CHAPTER - III

EQUILIBRIUM STUDIES ON CAMPHENE→TRICYCLENE TYPE SYSTEMS

INTRODUCTION

As has been pointed out earlier(preceding chapter) in our synthetic approach to α-santalol and α-santalene, the key step was to convert camphenic system into the tricyclic one. We wanted to evolve a general method for achieving this goal. Even before we do this, it would be relevant to summarize the work known in the literature regarding isomerization of pinene to camphene and further, to tricyclene(this would include camphene to tricyclene and also longifolene to longicyclene).

PAST WORK

1. PINENE: Isomerization of α-pinene using titanic acid[1](129.5°C) or titanium dioxide[2](110°C) gives camphene and tricyclene along with several other products. Similarly, using vermiculite[3] as catalyst (~120°C), camphene(58%) and tricyclene(8%) are produced from α-pinene along with other monoterpenic components. In the acid-activated kaolin-catalyzed[4] isomerization of α-pinene also, camphene(47.7-53.0%) and tricyclene (4.8-7.7%) are the major products. Another example yielding similar product composition is hydrobiotite[5] (activated with H_2SO_4) catalyzed isomerization. Vapour-phase isomerization[6] of α-pinene using diatomite as

the catalyst is no different from the above isomerizations.

From the above, since small quantity of tricyclene is always present in the product, it becomes clear that at least a portion of camphene, the major isomerization product of pinene, undergoes further isomerization to tricyclene. Various attempts which involve transformation of camphene into tricyclene and longifolene into longicyclene are briefly reviewed below:

2. CAMPHENE

Swann and Cripwell[7] studied the interconversion of camphene and tricyclene in the presence of $MgSO_4.H_2O$ and TiO_2 and found it to be an equilibrium reaction which establishes rapidly at the boiling point. At least, in the case of titanic acid, a ratio of 1:5.7 of camphene and tricyclene is reported by Rudakov[8]. Using 2% SiO_2-Ac_2O_3[9] as catalyst(~140°C), camphene rapidly isomerizes to yield[9] tricyclene with bornylene as a byproduct.

3. LONGIFOLENE

Longifolene, on reflux with AcOH and $Cu(OAc)_2$, gives[10] a product mixture comprising longicyclene(24%), isolongifolene(19%), and the unreacted longifolene (55%). Similarly, longicyclene, under above conditions, gives[10] a mixture of isolongifolene(15%), longicyclene(29%), and longifolene(51%). A product mixture consisting of longifolene(80%), longicyclene(8%), and isolongifolene(12%) is produced[11] when longibornyl chloride is treated with AcOH and NaOAc at reflux temperature.

The intermediacy of longibornyl cation in above isomerizations has been suggested[10,11].

PRESENT WORK

In continuation of the above work, we wanted to find out (a) if the presence of inorganic salts (e.g., $Cu(OAc)_2$ and NaOAc) is really necessary to bring about this isomerization and (b) what would be the effect of using other acetates, e.g., $Mn(OAc)_2$, $Mg(OAc)_2$, $Zn(OAc)_2$, $CO(OAc)_2$, KOAc, etc., on the yield of longicyclene.

We also found that 10% H_3PO_4 in dioxan brings about this type of isomerization in all the three series that we have tried, viz, camphene → tricyclene, longifolene → longicyclene, and β-santalene → α-santalene. C-3 epimeric products have been isolated from the reactions of 9-substituted camphenes.

The reaction is conceived to proceed through a carbonium ion derived from protonation of the exo-methylene group in Markonikoff fashion. It has also been found that nucleophilic moieties in the side chain at C-9 further complicate the reaction. All these points are brought out in some detail in this Chapter.

We have carried out these isomerizations using(a)acetic acid and (b) 10% H_3PO_4 in dioxan on camphene, longifolene, and 9-substituted camphenes. These are described below:

AcOH CATALYZED ISOMERIZATION

(a) Isomerization of Longifolene:

A 5% solution of longifolene in AcOH was refluxed for 24 hours. The product, obtained after usual work-up, was a mixture of isolongfolene(10.9%),longicyclene(22.1%), the unreacted longifolene(57.8%), and some other products (9.2%; not further investigated). When catalytic quantity of $Cu(OAc)_2$ was incorporated, the product contained, besides longifolene, isolongifolene(12.9%), longicyclene(21.2%), and other unidentified products (3.6%)(the reported[10] values are 19,24, and 2%, respectively). Other acetates like $Hg(OAc)_2$, $Zn(OAc)_2$,$CO(OAc)_2$,$Mn(OAc)_2$, $Mg(OAc)_2$,NaOAc, and KOAc were used and the results are summarized in Table 1.

