PART - I

CHAPTER - 1

BASE-CATALYZED REARRANGEMENT OF TERPENE OXIRANES TO ALLYLIC ALCOHOLS

Abstract

This Chapter describes a key reaction for the transformation described in the next Chapter. Few terpene oxiranes, were subjected to a variety of bases and the products from each reaction were suitably analyzed and best preparative method worked out for the isomerization of (+)-carene epoxide and (-)-pinene epoxide to the corresponding allylic alcohols.

BASE-CATALYZED REARRANGEMENT OF TERPENE OXIRANES TO ALLYLIC ALCOHOLS

INTRODUCTION.

The reaction of epoxides with strong bases constitutes a well-known method for the preparation of allylic alcohols.

Most of the prior work on the rearrangement of epoxides induced by strong bases derives from the studies of Cope and coworkers.[1,2,3] Crandall and Chang[4] developed a general understanding of base promoted reactions of epoxides and, in particular, determined the features of a substrate via carbene-like intermediate which leads to different products. α-Pinene oxide (1) rearranges to allylic alcohol (2) exclusively[4]. β-Diisobutylene oxide (3) was also converted into a single allylic alcohol (4). These are clean, high-yielding reactions of preparative value. Recent work has shown that the formation of allylic alcohols is highly selective involving proton abstraction by the bulky lithium diethylamide from the least substituted carbon atom[5], and proceeds by a syn-elimination[5,6,7]; cyclohexene oxide, for example, is converted into (6) via the adduct (5)[4,5], (Fig. 1).

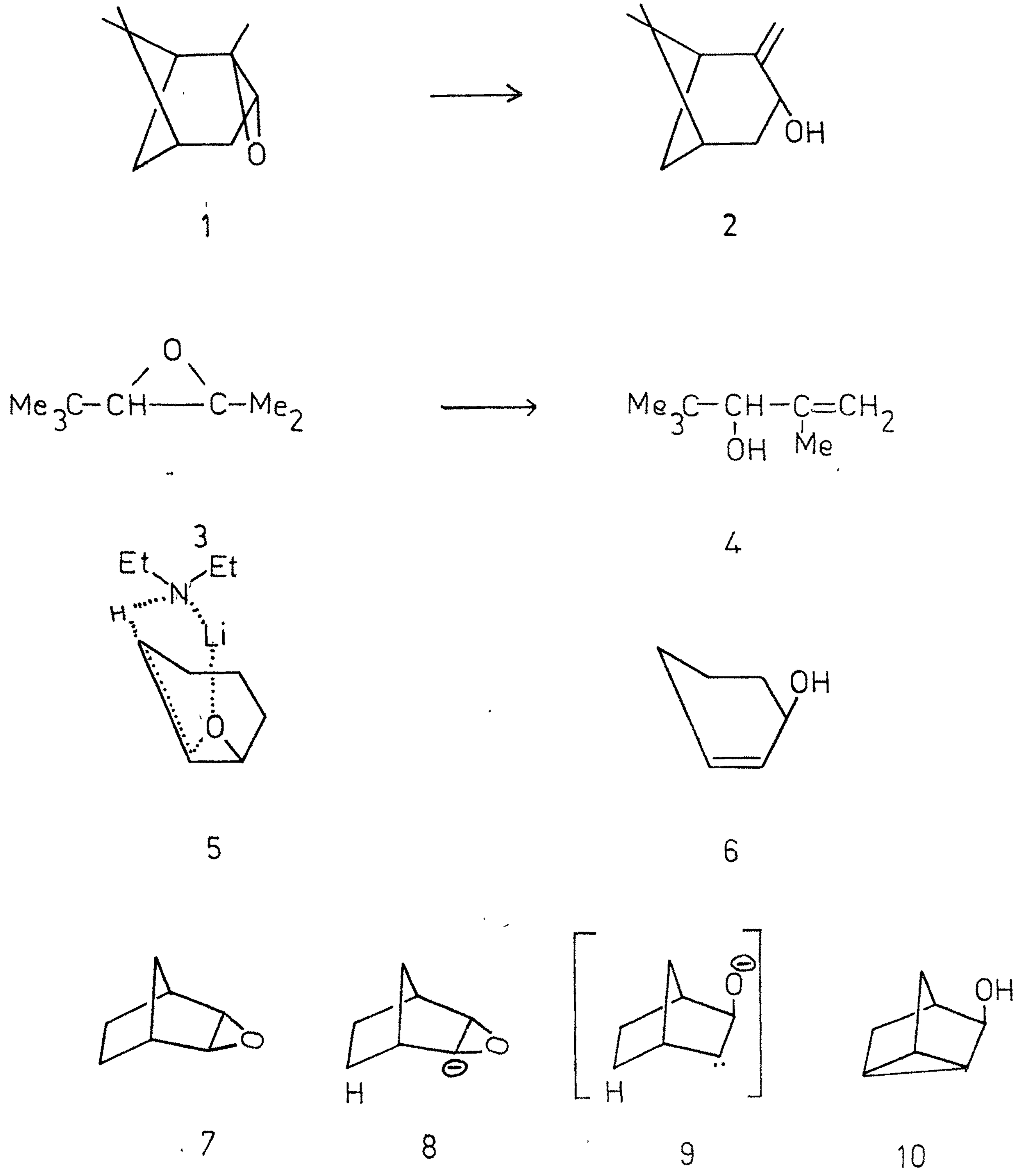
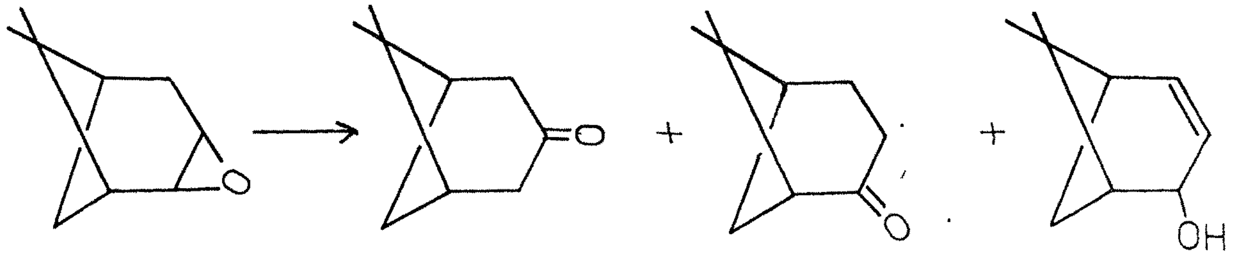


Fig. 1. Rearrangement of epoxide to allylic alcohol

For the transformation of epoxides to allylic alcohols, various basic agents were used, but most often lithium diethylamide was employed in different solvents[5,6,7]. A number of transformations have been carried out by means of alumino organic compounds[8a-g], lithium aluminium hydride[9], sodium metal[10], lithium in n-butylamine[11], boron compounds[12], Me_2NH[13] and solid acid-bases[14]. Also, isomerization of α-pinene oxide (1) in DMSO solvent without a catalyst is known in literature[15] to give ℓ-*trans*-carveol as the major product along with α-pinene, p-cymene, camphelene aldehyde, pinocarveol and pinocamphone.

However, a few reports relating to isomerization by means of pottasium *t*-butoxide, a cheap and easily available reagent were published. The basicity of potassium butoxide is increased in aprotic solvents due to stronger sovation of potassium cation than that of *t*-butoxy anion[16a-d, 17a], and this effect is particularly visible in DMSO solution[17a,18a-b]. Potassium *t*-butoxide (*t*-BuOK) has occupied a unique position among alkoxide bases[19]. First, it has been the strongest alkoxide of known pKb, and second, it has been the most hindered base of which conjugate acid available in quantity and at reasonable cost[17b].

Earlier, the best method for the transformation of an epoxide into the corresponding allylic alcohol, using a strong base (discovered by Cope[1,3] and further developed by Crandall[4,6] and Rickbarn[5,7]) involved isomerization with lithium diethylamide. Three main types of reactions may be discerned: formation of allylic alcohols by β-elimination, skeletal rearrangement *via* a carbenoid intermediate produced by α-elimination, and formation of ketones. Carbenoid intermediates were proposed by Cope[2] to account for rearrangement products arising from medium-ring epoxides. Crandall[20] has shown that the C-H bond approaches the carbenoid carbon from the side opposite the departing oxygen atom as in (8) and (9) (Fig. 1). Because of their need to carryout such transformation under very mild conditions, Crandall and Rickborn developed a new method based upon diethylaluminium dialkylamide. The method takes advantage of the affinity of aluminium metal for oxygen[21]. In case of apopinene epoxide (11), the demethylated derivative of (1), elimination to give allylic alcohol (14) is still not the major reaction process but instead ketonic products (12) and (13) results (Fig. 2). In actual event, no insertion products were found although ketones predominated over allylic alcohol in



