the similar retention times of IIa and IV; however, this difficulty was resolved by using a QF-1 liquid phase supported by Chromosorb G. The separations thus effected were checked by thin layer chromatography and infrared spectroscopy.

Compound IV proved to be a white crystalline solid, mp 50–51°, having a camphoraceous odor. Microanalysis and mass spectroscopy established a $C_{10}H_{16}O_2$ molecular formula; and infrared absorption at 1682 cm^{-1} (shoulders at 1658 and 1702 cm^{-1}), a negative ferric chloride test, and formation of a disemicarbazone derivative, mp 215–217°,[12] suggested a nonenolic diketone. The nmr spectrum of IV displayed a six-proton singlet at τ 8.86, a three-proton doublet (J = 6.0 cps) at τ 8.96, and a broad multiplet around τ 7.7. An attempt to exchange all the hydrogen atoms α to the carbonyl groups by treating IV with a solution of potassium carbonate in heavy water was frustrated by a remarkably facile cleavage to a keto acid mixture. Compound IV is thus a β-diketone, and the structure assigned here best accommodates these facts. Furthermore, treatment of Ia or Ib with boron trifluoride etherate in refluxing toluene resulted in rearrangement to IV, a transformation for which there is precedent.[13]

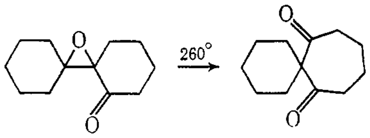
In order to evaluate better the thermal rearrangements of Ia and Ib, we briefly examined the acid-catalyzed reactions of these epoxy ketones. When treated with boron trifluoride etherate for 5 min, a benzene solution of Ia was converted into the fluorohydrin Va. This material was purified by preparative glpc and identified by the characteristic infrared (O–H str 3450, C=O str 1708, C–F str 1115 cm^{-1}) and nmr spectra (methyl doublets at τ 8.92, 8.88, and 8.50, the latter two being produced by vicinal F–H coupling, J = 18 cps). Treatment of Va with methanolic base regenerated Ia. Analogous transformations were observed with Ib. The major product from the reaction of this isomer with boron trifluoride etherate in benzene was assigned structure Vb on the strength of the infrared (3440, 1705, and 1120 cm^{-1}) and nmr spectra (methyl doublets at τ 9.07, 8.92, and 8.56, J_{F-H} = 15 cps), as well as conversion back to Ib on treatment with base. Fluorohydrins Va and Vb could be distilled at reduced pressure; however, when the neat liquids were heated to 150°, decomposition characterized by vigorous foaming and darkening was observed. The resulting brown tarry residue consisted mainly of compound IV (Scheme II).

Scheme II



The acid-catalyzed rearrangement of the pulegone oxides takes a different course when an arylsulfonic acid is used instead of boron trifluoride. Treatment of a benzene solution of Ia with p-toluenesulfonic acid gave the allylic ketol VIa, tentatively identified by its characteristic infrared and nmr spectra (described in the Experimental Section). A similar reaction employing Ib gave VIb as the major product.

We conclude from these studies that the gas phase pyrolysis of pulegone oxide involves rearrangement of epoxy ketone molecules adsorbed at Lewis acid sites on the Pyrex glass surface. This manner of reaction was suggested recently[1] to explain certain high-temperature transformations of isophorone oxide, and may also be responsible for the thermal rearrangement of 2-cyclohexylidenecyclohexanone oxide (eq 2).[13a]



(2)

Since the rate of thermal rearrangement to IV will be proportional to the number of acidic sites occupied by pulegone oxide molecules, a simple calculation of relative surface areas and sample concentrations should reflect the extent to which this rearrangement will also take place in the liquid phase. The Carius tubes used for the gas phase reactions have an internal surface area slightly larger than 300 cm^2. Therefore a maximum of *ca.* 3 × 10^{17} active sites having an area not smaller than 10^{-15} cm^2 can be present, and the 7 × 10^{20} sample molecules outnumber these by over 1000:1. At 200° the pressure in the pyrolysis tube is *ca.* 200 mm; thus most available surface sites should be occupied during the major portion of the reaction. Now the surface area (and hence the available active sites) exposed to the liquid phase sample is less than one-hundredth that

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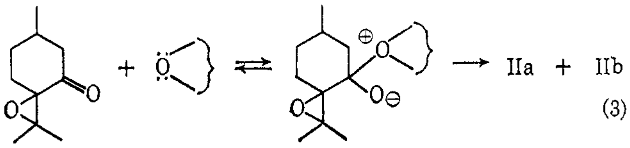
(12) One of the liquid isomers obtained by Kozhin, *et al.*,[6] is reported to give a disemicarbazone having the same melting point.