TABLE 1

LONGIFOLENE - LONGICYCLENE - ISOLONGIFOLENE ISOMERIZATION

Longifolene(0.5 g), Catalyst(inorganic acetates) + AcOH(10 ml) was refluxed for 24 hours

	CATALYST	PRODUCT COMPOSITION (%)			
		ISOLONGIFOLENE	LONGICYCLENE	LONGIFOLENE	OTHERS.
1.	- - - -	10.9	22.1	57.8	9.2
2.	$Cu(OAc)_2$ (0.55 m moles)	12.9	21.2	62.4	3.6
3.	$Hg(OAc)_2$ "	15.9	17.9	61.8	4.5
4.	$Zn(OAc)_2$ "	13.4	18.8	61.7	6.1
5.	$CO(OAc)_2$ "	7.0	21.7	61.0	10.3
6.	$Mn(OAc)_2$ "	6.8	23.2	68.4	1.7
7.	$Mg(OAc)_2$ "	5.4	22.0	64.6	8.0
8.	NaOAc "	4.8	19.1	62.9	13.3
9.	KOAc "	6.6	22.6	68.3	2.6
10.	KOAc (1.10 m moles)	3.0	24.8	68.2	3.4
11.	KOAc (5 m moles)	7.0	24.1	67.6	1.3

Thus, it is found that the presence of inorganic salts for the above-said isomerization is not necessary but they do affect the course of the reaction as different product composition is obtained. Also, among the several acetates used, KOAc was found to be the best in the sense that it gives (a) the maximum amount of longicyclene(~25%), (b) comparatively less isomerization to isolongifolene(~3%), and (c) the minimum amount of side products.

(b) Isomerization of Camphene:

Camphene, when treated with AcOH at reflux temperature for 24 hours, gave, besides the unreacted starting material (35.64%), tricyclene(6.3%) and isobornyl acetate(58.1 %). Use of KOAc did not make much difference in the tricyclene content but the content of isobornyl acetate was definitely decreased by ~6.3%. Lower reaction temperature(~90°) was found better as it further suppresses the formation of isobornyl acetate. In this case, tricyclene constituted ~5% of the total product mixture. These results are summarized in Table 2.

TABLE 2

CAMPHENE - TRICYCLENE - ISOBORNYL ACETATE ISOMERIZATION

Camphene(330 mg) + Catalyst (inorganic acetate+
AcOH(10 ml) was refluxed for 24 hours.

	CATALYST	REACTION CONDITION	PRODUCT COMPOSITION(%)		
			TRICYCLENE	CAMPHENE	ISOBORNYL ACETATE
1.	- - - -	Reflux, 24 hours	6.3	35.7	58.1
2.	KOAc(1.10 m moles)	Reflux, 24 hours	6.6	41.6	51.8
3.	KOAc(1.10 m moles)	~90°C, 24 hours	5.0	79.3	15.7

Since under the above conditions, with camphene, isobornyl acetate was the major product and also the isomerization to tricyclene was less, we wanted to have a suitable reagent which would be of rather general applicability and would cover camphene to tricyclene type systems also. We tried 10% H_3PO_4 in dioxan on various systems discussed below and found it to be the catalyst of choice. This reagent was selected because of its(a) mild acidity and (b)easy availability.

Now, we describe the 10% H_3PO_4 in dioxan catalyzed isomerization of camphene, longifolene, and several 9-substituted camphenes, in sequel. Under the head of 9-substituted camphene, we shall discuss the isomerization of β-santalene, 9-bromomethyl camphene, 9-cyanomethyl camphene, and 9-hydroxymethyl camphene.