11 12 13 14

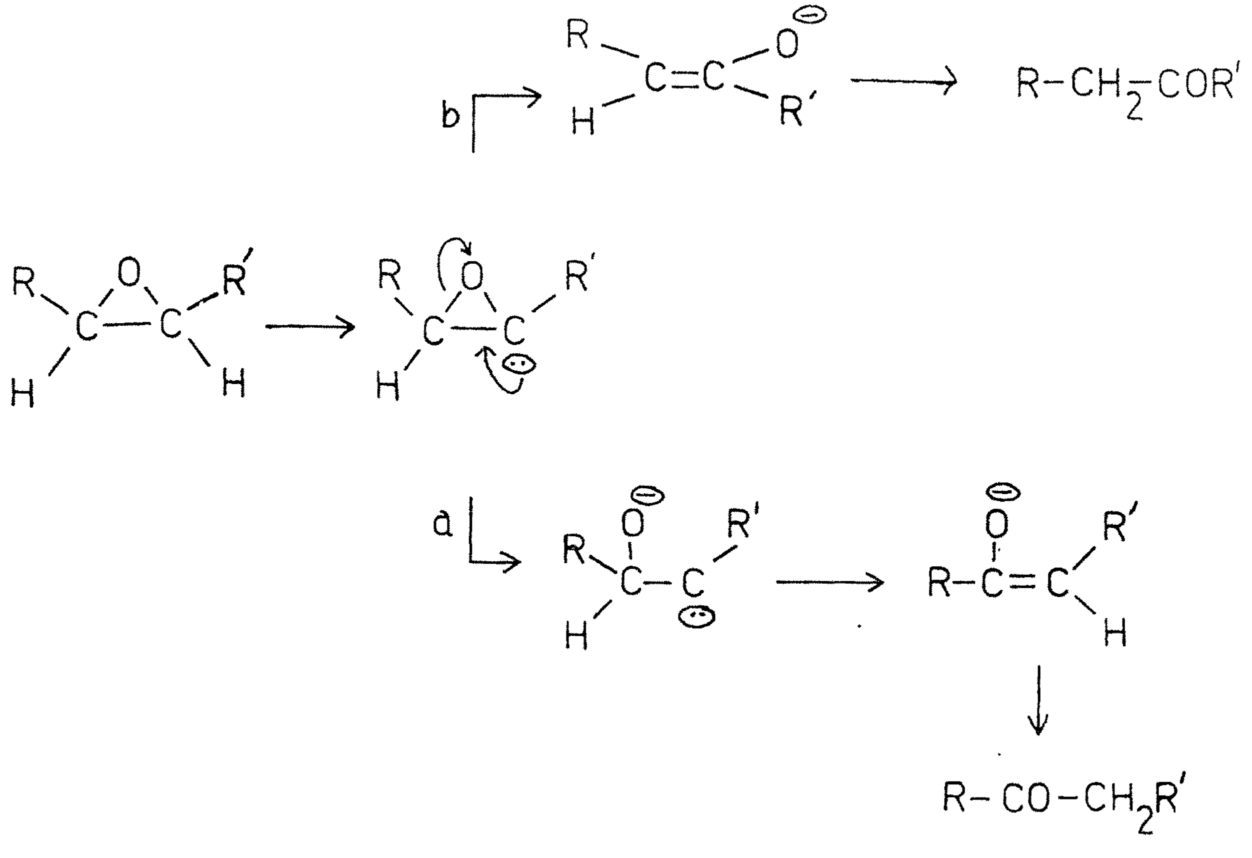
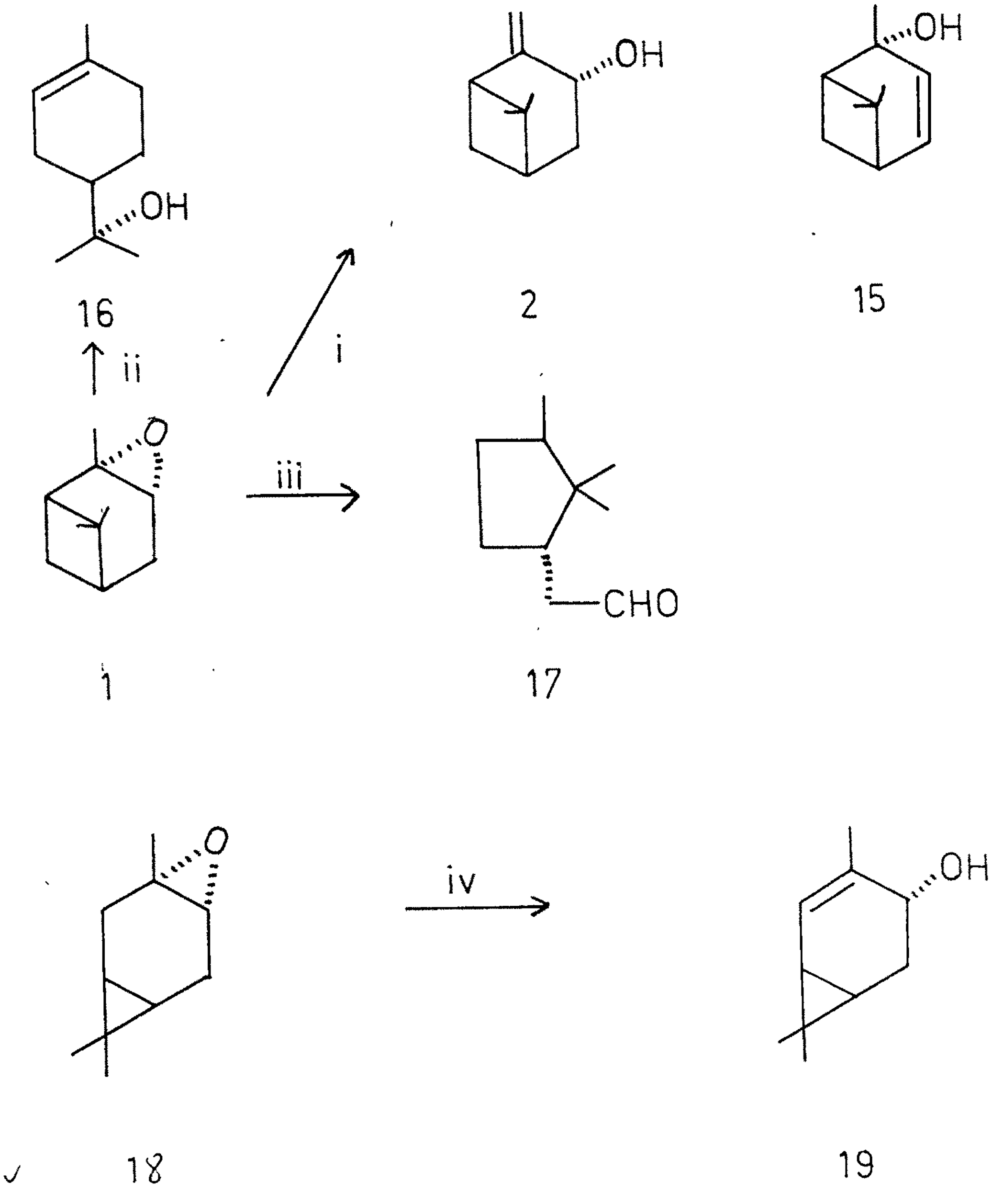


Fig. 2. α- and β-Elimination mechanism of epoxide opening to ketone.

the product mixture. It is tempting to speculate that ketones also came about by an α-elimination mechanism involving a 1,2-hydrogen shift from a carbenoid intermediate as depicted in Fig. 2 (pathway a). Although such a process is destinguishable from the alternate and equally likely β-elimination route (pathway b).

α-Pinene oxide (1) has been isomerized under a variety of conditions (Fig. 3). Lithium in diethylamine[22] as well as aluninium alkyls[15] yielded trans-pinocarveol (2). Lewis acids gave camphonelenic aldehyde (17) as the major product[8c, 23]. Active alumina gave a mixture of products[24] and protic acid yielded sobrerol (16) by hydration[5]. The isomerization of α-pinene oxide (1) with t-BuOK-DMF[25,26] (or DMSO) gave two allylic alcohols (2) and (15).

Though, the conversion of carene epoxide (18) to corresponding allylic alcohol (19) has been described in literature[27], and its exclusive formation in a yield of 90% has been claimed, we were unable to reproduce the results (discussed in Chapter 2 of this Part). This led to a reinvestigation of the reaction. Isomerization conditions were just well-standardized for α-pinene epoxide (1) and then for carene epoxide (18).



Reagents: i) t-BuOK-DMF; ii) PROTIC ACID
iii) Lewis acid; iv) t-BuOK-Pyr.

Fig. 3. Isomerization of α-pinene epoxide under various conditions.

PRESENT WORK

A survey of literature indicates that isomerization of epoxides to allylic alcohols with bases in presence of cheap and accessible reagent polyethylene glycol (PEG) has not been carried out. PEG as a phase transfer catalyst is known in the literature[28a-c].

Phase transfer catalysis, as we know it to-day, originated in the work of Makosza and coworkers[29] (1965) and the term was coined by Stark[30] (1968). Phase transfer catalysis concerns reaction between, on the one hand, salt dissolved in water or present in the solid state, and, on the other hand, substances dissolved in organic media. Without a catalyst such a reaction is usually slow and inefficient or does not occur at all.

Phase transfer catalysis has considerable advantages over conventional procedures:

- expensive anhydrous or aprotic solvents need no longer be used.
- improved reaction rate and/or lower reaction temperatures
- in many cases easier work-up.

- aqueous alkali metal hydroxides can be employed instead of alkoxides, sodamide, sodium hydride or metalic sodium.

Further advantages have also been found, e.g.:

- occurrence of reactions that do not otherwise proceed
- modification of the selectivity
- modification of product ratio (e.g. O̲ Vs C̲ alkylation)
- increased yield through the suppression of side reactions.

In many cases, phase transfer catalysis consists of the extraction of ionic molecules into organic solvent or their solubilization therein. Polar protic solvents readily solvate both the cation and anions. However, polar aprotic solvent (e.g. DMSO, DMF) readily solvate cations, and anions are poorly solvated. Since the positive end of the solvent dipole cannot be approached easily, the reaction rates are high. Addition of polar solvent such as DMSO to a solution of $KO(CH_3)_3$ in t̲-butanol enhances the basicity in a number of ways: it increases the dielectric constant, specifically solvates the potassium cation. Potassium t-butoxide in DMSO, therefore behaves as a much stronger base than in t-butanol.

The use of Crown ethers[31] as strong complexing agent for metal cations, especially those of alkali metals has been well-documented over the past several years[32].

Acceleration of bimolecular reaction can be achieved using polar protic and dipolar aprotic solvents which make possible the mutual dissolution of salt and organic substrate[33]. Recently, it has been shown[34] that carbowax, i.e., linear polyethylene glycol (PEG) can be regarded as protic solvent with aprotic sites of binding constituted by some monomeric units (CH_2-CH_2-O) and also it can complex with alkali ions (notably K^+) and transfers the complexed salt into organic phase with an efficiency comparable to that of 18-crown-6.

Indeed PEG, an inexpensive material, can be successfully used as a PTC for a variety of organic reactions. D. Balasubramanian <u>et.al.</u>[28a,24a] have found that PEG of a molecular weight 400 or above can be used as

PTC (PEG-200 is not efficient in ion binding)[34].

In order to evaluate the potential of PEG (with alkali metals) as a reagent for isomerization, systematic work has been carried out. In this context, a standard procedure has been developed for epoxidation of α-pinene, limonene, terpinolene and 3-menthene using azeotropic peracetic acid in chloroform solvent in presence of sodium bicarbonate as buffer[35]. Carene epoxide (18) was prepared from (+)-car-3-ene by a standard procedure[36] using peroxy acetic acid (50% azeotrope with acetic acid and water). Epoxidation[35-49] reaction is stereospecific leading to cis-addition of oxygen atom to the double bond. Results are summarized in Table-1 (Fig. 4).