(13) (a) H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **78**, 4394 (1956); (b) J. C. Sheehan and R. M. Wilson, *ibid.*, **89**, 3457 (1967).

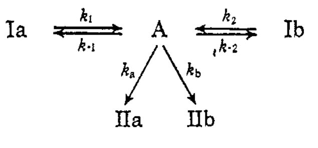
described above for the gas phase system. The yield of IV expected under the liquid phase conditions must therefore be less than 1%. This amount would be difficult to detect in the presence of significant conversion to IIa and IIb.

The liquid phase thermal rearrangement of Ia and Ib to IIa and IIb is apparently unique. The reaction is not catalyzed by acids, bases, or radicals and is not sensitive to an increase in the surface area. Only the photochemical rearrangement of epoxy ketones results in an equivalent transformation.[2] The absence of significant amounts of IIa and IIb as products in the gas phase reaction rules out a unimolecular rearrangement mechanism, and we propose that a solvation complex is the reactive species in the liquid phase reaction. Support for this suggestion has been obtained from a study of the pyrolysis of dilute pulegone oxide (Ib) solutions, using a variety of solvents. These experiments (Experimental Section) were complicated by decompositions to products having relatively short retention times in glpc analysis; however, the results show a clear dichotomy. Hydrocarbon solvents (cyclohexane, cyclohexene, and *p*-cymene) favor the gas phase mode of rearrangement, whereas IIa and IIb are the major products from solvents incorporating an oxygen atom (cyclohexanone, *t*-butyl alcohol, and 1,4-dioxane). There appears to be no correlation of reaction path with dielectric constant, but the solvent effect can be adequately explained if a bimolecular (or larger) solvation complex is a necessary intermediate in the rearrangement to IIa and IIb (*e.g.*, eq 3). A surprising aspect of the solvent study was the absence of significant epimerization of Ib, even under conditions that favor rearrangement to IIa and IIb. This may be due to the increased importance of alternate decomposition pathways available to certain key intermediates (see below) under the conditions of these reactions.

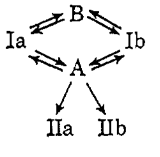


(3)

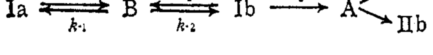
It is important to determine whether the relatively constant ratio of IIa:IIb observed in the liquid phase rearrangement is a fundamental characteristic of this reaction or the result of a subsequent equilibrium process. To this end, samples of both IIa and IIb were heated at 200° for 15–18 hr. Decomposition of IIa occurred to a very minor degree (*ca.* 5%) and IIb was not affected. The constant ratio is therefore an intrinsic feature of the reaction and can be explained by a common precursor (A), in which the C_4–O bond of the oxirane ring is broken.[14] Intermediate A may also play a role in the epimerization process (eq 4 and 5); however, another path (eq 6), involving an intermediate B, in which the oxirane C–C bond is broken, might represent the major route for epimerization. In this last mechanism (eq 6), the more reactive isomer (Ib) is necessarily the source of A. Since the less reactive isomer (Ia) rearranges more rapidly (*ca.* three times faster) than it is epimerized, eq 6 requires that isomer Ib be rapidly converted to A (*i.e.*, $k_3 > k_2$ and k_1). However, epimerization of Ib actually proceeds at roughly the same rate as rearrangement (Table I), and we therefore favor a mechanism based on either eq 4 or eq 5. Using eq 4 to illustrate this point, the approximate rate constant relationship $k_{-1} = k_a = 2k_{-2} = 2k_b$ is in accord with the data presented in Table I.



(4)



(5)



(6)

Although the thermal and photochemical rearrangements of the pulegone oxides appear to be the same, there is as yet no evidence as to whether a common mechanism exists. We plan further studies on this question.