10% H_3PO_4 IN DIOXAN* CATALYZED ISOMERIZATION

(a) Isomerization of Camphene:

A solution of camphene in 10% H_3PO_4 in dioxan was refluxed and the reaction was monitored by glc at different intervals. Besides the starting material,

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* This reagent was prepared by adding water(2.8 ml) to a mixture of P_2O_5(7.25 g) and dry dioxan (50 ml). After dissolution of P_2O_5, volume was made up to 100 ml by adding dioxan.

tricyclene was the only product of the reaction which reached the maximum (21.5%) after 28 hours. A further increase in reaction time (34 hours) made practically no change in the composition of the product mixture. It can be, thus, concluded that during the reaction, the equilibrium condition is achieved essentially after 28 hours. These results are summarized in Table 3.

TABLE 3

CAMPHENE-TRICYCLENE ISOMERIZATION.

Camphene(0.33 g) + 10% H_3PO_4 in dioxan(10 ml), refluxed.

REACTION TIME(HOURS)		PRODUCT COMPOSITION(%)	
		TRICYCLENE	CAMPHENE
1.	4	4.5	95.5
2.	8	6.98	93.02
3.	12	9.52	90.48
4.	16	12.63	87.37
5.	24	16.48	83.52
6.	28	21.51	78.49
7.	34	21.62	78.36

b. Isomerization of Longifolene:

Longifolene also behaved similarly under the above conditions and furnished longicyclene besides longifolene; no isolongifolene formed upto 12 hours. The product mixture consisted of longicyclene(19.82%) and longifolene(80.18%). An aliquot analyzed after 22 hours gave the maximum yield of longicyclene(25.70%) but isolongifolene was also formed in small amount(5.56%).

It is surprising that no isolongifolene is detected in aliquots withdrawn upto 12 hours, but its formation is noted after 22 hours and further, after 34 hours, all the longicyclene and longifolene is isomerized to isolongifolene. This indicates that among isolongifolene, longifolene, and longicyclene, isolongifolene is thermodynamically the most stable product under these conditions. These isomerization results are summarized in TABLE 4.

TABLE 4

LONGIFOLENE-LONGICYCLENE-ISOLONGIFOLENE ISOMERIZATION

Longifolene(0.50 g) +10% H_3PO_4 in dioxan(10 ml), refluxed.

REACTION TIME(HRS)	PRODUCT - COMPOSITION(%)			
	ISOLONGIFOLENE	LONGICYCLENE	LONGIFOLENE	OTHERS
1. 2	0.00	9.28	90.72	0.00
2. 4	0.00	12.63	87.37	0.00
3. 6	0.00	15.32	84.68	0.00
4. 8	0.00	16.81	83.19	0.00
5. 10	0.00	18.64	81.36	0.00
6. 12	0.00	19.82	80.18	0.00
7. 22	5.56	25.70	66.64	2.08
8. 34	96.50	00.00	00.00	3.50