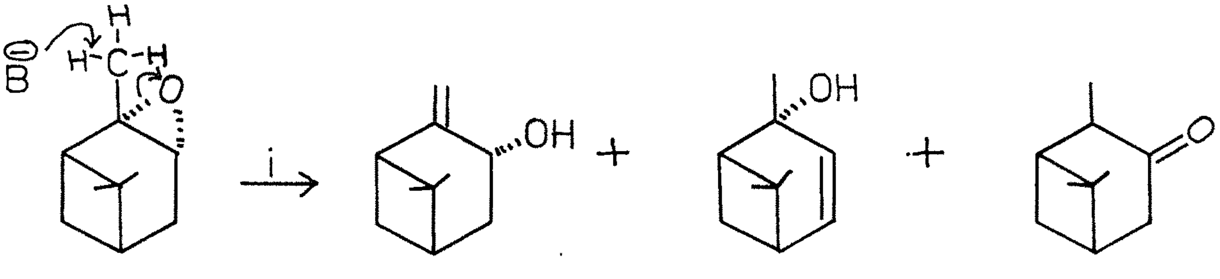
Isomerization conditions were worked out using α-pinene epoxide (1) as a model compound. Isomerization of α-pinene epoxide (1) using alkali metal(s) and PEG-400 gave both t-pinocarveol (2)[25,26] and tertiary alcohol (15)[25,26] as products along with trace amount (2-4%) of ketone (22) as shown in Fig. 5. Highest conversion of (1) to allylic alcohols (2) and (15) was obtained using potassium with PEG-400. Under similar conditions, conversions were lower when sodium metal was used, while with lithium the reaction

Table 1 - Epoxidation

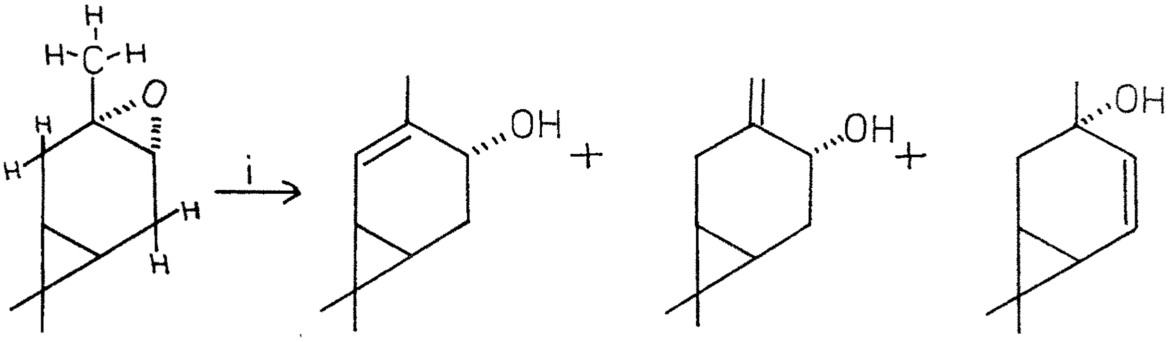
Sr. No.	Olefine[a,b] gm.	mole	Peroxy acetic[c d] acid ml	% (mole)	Products Crude gm(%)	Dist. gm(%)	Res. gm(%)	GC analysis Epoxide %	10 w boilers %	Others %	Recovery %	GC yield (%) (isolated yield %[e])
1.	α -pinene 52	0.382	64	53 (0.45)	56.9196 (97.95)	53.62 (92.26)	0.200 (3.4)	73.77	15.3	10.93	95.66	85.3 (75.74)
2.	p-3-menthene 27.2	0.2	45.6	40 (0.24)	33.4 (traces of solv.)	32.52 (traces of solv.)	0.16 (0.55)	89.27	9.58	1.19	99	95.6 (73.9)
3.	Terpinolene 34	0.25	45	39 (0.225)	40.38 (traces of solv.)	36.1651 (95.12)	1.1209 (3.0)	86.2	9.13	4.67	98.12	82.02 (60.42)
4.	Limonene 27.2	0.2	45.6	40 (0.24)	29.46 (46.9)	1)1.8085 2)18.0274 3)4.3941 (78.74)	2.9 (9.5)	1) 68.75 2) 81.85 3) 71.67	31.2 7.9 3.84	- 10.41 24.44	89.24	62.98 (49.3)

[a] Chloroform (1:3 times to that of olefine) was used as solvent
[b] Sodium bicarbonate (1:1.3 mole to that of olefine) was used as buffer
[c] Reaction time 3 to 5 hrs.
[d] Reaction temp. -4 to + 1°C
[e] Pure epoxide was isolated by precise fractionation.

Fig. 4



1 2 15 22



18 19 20 21

Reagents: i) Li, Na or K-PEG-400

Fig. 5. ISOMERIZATION PRODUCTS OF α-PINENE EPOXIDE AND CARENE EPOXIDE USING ALKALIMETAL AND PEG-400

was extremely sluggish and at higher temperatures and longer reaction times, only moderate conversions (72%) could be affected. Selectivity of t-pinocarveol (2) formation in the product mixture increases dramatically as we go from potassium to lithium. Ratio of the two allylic alcohols (2) and (15) in the product mixture when Li, Na and K were used along with PEG-400 was 27:1, 7:1 and 3:1 respectively (Table-2, Fig. 6). Formation of (2) and (15) from (1) during isomerization has been already reported and well-established earlier[19].

Higher reactivity and lower selectivity for (15) of potassium with PEG-400 is attributed to the known[34] ability of PEG-400 to coordinate more effectively with potassium cation resulting in a more reactive but sterically less demanding alkoxide end of PEG. Even in absence of coordination by PEG chain, the basicity of a given alkoxide decreases with decreased electropositivity of metal ions.[16] This pattern is clearly reflected in the results obtained with sodium and lithium metals. Consequently, with sodium metal where ion pair formation may be more pronounced than with potassium metal, reaction proceeds at a slower rate resulting in lower conversions, but formation of t-pinocarveol (2) selectively in larger amounts. In case of lithium, there is a radical decrease in reactivity with

Table 2. Isomerization of pinene-epoxide (1)

Sr. No.	Alkali metal[a]		Time (hr)	Crude gm(%)	Products Dist. gm(%)	Res. gm(%)	GC Analysis[d]					Recovery % (Con. %)	Yield[e] %
	gm.	mole					Epoxide 1(%)	Ketone 22(%)	3°-alc. 15(%)	2°-alc 9(%)	others %		
1.	Potassium 0.78	0.02	5.25[b]	3.1703 traces of solv.	2.3478 (80)	0.1231 (4.1)	3.8	1.9	23.43	69.75	1.01	84.1 (96.96)	57.75
2.	Sodium 0.46	0.02	5.25[b]	2.9747 (93.25)	2.5589 (80.21)	0.2157 (6.85)	12.17	4.9	8.32	60.00	14.1	87.07 (90.24)	53.34
3.	Lithium 0.14	0.12	14c	2.8040 (93.2)	2.4857 (82.86)	0.2857 (9.52)	30.69	2.06	2.58	55.16	0.51	92.38 (72.1)	53.76

[a] Epoxide (3.04 gm, 0.02 mole) and PEG-400 (12g, 0.03 mole) were used for the isomerization.

[b] Reaction temp. 135°C

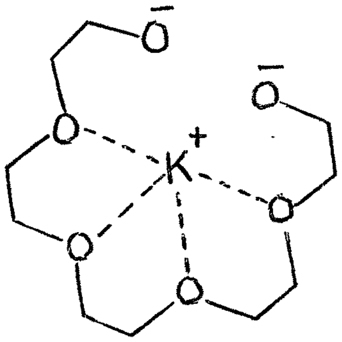
[c] Reaction temp. 150°C

[d] GC analysis was performed by programmed Glc (tracing enclosed, Fig. 10)

[e] Yield was calculated based on epoxide consumed.

Fig. 6

concomitant improved selectivity for (2) in the product mixture.


Complexed salt

$Li^{+}\,{}^{-}O\!\left(CH_2-CH_2-O\right)_n CH_2-CH_2-O^{-}\,Li^{+}$

ion pair formation

Pedersen[31] has observed that the complexing power can be expected to be weak when the hole in polyether is too small or two large for the cation, because the salt polyether complexes are formed by ion-dipole interaction between the cation and the negetively charged oxygen atoms symmetrically arranged in the polyether ring. Poor reactivity of lithium metal is evidently due to small size of its cation[50a] (ionic diameter 1.20 A^{o}).

Carene epoxide (18) upon isomerization using Na-PEG-400 (bath 135°, 5.25 hr) gave product consisting of all the three allylic alcohols (19), (20) and (21) as shown in Fig. 5 with moderately good recoveries (76.5%). Ratio of 2°-allylic alcohols (19)[50b] and (20)[50b] to that of 3°-alcohol (21) was almost 1:1 as detected from PMR.

Menthene epoxide under the reaction conditions gave poor recovery of the products with poor conversion. Limonene epoxide on the other hand led to extensive polymerization. Terpinolene epoxide gave a complex mixture as products consisting hydrocarbon (p-cymene) as the major constituent.

One of the advantage of doing reaction with phase-transfer catalyst is that, alkali metal hydroxides can be employed instead of alkali metals. So next attempts were directed towards using alkali metal hydroxides along with PEG-400. When α-pinene oxide (1) was subjected to isomerization using PEG-400 and NaOH, under usual reaction conditions (bath 135-140°C, 8 hrs) it showed no isomerization, but at very high temperature(bath 175°C, 2.5 hrs), TLC monitoring showed traces of epoxide (1). Product after usual work-up was analyzed by PMR and found to be a complex mixture consisting of unreacted epoxide (1), aldehyde (17), t-pinocarveol (2), ketone (22) and 3°-alcohol (15). Carene epoxide (18) with same reagent under the usual reaction conditions (bath 140 ± 3°, 3.5 hr) gave a mixture of allylic alcohols (19), (20) and (21) in ratio of 28.57: 12.78: 33.83% respectively along with some unchanged epoxide (16.9%) with moderately good recoveries (83.4%).

It is clear from the above study, that PEG-400 with different alkali metal hydroxides were not very effective reagents for isomerization of epoxides. It was then thought worthwhile to use a solvent along with PEG-400 and alkali metal hydroxides; with the assumption that it will help reducing polymerization, thus increasing the total recovery of the products.

When less polar solvents like toluene and xylene were used alongwith PEG-400-KOH for the isomerization of α-pinene epoxide (1), no isomerization was observed even when reaction mixture was refluxed for 6 hours at pot temperature 108° (toluene) or 132°(xylene). Azeotropic removal of water, did cause some isomerization but it was found that required alcohol (2) was further isomerized to ketone (22) under the reaction conditions as evident from IR (λ_{max} 1712 cm^{-1}) and GLC.

Since polar aprotic solvents readily solvate the cations and thereby enhance basicity of many metal alkoxides, they were next tried along with PEG-400 and alkali metal hydroxides for isomerization of epoxides. Out of pyridine and dimethyl sulfoxide (DMSO) were studied, the later was found to be superior as reaction proceeds at a faster rate in it.