Experimental Section[15]

Pulegone Oxides Ia and Ib. Oil of Pennyroyal from Fritzsche Brothers Inc. was distilled; the fraction boiling at 76–82° (15 mm) was treated with alkaline hydrogen peroxide in a manner described in an earlier publication.[5] The isolation of pure stereoisomers also followed a published procedure.[5]

Solvents and Other Reagents. The following materials were used without special purification: 2,6-lutidine, Reagent Grade, Eastman Organic Chemicals; 1,4-dioxane, Spectro Grade, Matheson Coleman and Bell; cyclohexane, Spectro Grade, Matheson Coleman and Bell; cyclohexene, Chromatoquality, Matheson Coleman and Bell; *p*-cymene, terpene free, Matheson Coleman and Bell; *t*-butyl hydroperoxide, Wallace and Tiernan. Cyclohexanone was purified by formation of the bisulfite addition compound, decomposition with 10% sodium hydroxide, and distillation (bp 153–155°). N,N-Dimethylaniline was purified by refluxing with acetic anhydride followed by distillation, bp 102–104° (12 mm). *t*-Butyl alcohol was purified by distillation from calcium hydride (bp 81–83°).

Pyrolysis Procedures. Sample vials for the liquid phase reactions were prepared from Pyrex tubing (0.8 cm o.d., 0.4 cm i.d.) cut to 20-cm lengths, heated for 12–15 hr in concentrated nitric acid, rinsed five times with distilled water, immersed in concentrated ammonium hydroxide for 30 min, rinsed again with distilled water, and dried for 24 hr at 150°. The material to be studied (*ca.* 200 mg) was placed in a vial constructed from the treated tubing, de-

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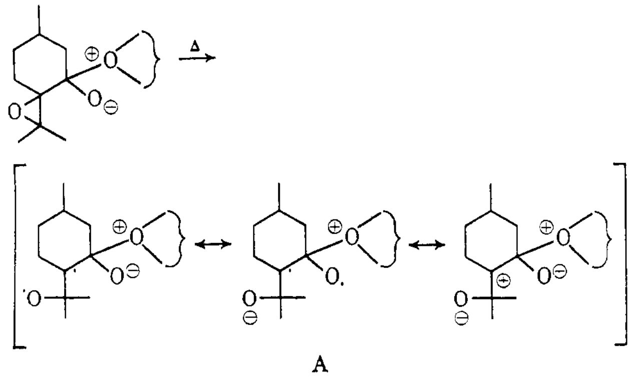
[14] The previously proposed solvation complex must be the progenitor of A, perhaps in the manner



A

[15] Nuclear magnetic resonance spectra were determined at 60 Mc on a Varian Associates A-60 spectrometer. Chemical shifts were obtained with reference to tetramethylsilane as an internal standard. An Aerograph A-90-P gas chromatograph was used for the glpc analyses. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are not corrected.

gassed, and sealed under nitrogen at *ca.* 700 mm. The sealed vials (4–6 cm long) were placed in an electrically heated aluminum block maintained at 200 ± 2°. Analysis by glpc was conducted with duplicate samples. Pyrex glass chips were added to increase the surface area in several experiments.

Carius combustion tubes made of Pyrex glass (2.5 cm o.d., 1.9 cm i.d., 55 cm long) were used for the gas phase experiments. These tubes were cleaned and dried in the manner described above. A 200-mg sample of the pulegone oxide isomer being studied was placed in the tube, degassed, and sealed at 0.5 mm of nitrogen. By packing the combustion tube with long pieces of washed Pyrex tubing, the surface area could be increased by over 100%. A combustion tube furnace (Precision Scientific Co.) was used to heat the gas phase reactions.

Thermal Rearrangement of Ib in Various Solvents. Liquid phase sample vials were charged with 0.5-ml portions of 5% solutions of pulegone oxide Ib in various solvents. These samples were degassed and sealed under an atmosphere of nitrogen. After being heated at 200° for 6–10 hr, the reaction vials were cooled and the samples analyzed by glpc. Low-boiling products were not identified; however, the formation of IIa, IIb, and IV was confirmed by infrared analysis of the appropriate glpc peaks. The results of these experiments are presented in Table III.

Table III. Thermal Rearrangement of Ib in Solution

Solvent	Reaction time, hr	IIa, %	IIb, %	IV, %	Low boilers, %
Cyclohexane	10	. .	. .	13	33
Cyclohexene	10	. .	. .	41	15
p-Cymene	8	. .	. .	44	*a*
1,4-Dioxane	8	19	10	. .	49
Cyclohexanone	6	31	14	. .	*a*
t-Butyl alcohol	6	26	15	. .	*a*

[a] Low-boiling products could not be analyzed due to interference by the solvent.

Identification of IIa and IIb. Pure samples of these isomers were isolated by preparative glpc (4% QF-1 on Chromosorb G or 15% NPGS on Chromosorb W) in sufficient quantity for spectroscopic examination and derivative preparation. When 15 g of Ia and Ib was heated under nitrogen at 200° for 18 hr, a mixture of low-boiling materials (including acetone), 2,5-dimethylcyclohexanone (5%), IIa (50%), IIb (25%), and pulegone oxide (5%) was obtained. Isomers IIa and IIb could not be completely separated by distillation.

Isomer IIa gave a positive iodoform test and a negative tetranitromethane test. Absorption at 1705 cm^{-1} in the infrared spectrum and 286 mμ (ε 71) in the ultraviolet spectrum indicated the presence of a carbonyl group. This was confirmed by formation of a semicarbazone derivative, mp 211.5–212.5°.

Isomer IIb gave similar chemical tests and exhibited absorption at 1705 cm^{-1} in the infrared spectrum and 291 mμ (ε 73) in the ultraviolet spectrum. A disemicarbazone, mp 222–223°, and a 2,4-dinitrophenylhydrazone, mp 230–231°, were prepared. The latter derivative was analyzed.

Anal. Calcd for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.09. Found: C, 54.71; H, 6.02; N, 15.78.

The mass spectra of IIa and IIb (Table IV) confirm the structures assigned in this paper (ionization voltage 70 V). The intensity of the P + 1 ion was 11.5% for IIa and 10.0% for IIb (calcd for $C_{10}H_{16}O_2$ 11.14%).

Alkaline Cleavage of IIa and IIb. A solution of IIa (150 mg) in 1.5 ml of 5% sodium hydroxide solution containing a little methanol was refluxed for 2 hr, cooled, and extracted with two 3-ml portions of ether. The usual work-up of the ether extracts gave 110 mg (88%) of 2,5-dimethylcyclohexanone, identified by comparing the infrared spectrum and glpc retention time with that of authentic material. The basic water layer was acidified and extracted with ether. This extract yielded acetic acid as the only product.

A similar hydrolysis of 200 mg of IIb gave 2,5-dimethylcyclohexanone, isolated in 48% yield as the 2,4-dinitrophenylhydrazone (mp 156–161°), acetic acid, and a keto acid which could be converted into oily semicarbazone, 2,4-dinitrophenylhydrazone, and methyl ester derivatives.

Table IV

IIa *m/e*	IIa Base peak, %	IIb *m/e*	IIb Base peak, %
55	39.4	55	46.0
69	39.4	56	13.6
70	4.0	69	42.5
83	15.2	70	11.8
84	39.4	83	20.4
97	15.2	84	41.0
98	15.2	85	10.8
111	39.4	97	18.0
125	24.3	98	18.6
126	100.0	111	42.2
127	9.1	125	30.5
168	3.5	126	100.0
		127	9.3
		168	5.9

2,5-Dimethylcyclohexanone, bp 88–89° (40 mm), was prepared by chromic acid oxidation of 2,5-dimethylcyclohexanol. This ketone yielded a 2,4-dinitrophenylhydrazone derivative, mp 162–164° (lit.[16] mp 162–163°).

4-Methylisopulegone (IIIa and IIIb). The methylation of (+)-pulegone was accomplished according to the procedure of Djerassi, *et al.*[9b] Distillation of the crude product gave a mixture of IIIa and IIIb, bp 110–114° (25 mm), which proved to be 76% of the former and 24% of the latter by glpc analysis. Pure samples of each isomer were obtained by preparative glpc. Isomer IIIa formed a semicarbazone having mp 196–198° (lit.[9b] mp 197–198.5°), and isomer IIIb gave a semicarbazone melting at 201–203° (lit.[9b] mp 201–202.5°). The infrared spectra of both isomers were consistent with the assigned structure.