It has been well documented in the literature[19], that under highly dissociating conditions such as alkoxides in DMSO, a more "E-1$_c$B-like" mechanism would impose less base discrimination by virtue of decreased directionality imposed by the counter ion. Testing this explanation by isomerizing (1) in t-BuOM-DMSO while varying the cation and thus the degree of dissociation gave result that are in agreement with but do not provide the dramatic difference in selectivity. Lithium, sodium and potassium *t*-butoxide provided (2) and (15) in ratio of 3.9:1, 3.4:1 and 2.8:1 respectively. In our case, change in alkali metal hydroxide, i.e. change in cations, does show more significant difference yielding (2) and (15) in ratio of 7.2 : 1 and 2.75 : 1 with sodium hydroxide and potasium hydroxide respectively (Table 3, Fig. 7). Lithium hydroxide-PEG-400 in DMSO shows no isomerization under the reaction conditions may be because of its very low dissociation. In case of alkali metal-PEG-400, change in cation had shown a more dramatic difference and provided (2) and (15) in ratio of 21.37 : 1, 7.2 : 1, and 3: 1 respectively for Li$^+$, Na$^+$ and K$^+$ (Table, 2, Fig. 6).

For the same metal hydroxide, say KOH-PEG-400, reaction in pyridine gave better selectivity by yielding (2) in considerable large amounts - of course with lower rate of conversion as compared to that in DMSO as solvent clearly, this is a result of lower dielectric constant (12.3) and poor solvating ability of pyridine compared to those of DMSO (Dielectric constant = 45).

Carene epoxide (18) does not show much selectivity yielding both (19) and (21) in the ratio 1: 1.3 using KOH (or NaOH) in DMSO (or pyridine). Once again reaction rate

Table 3
Isomerisation of pinena epoxide (1)

Sr. No.	Reactants[a]		Time[d] (hr)	Products			GC analysis[e]				Recovery[f] % (conversion %)	Yield[g] (%)
	PEG-400 gm(%)	M^+-OH gm(%)		Crude gm(%)	Dist. gm(%)	Res. gm(%)	Epoxide 1 (%)	Ketone 22(%)	3°-alc. 15(%)	2°-alc 2(%)		
1.	-	KOH[b] 1.68 (0.03)	18	4.3 (94.3)	3.43 (75.2)	0.775 (17)	4	major	minor	traces	92.2 (-)	-
2	9.6 (0.024)	KOH[b] 1.68 (0.03)	18	4.8 (traces of solv)	3.95 (86.6)	0.175 (3.95)	18	-	15 (1 : 4.47)	67	90.5 (84.5)	69
3	9.6 (0.024)	Na.OH[b] 1.2 (0.03)	18	4.15 (91)	3.97 (87.1)	0.135 (3)	35	-	8 (1 : 7.13)	57	90.0 (69.5)	71.38
4.	-	KOH[c] 1.68 (0.03)	6	4.7 (traces of solv.)	3.83 (84.0)	0.628 (13.78)	6.5	-	25 (1 : 2.6)	64.6	97.78 (94.54)	57.4
5.	9.6 (0.024)	KOH[c] 1.68 (0.03)	11	4.46 (98)	4.15 (91)	0.253 (5.55)	12.25	-	23.5 (1 : 2.74)	64.3	96.55 (88.85)	66.0
6.	-	Na-OH[c] 1.2 (0.03)	9	3.9 (85.5)	3.7 (81.1)	0.15 (3.3)	90	-	(10)		84.4	-
7.	9.6 (0.024)	Na-OH[c] 1.2 (0.03)	18	4.84 (traces of solv.)	4.0 (87.72)	0.293 (6.4)	13.5	-	15.48 (1 : 4.6)	71.03	94.12 (88.16)	70:68
8.	9.6 (0.024)	LiOH[c] (0.03) 0.72	20	4.46 (98)	4.3 (94)	0.12 (3.1)	96	-	-	-	97.0	-

[a] 4.56 gm of epoxide (0.03 mole) was used; [b] Pyridine was used as solvent (25 ml); [c] DMSO was used as solvent (15-25 ml)
[d] Temp. of the reaction 125 ± 2°C; [e] GC: tracing enclosed, Fig. 12; [f] Recovery = distillate + residue;
[g] Yield was calculated based on epoxide consumed.

Fig. 7

in DMSO solvent was found to be superior which gave almost quantitative (99%) conversions (Table 4, Fig. 8).

Surprizingly KOH in DMSO alone (in absence of PEG) was found to be a stronger base which gave 94.5% conversion after just 6 hours. While KOH-DMSO-PEG-400 combination gave 88.2% conversions even after 11 hours (entries 4 & 5, Table 3, Fig. 7). Also NaOH-DMSO was found to be practically in-effective in bringing out isomerization of epoxide whereas addition of PEG-400 to this reagent effectively isomerizes epoxide (entries 6 & 7, Table 3, Fig. 7). These results can be rationalized by presuming that DMSO strongly solvates K^+ ions, thus producing a strong but less selective base[51]. Solvation of Na^+ ions, on the otherhand, is reported to be much less, in addition, the basicity of alkoxide ion is weakened by ion pair formation with sodium ion, Na^+ CH_2-SO-CH_3. The results of alkali metal hydroxides in DMSO-PEG combination can be explained by presuming that the two solvents interact with each other in a manner that different size holes are formed when both K^+ and Na^+ ions can be coordinated. NaOH-pyridine-PEG was found to be a less reactive (69.5% conversion) but more selective reagent (entry 3, Table 3, Fig. 7.)

Table -4 - Isomerization of carene epoxide

Sr. No.	Reactants PEG-400 gm (mole)	M^+-OH gm (%)	Time[e] (hr)	Crude gm(%)	Products Dist. gm(%)	Products Res. gm(%)	GLC Analysis[f] Epoxide <u>18</u>(%)	GLC Analysis[f] 3°-alc. <u>21</u>(%)	GLC Analysis[f] 2°-alc. <u>19</u> (%)	Recovery[g] % (conversion %)	Yield (%)
1	(-)[a]	KOH[c] 1.68 (0.03)	6	4.4 (96.49)	3.92 (85.96)	00.38 (8.3)	6.1	50.7 (1.2: 1)	41.1	94.26 (93%)	35.33
2	4.0[b] (0.01)	KOH[c] 2.8 (0.05)	5	7.3 (96)	6.99 (92)	0.288 (3)	-	53.8 (1.26: 1)	42.6	95 (100%)	39.18
3	6.0[b] (0.015)	NaOH[c] 2.0 (0.05)	16	7.4 (97.4)	6.9 (90.8)	0.22 (2.9)	5.6	44 (1.0: 1.06)	46.8	93.7 (93.4)	42.49
4	(-)[a]	KOH[d] 1.68 (0.03)	2.5	4.4 (96.5)	4.003 (87.8)	0.227 (5)	-	53.8 (1.39: 1)	38.5	92.8 (100)	33.8
5.	(-)[a]	NaOH[d] 1.2 (0.03)	7	-	-	-	90	traces	traces	-	-
6.	6.0[b] (0.015)	NaOH[d] 2.0 (0.05)	5	7.4 (97.4)	6.9 (90.8)	0.30 (4)	1.4	52.5 (1.27:1)	42.8	94.8 (99)	38.85

[a] 4.56 g (0.03 mole) of epoxide was used. [b] 7.6 g (0.05 mole) of epoxide was used. [c] Pyridine (10-15 ml) was used as solvent [d] DMSO (10-15 ml) was used as solvent.

[e] Temp. of the reactions 130 ± 5°C.

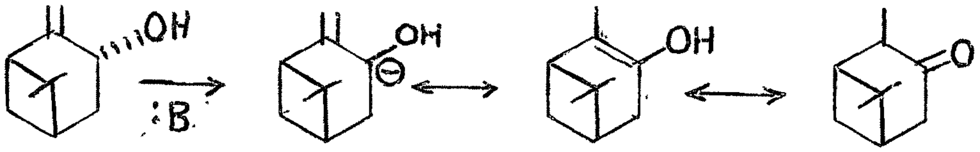
[f] GC: tracing enclosed (Fig. 13)

[g] Recovery = distillate + residue)

[h] Yield was calculated for 2°-alcohol (<u>19</u>) based on epoxide consumed.

Fig. 8

KOH-pyridine isomerization (without PEG-400) of (3) gave ketone (22) as the major product of isomerization along with 3^{0}-alcohol (15) (entry 1, Table 3, Fig.7). Formation of ketone may be expla~~i~~ined by further isomerization of (2) via. carbanion formation at the carbon and to the hydroxyl group under the reaction conditions.



Finally we can conclude from the data available:

(i) using alkali metals and PEG-400, Lithium metal gave selective product but with very low conversion whereas potassium metal gave both (2) and (15) with better conversion with poor selectivity.

(ii) using pyridine-KOH, t-pinocarveol (2) further isomerized to ketone (22) under the reaction conditions which was not the case if we use PEG-400 (entries 1 & 2, Table 3, Fig. 7).

(iii) DMSO-KOH gave both (2) and (15) in ratio comparable to reported[19] results earlier

(iv) For NaOH, either using DMSO or pyridine as solvent, PEG-400 is must to carry out the transformation.

(v) DMSO as solvent for any combination of base, gave better conversions but with poor selectivity, whereas pyridine as solvent shows better selectivity with poor conversion.

Carene epoxide (18) behaves similarly for all the above mentioned combinations and isomerizes to (19) and (21) in ratio of 1: 1.25 to 1:1.35 (Table 4, Fig. 8). Even with KOH-pyridine it gave (19) and (21) whereas same reagent cause further isomerization of (2) in case of pinene epoxide (1). This can be explained as, in case of carene epoxide (18), once the allylic alcohol (20) has formed, methylene proton adjescent to cyclopropane ring can be easily abstracted by the base, resulting in the formation of stable endocyclic isomer (19). The ratio of (19) and (21) was found to be 1.06 : 1 when carene epoxide (18) was isomerized using NaOH-PEG-400 in pyridine as solvent, as detected from GC.

Menthene epoxide, limonene epoxide and terpinolene epoxide, behaves similarly as described earlier, hydrocarbon being the major product of isomerization.

It is clear that carene epoxide (18) up on isomerization using any combination of base (described earlier), gave both 2^{0}-alcohol (19) and 3^{0}-alcohol (21) in almost 1 : 1.3 ratio. (Formation of (21) is described in Chapter 2 of this part). So, efforts had been diverted to develop an isomerization process in which formation of (21) will be suppressed. Aluminium alkoxide (aluminium t-butoxide or aluminium isopropoxide) did suppress its formation when isomerization was carried out in aprotic solvent (pyridine or DMSO)*.