Ozonolysis of IIIa and IIIb. A mixture (76% IIIa and 24% IIIb) of the 4-methylisopulegone isomers (500 mg) was dissolved in 10 ml of methylene chloride. This solution was cooled by a Dry Ice bath and ozone was bubbled in until a blue color persisted. The reaction mixture was allowed to warm slowly to room temperature, 10 ml of water and 2 g of zinc dust were added, and the methylene chloride in the mixture was carefully distilled into a methone solution. The remaining aqueous solution was refluxed for 2 hr, cooled, and extracted with ether. The ether extracts yielded 0.3 g (60%) of a 75:25 mixture of IIa and IIb. These isomers were compared with the products from pulegone oxide pyrolysis and proved to be identical. The methone solution yielded 0.06 g (7%) of the formaldehyde derivative.

Thermal Decomposition of IIa and IIb. A small sample of IIa was degassed and sealed in a Pyrex vial. After being heated at 200° for 18 hr, this sample was analyzed by glpc. Only 5% decomposition had occurred, and half of this was to 2,5-dimethylcyclohexanone. A similar study with IIb showed that less than 0.5% decomposition had occurred.

Reaction of Ia with Boron Trifluoride Etherate. A solution of Ia (2 g) in 50 ml of dry benzene was treated with 1.9 ml of freshly distilled boron trifluoride etherate. After standing for 5 min at room temperature, the reaction mixture was washed with 5% sodium bicarbonate and distilled water. The solvent was evaporated from the dried benzene solution, leaving 1.9 g of a pale yellow liquid which was distilled, bp 75–78° (2 mm), and analyzed by glpc. A pure sample of the major product (Va) was obtained by preparative glpc and exhibited infrared absorption at 3450, 1708, and 1115 cm^{-1} and nmr signals at τ 8.92 (doublet, J = 6 cps), 8.88, 8.5 (doublets, J = 18 cps), 6.00 (singlet), and a complex multiplet centered at τ 7.70. Fluorine resonance was observed with a Varian HR-60 instrument, but the resolution was very poor.

Fluorohydrin Va (2 g), prepared from Ia as described above, was dissolved in 25 ml of methyl alcohol containing 1 g of sodium hydroxide dissolved in 5 ml of water. This solution was refluxed for 4 hr, cooled, and brought to a phenolphthalein end point with dilute acid. Ether extraction of the neutralized solution gave a product which proved to be mainly Ia, mp 57–59°.

Reaction of Ib with Boron Trifluoride Etherate. The reaction of Ib with boron trifluoride etherate was effected in the manner described above. Distillation of the crude product, bp 75–78° (2 mm), gave a colorless liquid which proved to be 80% Vb by glpc

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(16) M. Mousseron, R. Jacquier, and H. Christol, *C. R. Acad. Sci. Paris, Ser. C.*, **236**, 927 (1953).

analysis. The pure fluorohydrin was obtained by preparative glpc and exhibited infrared absorption at 3440, 1705, and 1120 cm^{-1} and nmr signals at τ 9.07 (doublet, J = 5 cps), 8.92, 8.56 (doublets, J = 15 cps), 8.00 (broad multiplet), and 6.38 (singlet).

Fluorohydrin Vb was converted into Ib, mp 53–55°, by treatment with refluxing methanolic base in the manner described for Va.

Thermal Decomposition of Va and Vb. A 50:50 mixture of Va and Vb (5.0 g) was heated at 150° in a small flask equipped with a reflux condenser. After 15–20 min the liquid turned pink and then brown, accompanied by vigorous foaming and evolution of a pungent, irritating gas. The dark tarry residue was dissolved in ether, washed with sodium bicarbonate solution and distilled water, separated from the aqueous phases, and dried. The dark oil remaining after evaporation of the solvent was chromatographed on silica gel, using methylene chloride as the eluting solvent. The light tan solid obtained by this procedure was sublimed to a volatile, white, crystalline substance (IV): mp 50–51°, yield *ca.* 50%.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.15; H, 9.58.

Compound IV exhibited infrared absorption at 1682, 1382, and 1262 cm^{-1} and nmr peaks at τ 8.96 (doublet, J = 6.0 cps, 3 H), 8.96 (singlet, 3 H), and 7.65 (multiplet, *ca.* 7 H). The mass spectrum of IV (ionizing voltage 70 V) confirms the basic differences in I, II, and IV (Table V). The *intensity of the P + 1 ion peak* was 10.70% P (calcd for $C_{10}H_{16}O_2$ 11.14% P).

The identity of IV obtained by rearrangement of fluorohydrins Va and Vb with the major product from the gas phase pyrolysis of Ia and Ib was established by direct comparison of melting points, glpc retention times, and infrared spectra and nmr spectra.