It was interesting to observe that using pyridine as solvent reaction was bit sluggish causing residue formation to an extent of 23% with moderate recovery of 84% along with hydrocarbon (10-15%) formation, whereas DMSO once again proved to be a superior solvent showing faster reaction with the least formation of hydrocarbons (3-4%) and residue (5.8%), recovery being more than 90%, giving (19) and (20) as product 39.68 and 50.8% respectively along with

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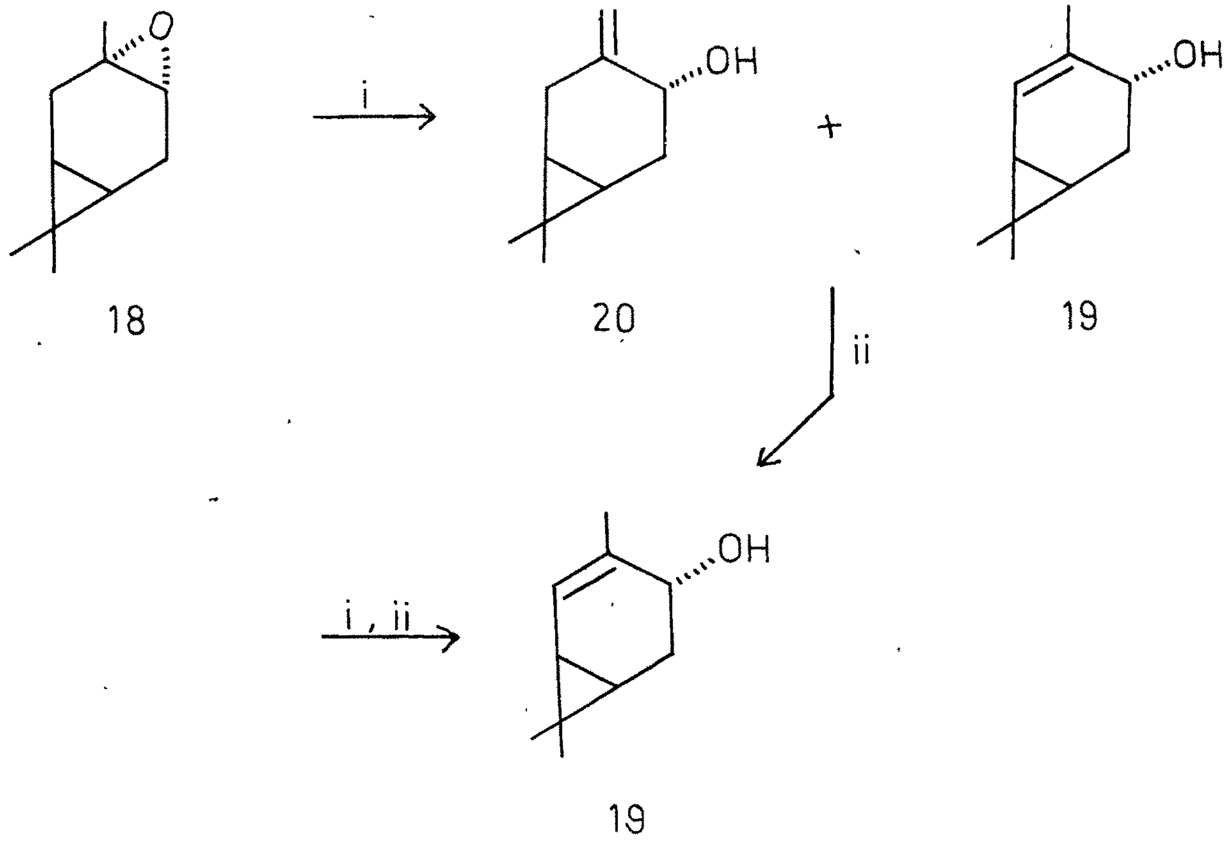
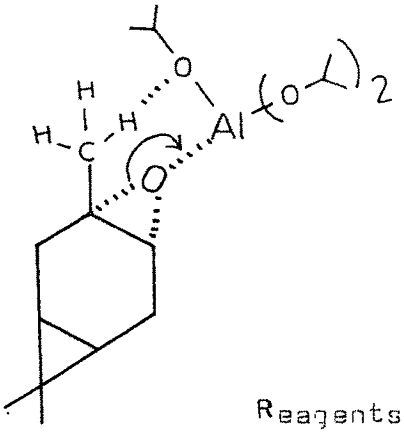
* Aluminium isopropoxide in toluene appears to be too acidic and gave mainly dehydration products beside minor amount of 2^{0}-alcohol (19) and unchanged α-epoxide (18).

unreacted epoxide (3.17%), hydrocarbon (3.17%) and unidentified products (3.17%).

The *exo*-alcohol (20) was isomerized to (19) either by insitu further isomerization by adding KOH powder to the reaction mixture or by subsequent isomerization of the products obtained after usual work-up, using DMSO-KOH, considering its ability to isomerize *exo*-alcohol (20) into (19) (from the earlier experiments in which using DMSO-KOH, in the products, only (19) was found to be present) and no exo-alcohol (20) was found even in trace amount. This transformation may be accounted for by the fact that the system of double bond conjugated with cyclopropane ring, resembles stable conjugated double bond system.

The formation of 3°-alcohol (21) was suppressed using aluminium alkoxide in aprotic solvent can be rationalized as being the result of metal co-ordination of metal cation with oxygen and a concurrent weakening of C-O bond in the direction which results in greatest stabilization of the incipent partial positive charge, i.e. C_2-O. This increases the acidity of a proton at C_{10} and favours the formation of (20) which under the reaction conditions further isomerizes partly to (19) (Fig. 9).





Reagents: i) Aluminium isopropoxide-DMSO
ii) DMSO-KOH

Fig. 9: ISOMERIZATION PRODUCTS OF CARENE EPOXIDE USING ALUMINIUM ISOPROPOXIDE

When α-pinene epoxide (1) was subjected to isomerization using aluminium isporppoxide under the similar reaction conditions, results in product to be a complex mixture consisting of *t*-pinocarveol (2) 69.7% along with ketone (22) 2.9%, aldehyde (17). 17%, and other unidentified products 5.4%, epoxide 5% being uncoverted with quantitative recovery, as detected from GLC.

EXPERIMENTAL

All b.ps are uncorrected. Light petroleum refers to fraction b.p. 60-80^o. All solvent extracts were finally washed with brine and dried (Na_2SO_4). Silica gel for chromatography (-100, + 200 mesh) was washed with hot water, till sulphate-free, dried and activated at 125-130^o for 6 hr and standarized[52]. TLC was carried out on silica gel layers (0.25 mm) containing 15% gypsum and activated at 110-115^o (2 hr); solvent system, 15% Ethyl acetate in toluene; spray reagent, 1% vanillin in 50% H_3PO_4 aq.

The following instruments were used for spectral/analytical data: Schmidt + Haensch electronic polarimeter model Polatronic 1; Perkin-Elmer model 267 Infrared spectrophotometer; Hewlett-Packard 5712A and 7624A Gas Chromatographs (Al columns, 180 cms x 0.6 cm, unless stated otherwise; support 60-90 mesh Chromasorb W; carrier gas H_2). All ^{1}H-NMR spectra were recorded with 15-20% soln in CCl_4 with TMS as internal reference; signals are reported in ppm(δ); while citing ^{1}H-NMR data, following abbreviations have been used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad).

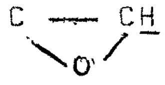
General procedure for the preparation of epoxides

Azeotropic peracetic acid (0.12 mole) was added dropwise to a stirred mixture of the olefin (0.1 mole) and $NaHCO_3$ (0.13 mole) in $CHCl_3$ (1:3 w/v of olefin) at -5 to 0^oC. The contents were stirred at the same temperature till epoxidation was completed (TLC and TNM test). It was then diluted with water (100 ml) and stirred well (15 mins.). The layers were separated and the aqueous layer was extracted with chloroform (15 ml x 2). The combined organic layers were washed with 5% $Na_2S_2O_3$ aq (30 ml), 20% Na_2CO_3 aq. (15 ml) and water (15 ml). Removal of the solvent followed by precise fractionation using a spinning-band column (45 theoritical plates) furnished the pure epoxide. Results are summarized in Table-1 (Fig. 4). The pure epoxides had the following characteristics:

(i) 2α,3α-Epoxy pinane (**1**):Colourless liquid

b.p. $73-79^o/12$ mm (Lit.[53], b.p. $91-93^o/27$ mm.

IR (liq.) Epoxide 860 cm^{-1}

^1H-NMR: 

$\underbrace{C - CH}_{O}$ (1H, bs, 2.9 ppm).

(ii) <u>p-3-Menthene epoxide</u>: Colourless liquid

b.p. $87^\circ/20$ mm (Lit.[53], b.p. $96\text{-}100^\circ/400$ mm)

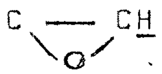
IR (liq.): Epoxide 855 cm^{-1}

^1H-NMR:  (1H, bs, 2.75-2.8 ppm)

(iii) <u>Limonene epoxide</u> : Colourless liquid

b.p. $91^\circ/18$ mm

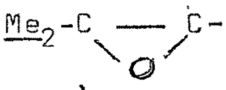
IR (liq.): Epoxide 845, 888 cm^{-1}.

^1H-NMR:  (1H, 2.89 ppm).

(iv) <u>Terpinolene epoxide</u>: Colourless liquid

b.p. $95^\circ/25$ mm

IR (liq.): Epoxide 855 cm^{-1}

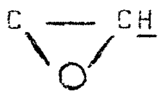
^1H-NMR:  (6H, 1.28 and 1.31 ppm)

(v) <u>3α,4α-Carene epoxide</u> (<u>18</u>): It was prepared by a known[36] procedure.

Colourless liquid

b.p. $82\text{-}5^\circ/10$mm (Lit.[54] b.p. 102-3/48 mm)

IR (liq.): Epoxide 840 cm^{-1}

^1H-NMR:  (1H, bs, 2.63 ppm)

General procedure for the isomerization of oxiranes using alkali metals and PEG-400:

To a 50 ml three-necked flask (equipped with thermowell, reflux condensor, nitrogen inlet and a magnetic bar) was charged PEG-400 (12 g, 0.03 mole) and alkali metal (0.02 g. atom) was dissolved (110°, 4 hr) while stirring under dry inert gas (N_2). The epoxide (0.02 mole) was then added at room temperature (25 ± 2°C) and the contents were stirred (130-135°C) till the maximum conversion of oxirane was obtained (monitored by TLC). The reaction mixture was then cooled (25 ± 2°C) and diluted with ice water (25 ml, exothermic) while stirring. The product was taken up in light petroleum (20 ml x 3). After the usual work-up, the crude product was distilled (Bath 100-120°C, 3-5 mm) and the distillate was analyzed by ^{1}H-NMR and a programmed GLC 3%, D(DEGS) on Chromasorb W 60-80, 6', 80-148-4°/min., carrier gas H_2), The results are summarized in Table I (Fig. 4)

(i) Isomerization of pinene epoxide (1)

The results are summarized in Table-2 (Fig. 6).
GC (Fig. 10).

(ii) Isomerization of carene epoxide (18)

Carene epoxide (18, 3.04 g, 0.02 mole) was isomerized using Na (0.46 g, 0.02 g atom) and PEG-400 (12 g, 0.03 mole) under the reaction conditions (135°, 5 hr). The usual work-up furnished a crude product (2.665 g, 87.28%) with comolete conversion of epoxide. The crude product was distilled to yield distillate (2.14 g, 70.1%) and the residue (0.1927g, 6.3%) with total recovery of 76.4%. The distillate was analyzed on ^{1}H-NMR and was found to be a mixture of 2°-allylic alcohols (19 and 20) and 3°-allylic alcohol (21). The ratio of 2°-alcohols (19 and 20) to 3°-alcohol (21) was found to be almost equal (1:1).

Isomerisation of pinene epoxide (1) using PEG-400 and NaOH:

NaOH (0.053 g., 0.0013 mole, oowder) was dissolved in PEG-400 (5.264 g., 0.01316 mole) at 80°(0.5 hr) while stirring under nitrogen atmosphere. The eooxide (1 g, 0.00658 mole) was then added and stirred at 140° (5 hr). It was found that the epoxide remain intat (TLC, ^{1}H-NMR). At higher temperature (170°, 2.5 hr), epoxide was present in traces (TLC). The usual work-up furnished a crude product (0.7765 g, 77.65%) which was analyzed by ^{1}H-NMR and found to be a comolex mixture consisting of unreacted epoxide (1), aldehyde (17), *t*-pinocarveol (2), ketone (22) and 3^o-alcohol (15).

Isomerization of carene epoxide (18) using PEG-400 and NaOH

NaOH (2 g, 0.05 mole, powder) was dissolved in PEG-400 (20 g., 0.05 mole) at 80^o (30 min.) under nitrogen atmosphere. The epoxide (18, 15.2 g., 0.1 mole) was then added at room temperature and the contents were stirred at 140 ± 3^{o}C (3.5 hr). The usual work-up and distillation of the crude product furnished a distillate (12.66 g., 79.34%) and the residue (0.6268 g., 4.0%) with 83.34% total recovery. The distillate was analyzed on GLC (glass column, 5% CW, 6', H_2 as carrier gas, 110^{o}C) as as well as by ^{1}H-NMR and was found to be a mixture consisting of unchanged epoxide (18, 17%), 3^o-alcohol (21, 34%), 2^o-alcohol (19, 29%) and an *exo*-alcohol (20, 13%), with some other unidentified products (7%), conversion being 86.84%).

Isomerization of pinene epoxide (1) using PEG-400 and KOH in toluene

KOH (1.12 g., 0.02 mole) was dissolved in PEG-400

(1.6 g., 0.004 mole) and toluene (10.15 ml) by removing water azeotropically. The epoxide (3.04 g., 0.02 mole) was then added and the contents were refluxed (109-110°C, 13.5 hr). The usual work up gave the crude product (2.36 g., 86.5%) which was distilled to furnish distillate (1.9 g., 62.5%) and the residue (0.68 g., 22.4%). The distillate was analyzed on GLC (Fig. 11., 5% P, support Chromosorb W 60-80, 6', carrier gas H_2, 110°) and was found to be a mixture of ketone (22) 31.5%), 3°-alcohol (15, 28%), *t*-pinocarveo (2, 21.8%), unreacted epoxide (1, 3%) and unidentified products (11%). Ketone was also confirmed by IR (λ_{max}^{neat}) 1712 cm^{-1}).

General procedure for the isomerization of epoxide using alkali metal hydroxides and PEG-400 in aprotic solvents (DMSO or pyridine)

To the dry assembly consisting of 25 ml three necked flask, equipped with thermowell, perkin triangle, magnetic bar and an addition funnel, were charged powdered alkali metal hydroxide (0.03 mole) and PEG-400 (0.024 mole) using solvent (10 ml). The metal hydroxide was dissolved while stirring (100-120°C, 0.5 hr) and the epoxide was then added at room temperature using solvent (15 ml). The contents of the flask were stirred at 125-127^{0}C till the maximum conversion of the epoxide was obtained. When pyridine was used as the solvent, to maintain a reaction temperature (125-127^{0}C), part of it (7-10 ml) had to be distilled off. The usual work-up gave the crude product which was distilled (bath 100-120^{0}/53 mm to furnish a distillate which was analyzed on GLC.

(i) Isomerization of pinene epoxide (1): The results are summarized in Table-3 (Fig. 7), GLC (Fig. 12).

(ii) Isomerization of carene epoxide (18): The results are summarized in Table-4 (Fig. 8), GLC (Fig. 13).

General Procedure for the isomerization of epoxide using KOH and DMSO or pyridine

KOH (0.03 mole, powder) was dissolved in solvent (25 ml) at 50-70^{0}C (20-30 mins.). The epoxide was then added at room temperature and contents were stirred at 125-127^{0}C (till maximum conversion was obtained (monitored by TLC). The usual work-up gave the crude product which was distilled and analyzed.

(i) Isomerization of pinene epoxide (1). The results are summarized in Table 3 (Fig. 7), GLC (Fig. 12).

(ii) Isomerization of carene epoxide (18). The results are summarized in Table 4 (Fig. 8), GLC (Fig. 13).

Isomerization of carene epoxide (18) using $Al(OiPr)_3$-DMSO.

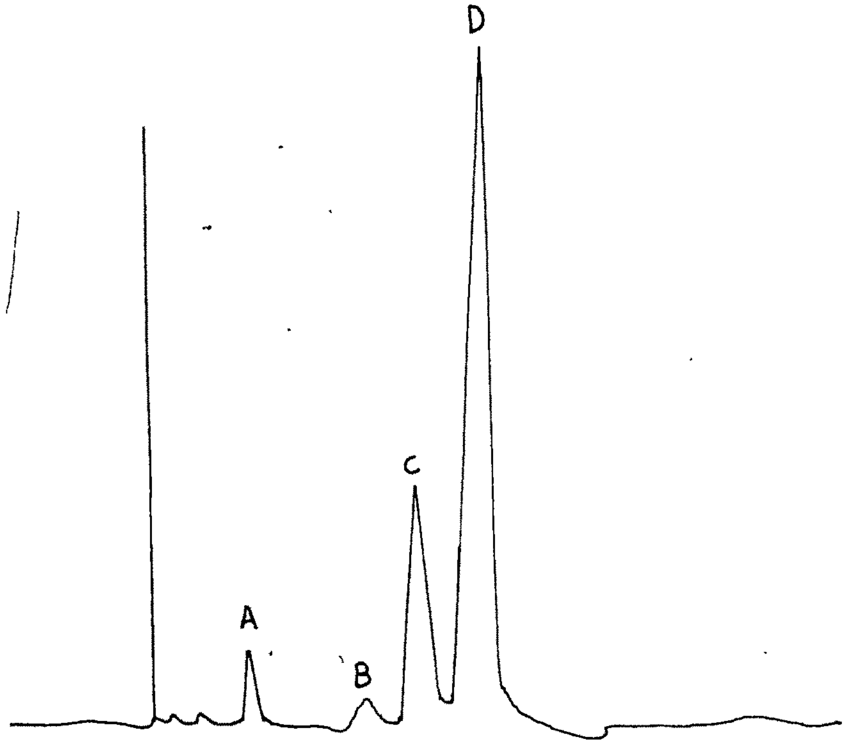
In a 100 ml three-necked flask, equipped with thermowell, magnetic bar, nitrogen inlet and a reflux condenser, were charged aluminium isopropoxide (10.2 g., 0.05 mole) in DMSO (30 ml) under nitrogen atmosphere. The epoxide (15.2 g, 0.1 mole) was then added and contents were stirred at 115°C (7.5 hr):

(a) 20% NaOH aq (15 ml) was added at 30°C (exothermic) and the reaction mixture was extracted with light petroleum (25 ml x 3). The usual work-up gave the crude product (14.5 g, 95.4%) which was distilled to furnish a distillate (12.8 g, 84.2%, b.p. 78-84°/5 mm) and the residue (0.89 g, 5.8%). The distillate was analyzed on GLC (Fig. 14, 5% CW, glass column, 6', H_2, 110°) to be a mixture consisting of the unreacted epoxide (18, 3.0%), hydrocarbons (3.17%), 2°-alcohol (19, 40%), an *exo*-alcohol (20, 51%) and unidentified products (3%) with total recovery of 90%, conversion being 97.4%. GC yield of (19) and (20) obtained was 78.24%. ^{1}H-NMR (Fig. 15).

(b) *In situ* isomerization by adding KOH (8.4 g, 0.15 mole, powder) and stirring the contents of the flask at 125°C (2 hr), after the usual work up gave the crude product (14.3 g., 94%) which was distilled to yield distillate (11.2 g., 74%) and residue (1.9 g., 12.5%) with total recovery of 86.5%. The distillate was analyzed on GLC (Fig. 14), also by ^{1}H-NMR and was found to be a 2°-alcohol (19, pure) with 59.5% yield.