Reaction of Ia with *p*-Toluenesulfonic Acid. To a solution of Ia (2.0 g) in benzene (50 ml) was added 0.1 g of *p*-toluenesulfonic acid, and the resulting solution was held at room temperature for 1 hr. The acid catalyst was removed by washing with sodium bicarbonate solution and the benzene solution was then washed with water, dried, and distilled. The crude reaction product proved to be largely (*ca.* 90%) a single compound (VIa), which was obtained pure by glpc. The infrared spectrum of VIa (3470, 3080, 1820, 1710, 1645, and 905 cm^{-1}) indicated the presence of a methylene double bond, a saturated carbonyl group, and a hydroxyl group.

Table V

m/e	Base peak, %	*m/e*	Base peak, %
53	24.4	83	50.0
55	71.2	84	24.3
56	19.4	97	42.1
67	24.2	98	31.5
69	71.2	111	29.0
70	100.0	123	29.0
71	18.3	124	14.5
81	24.3	125	97.2
82	25.5	140	18.4
		168	24.2

The nmr spectrum of VIa displayed signals at τ 9.02 (a three-proton doublet, $J \sim 6$ cps), 8.28 (a three-proton doublet, $J \sim 1$ cps), 6.18 (a one-proton singlet), 4.82 (a broad two-proton doublet), and an envelope of poorly defined peaks in the region τ 7.5–8.4.

Reaction of Ib with *p*-Toluenesulfonic Acid. The rearrangement of isomer Ib was conducted in essentially the same manner described above for Ia. Analysis of the crude reaction mixture by glpc disclosed the presence of a major component (*ca.* 60%); however, other products having similar retention times frustrated our attempts to obtain pure samples of this compound (VIb). Fortunately, we discovered that a glpc column (4% QF-1 on Chromosorb G), previously used for analysis and purification of fluorohydrins Va and Vb, cleanly rearranged Ib to VIb. This compound (VIb) exhibited an infrared spectrum (ν_{max} 3470, 3085, 1820, 1712, 1645, and 905 cm^{-1}) and nmr spectrum (τ 8.95, 8.86, 8.30, 7.4–8.8, and 4.85) consistent with the assigned structure and essentially the same as the spectrum of impure VIb obtained from the arylsulfonic acid reaction.

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Purine Nucleosides. XXII. The Synthesis of Angustmycin A (Decoyinine) and Related Unsaturated Nucleosides[1]

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Abstract: The antibiotic angustmycin A (decoyinine) (**10**) has been prepared in several steps from psicofuranine (**1a**). The synthesis of 1′,3′,4′-*O*-orthoformylpsicofuranine (**5**) proved the β configuration of **1a** and provided the required blocked derivative for the synthesis of 6′-*O*-*p*-toluenesulfonyl-1,′3′,4′-*O*-orthoformylpsicofuranine (**6**). Compound **6** was treated with potassium *t*-butoxide to give 1′,3′,4′-*O*-orthoformyldecoyinine (**7**), which was deblocked to yield 6-amino-9-(6-deoxy-β-D-*erythro*-hex-5-enofuran-2-ulosyl)purine (**10**), identical with natural angustmycin A and decoyinine. The synthesis of 6-amino-9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine (**8**) was accomplished from adenosine **16** by a similar base-catalyzed treatment of 5′-*O*-*p*-toluenesulfonyl-2′,3′-*O*-ethoxymethylideneadenosine (**3**). Reaction of 6-amino-9-(2,3-*O*-isopropylidine-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)purine (**13**) with bromine provided the first reported $N^3 \rightarrow 4'$-furanose cyclonucleoside, **14**. Palladium-catalyzed hydrogenation of **13** proceeded stereospecifically to yield 6-amino-9-(5-deoxy-α-L-*lyxo*-pentofuranosyl)purine (**15**) after deblocking. A new synthesis of the 4′ epimer of **15**, 5′-deoxyadenosine (**20**), was accomplished from adenosine.

Angustmycin A (**10**) was isolated and purified by Yüntsen and coworkers[2] in 1956. Degradation studies disclosed the presence of adenine and a hexose sugar. On the basis of these studies structure **11** was proposed.[3] Hoeksema, Slomp, and van Tamelen[4]

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(1) This research was supported by Institutional Research Grant No. CA-08109 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(3) H. Yüntsen, *ibid.*, **11**, 79, 233 (1958).

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