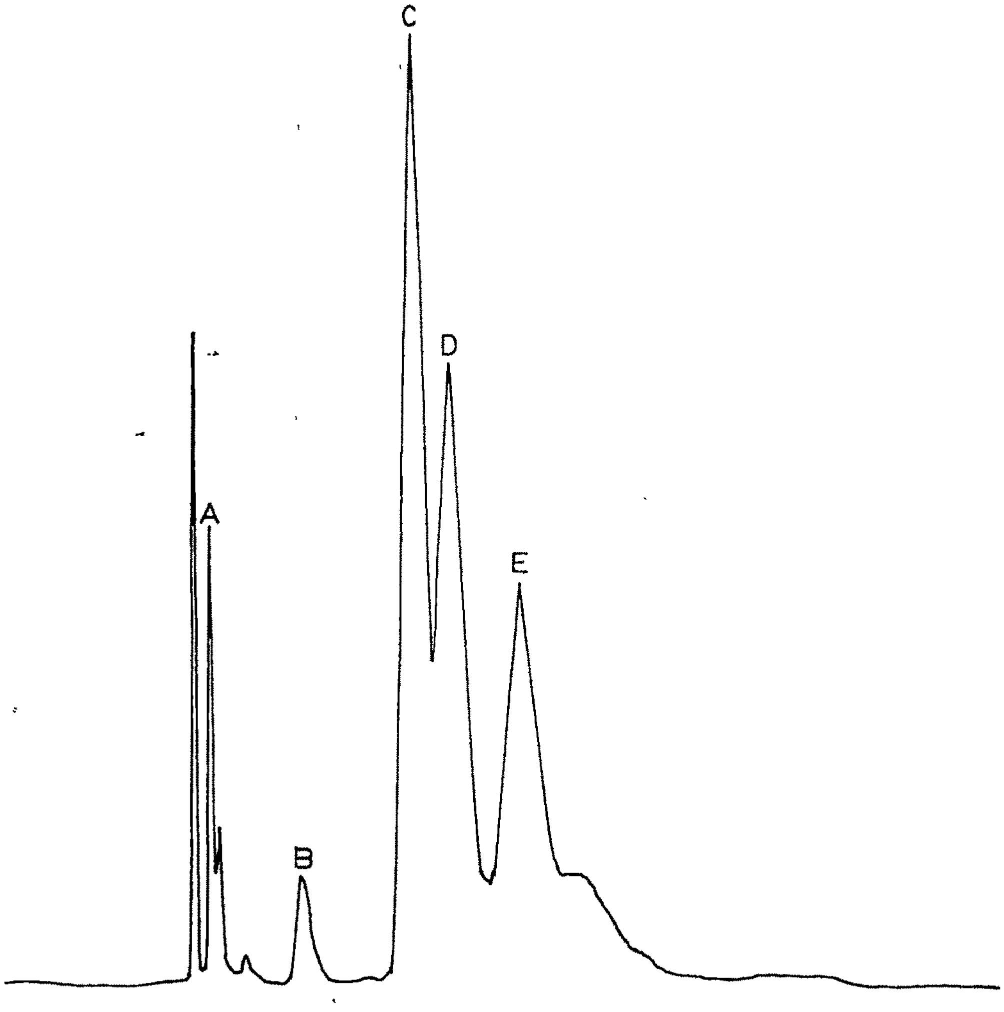
Isomerization of pinene epoxide (1) using $Al(OiPr)_3$

Pinene epoxide (1, 3.8 g, 0.025 mole) was isomerized using (2.5 g, 0.0125 mole) in DMSO (8 ml) at 90° (2 hr) while stirring under nitrogen. The usual work-up gave a crude product which was distilled to furnish a distillate (3.4 g., 89.5%) and residue (0.34 g, 8.9%) with complete conversion and recovery being 98.4%. The distillate was analyzed on GLC (Fig. 16, 10% CW, 12', 170°C) to be a mixture of 3°-alcohol (15, 5%), ketone (22, 2.3%), *t*-pinocarveol (2, 70%) and other products (22%) not investigated further. Percentage yield of *t*-pinocarveol obtained was 62.6%.



Column: 3% (P(DEGS) on chromosorb W-60-80
Hydrogen flow: 30 ml/min, Temp. 80°-140°, 4°/min.
A) Epoxide (1), B) Ketone (22), C) 3°-alcohol (15)
D) *exo*-Alcohol (2)

Fig. 10. PROGRAMMED GLC OF PINENE EPOXIDE ISOMERIZATION PRODUCT (USING POTASSIUM AND PEG-400)

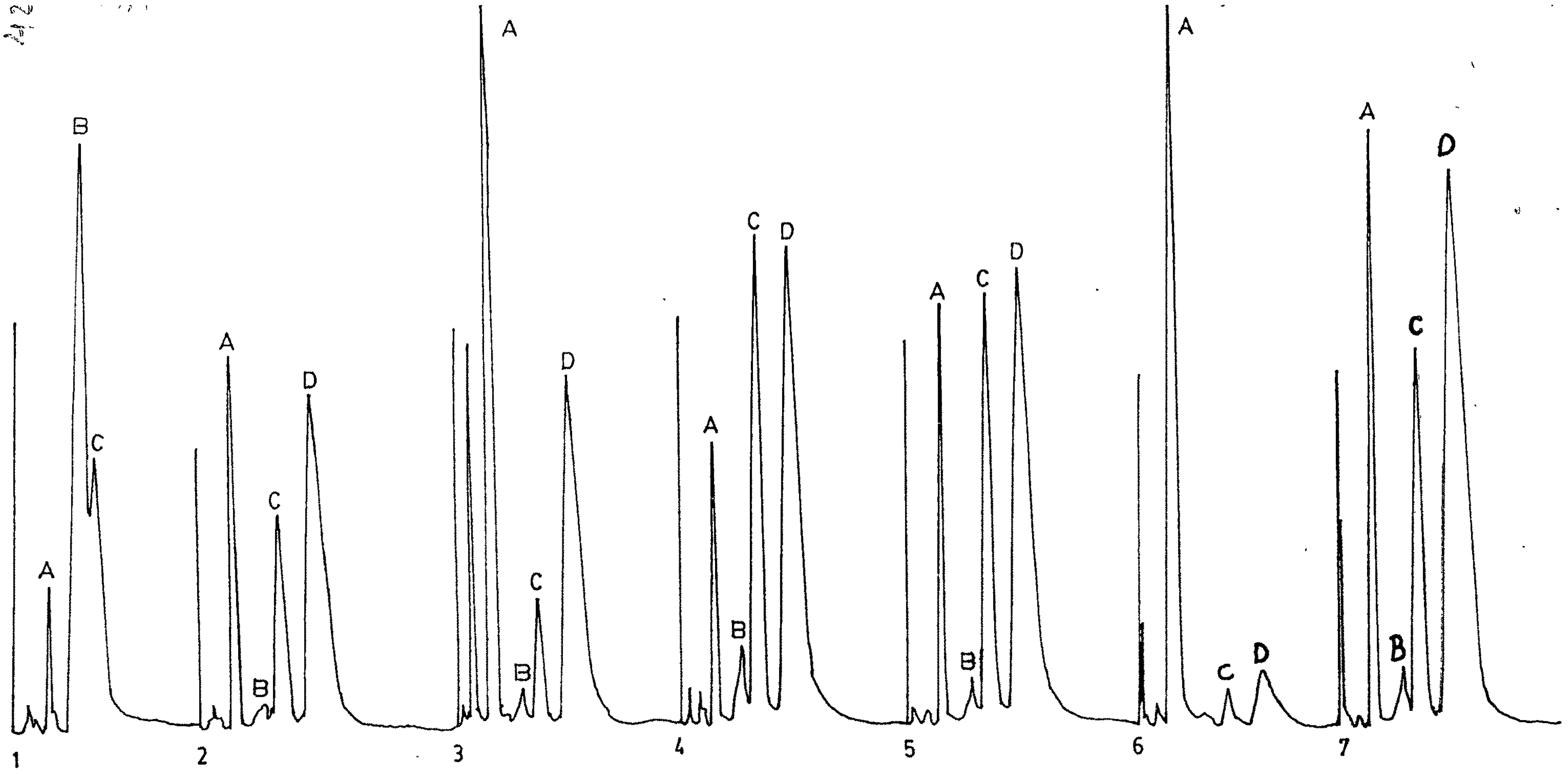


Column: 5% p on chromosorb W, HP 60-80
Hydrogen flow : 60 ml/min

Temp. 110°

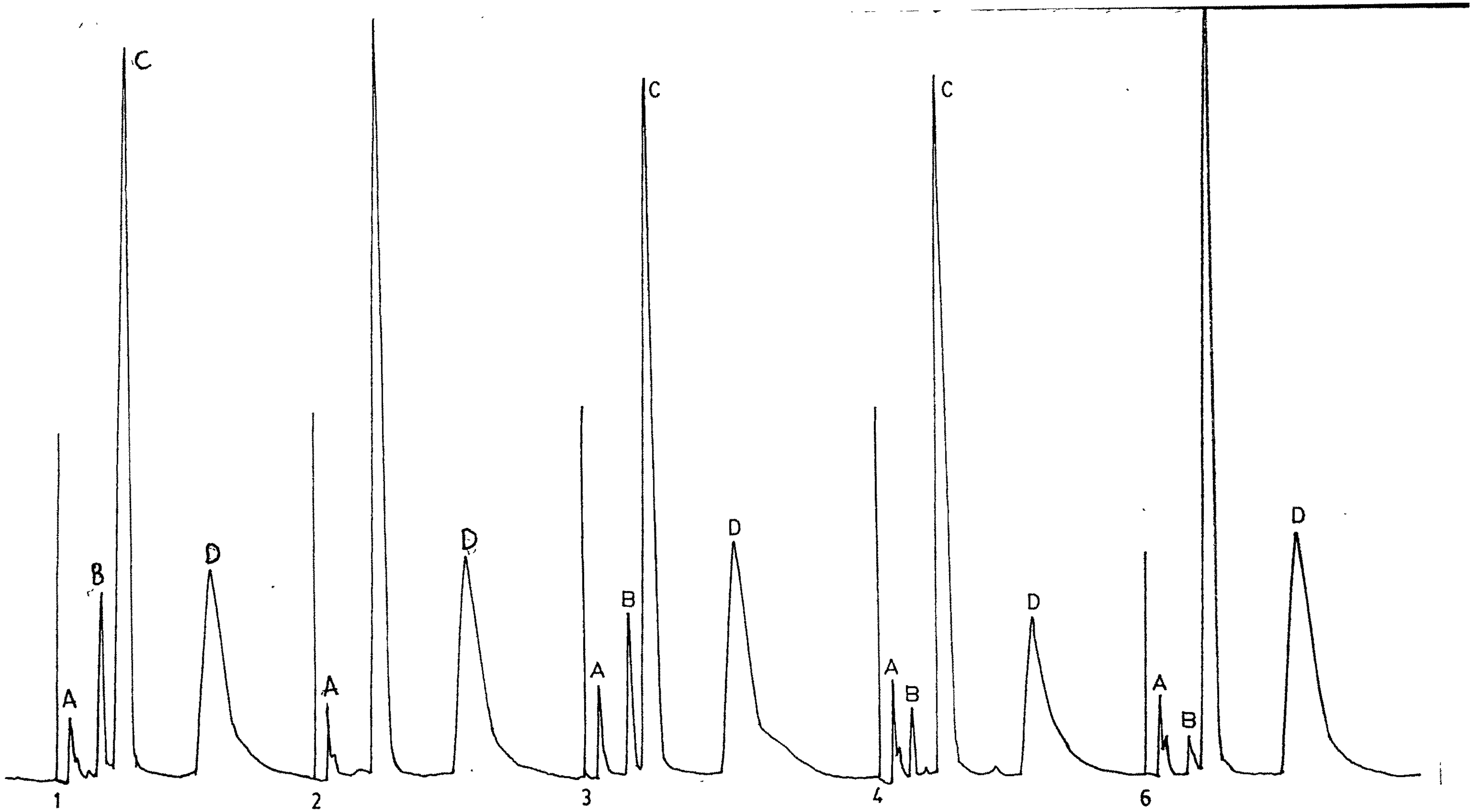
A) Solvent
B) Epoxide (1)
C) Ketone (22)
D) 3^{o}-alcohol (15)
E) *exo*-alcohol (2)

Fig. 11. GLC OF PINENE EPOXIDE ISOMERIZATION PRODUCT (USING KOH-PEG-400 IN TOLUENE)



Column: 5% CW 20M (6', glass column)
Hydrogen Flow : 60 ml/min, Temp. 110°
A) Epoxide (1): B) Ketone (22): C) 3°-Alcohol (15),
D) exo-Alcohol (2)

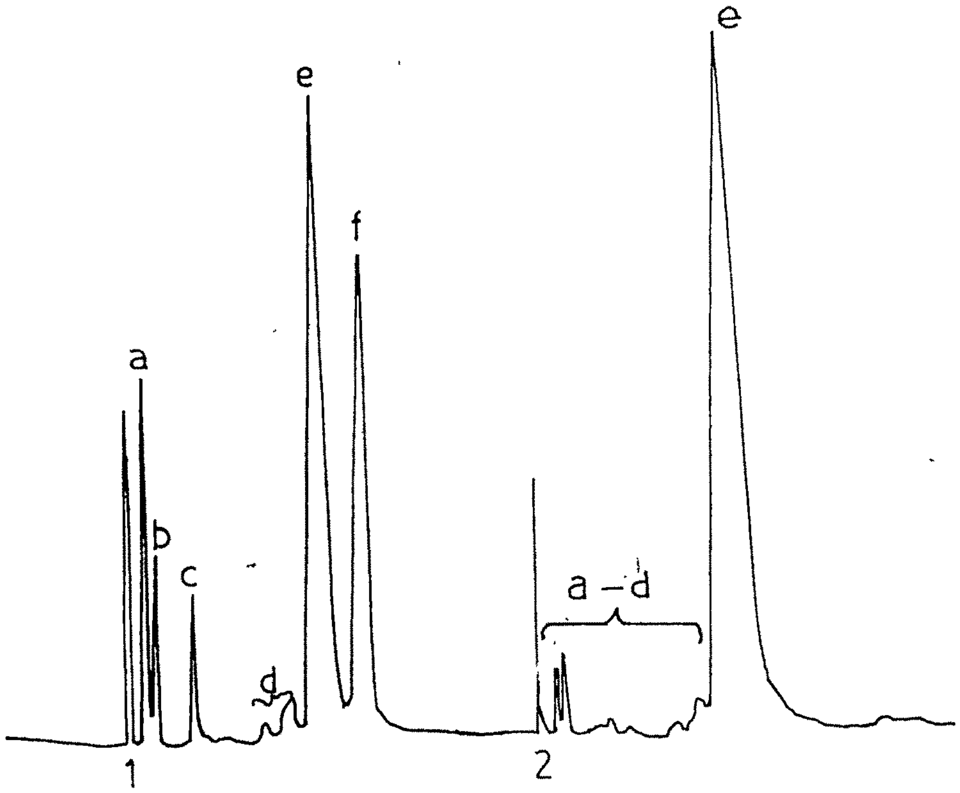
Fig. 12. GLC OF PINENE EPOXIDE ISOMERIZATION PRODUCTS



Column: 5% CW (6', glass column)
Hydrogen flow: 60 ml/min.: Temp. 110°

A) Solvent, B) Epoxide (18); C) 3°-alcohol (21); D) 2°-alcohol (19)

Fig. 13. GLC OF CARENE EPOXIDE ISOMERIZATION PRODUCTS (USING VARIOUS BASES)



Column: 5% CW 20M (6', glass column)
Hydrogen flow : 60 ml/min
Temp. 110

a-d) Hydrocarbons
e) 2^o-alcohol (19)
f) exo-Alcohol (20)

Fig. 14. GLC OF CARENE EPOXIDE ISOMERIZATION PRODUCT (USING ALUMINIUM ISOPROPOXIDE, ALUMINIUM ISOPROPOXIDE AND KOH).

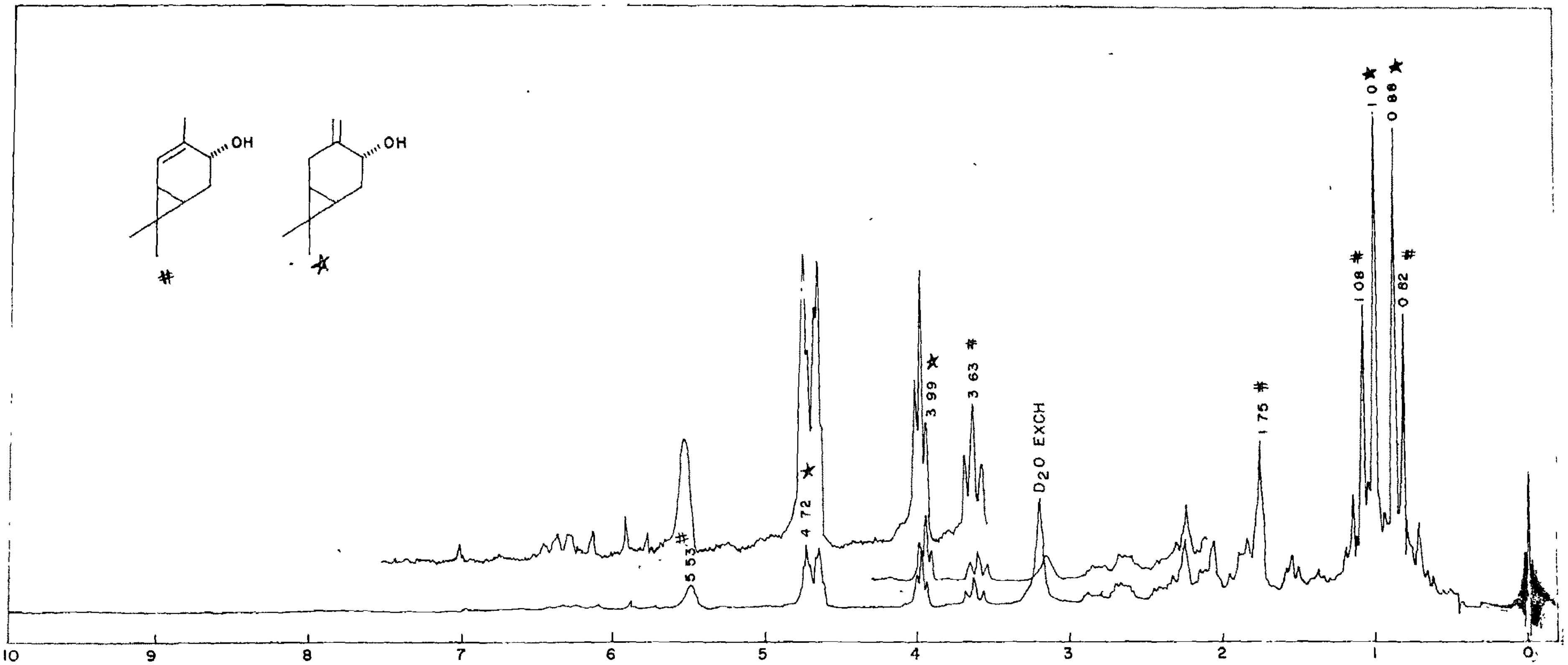
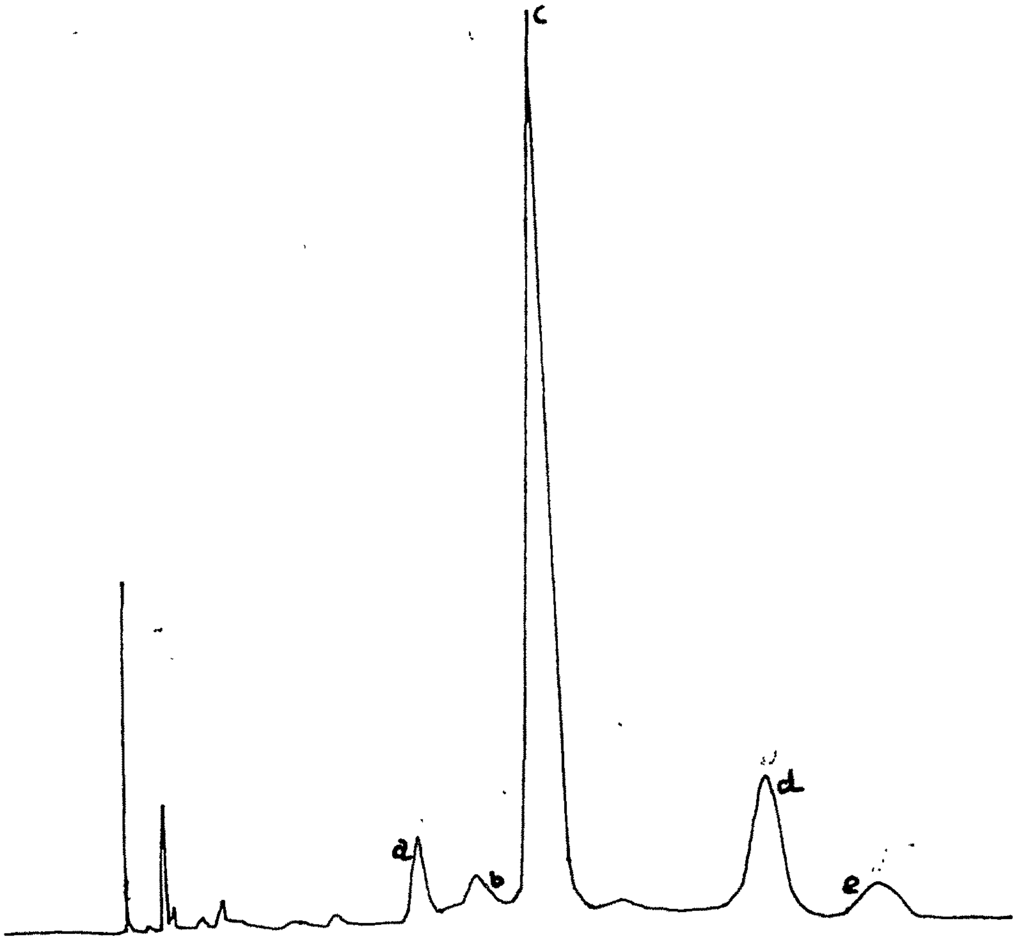


FIG.15 : ^{1}H-NMR SPECTRUM OF ISOMERIZATION PRODUCT OF CARENE EPOXIDE (USING Al(OiPr)$_3$ -DMSO.



Column : 10% CW 20M (360 cm x 0.6 cm, Al-column)
Hydrogen flow : 60 ml/min.
Temp. 170°

a) 3°-Alcohol (15)
b) Ketone (22)
c) *exo*-Alcohol (2)
d and e) Cleaved products.

Fig. 16. GLC OF PINENE EPOXIDE ISOMERIZATION PRODUCTS

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