c. Isomerization of 9-Substituted Camphenes

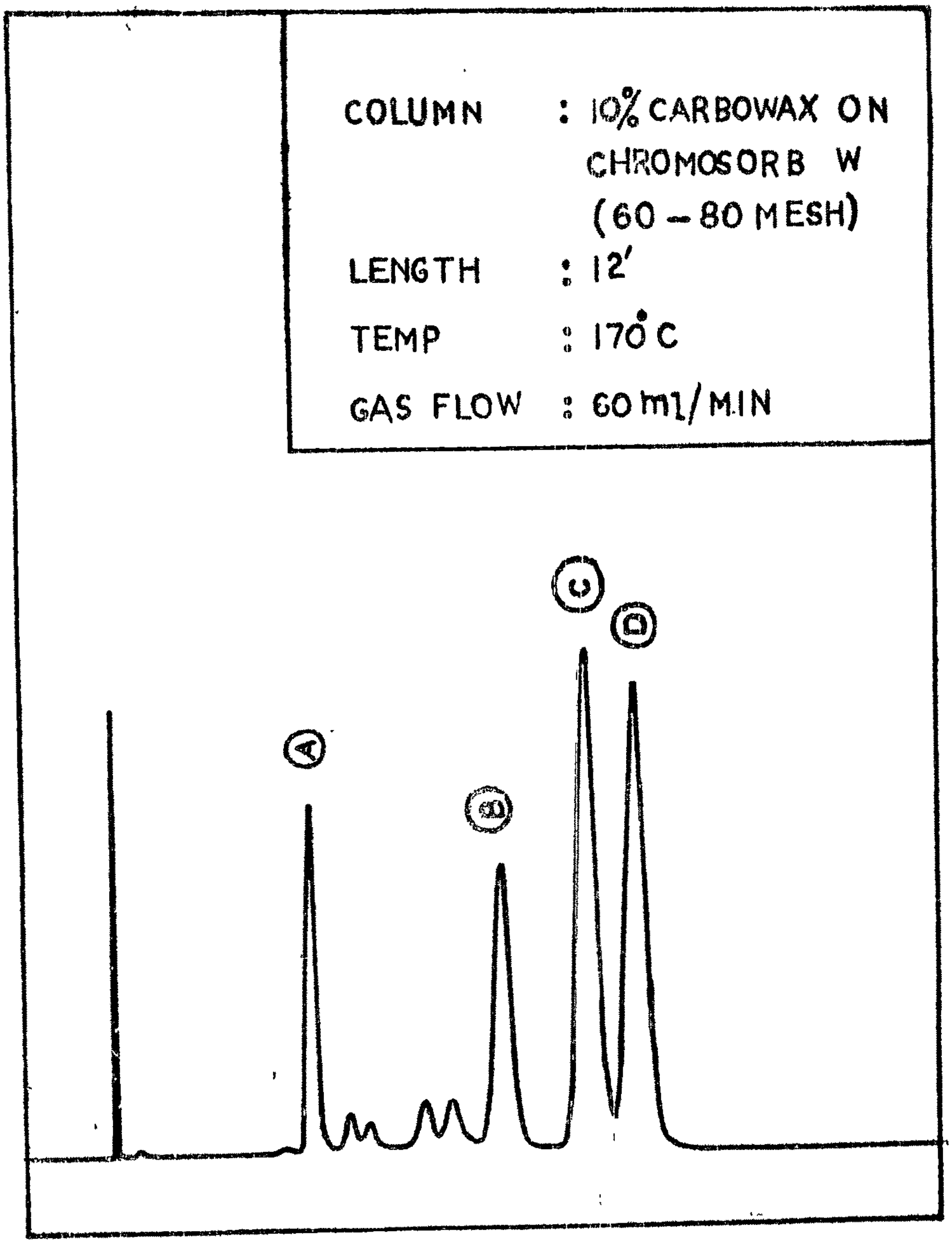
(i) Isomerization of β-Santalene:

Having tested H_3PO_4-dioxan reagent for the isomerizations of camphene and longifolene, we next turned to isomerize β-santalene and β-santalol directly to α-santalene and α-santalol, respectively. However, β-santalene, when refluxed with 10% H_3PO_4 in dioxan for 29 hours, gave, besides the expected α-santalene (∼14%) and the starting material (∼26%), products resulting from some deep-seated rearrangements. These products were not investigated further because of the paucity of the material. Because of these complications, we felt reluctant to apply the same to β-santalol.

The α-santalene formed during the isomerization of β-santalene was isolated pure by repeated preparative gas liquid chromatography and was found identical in all respects(IR and PMR) with an authentic sample obtained from fractionation of natural sandalwood oil.

(ii) Isomerization of 9-Bromomethyl Camphene

9-Bromomethyl camphene, on treatment with H_3PO_4-dioxan at reflux temperature for 29 hours, yielded a mixture comprising four major components having retention times(in seconds) 108(11.24%), 204(16.48%),252(31.83%), and 285(31.5%) in its gas liquid chromatogram(Fig.1).



IDENTIFICATION :

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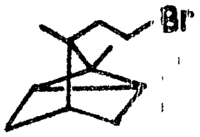

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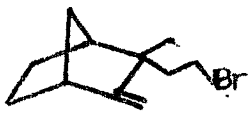

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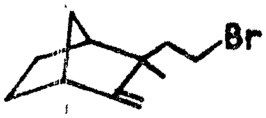
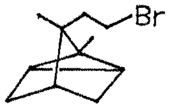


FIG-1

The compound having retention time 285 seconds was readily characterized as the starting bromide by (a) coinjection of the starting bromide and the product mixture in glc and (b) comparing the PMR spectra of the mixture and the starting material(9-bromomethyl camphene).

The compound of retention time 204 seconds was isolated in a state of purity by preparative gas liquid chromatography and was characterized as the tricyclic analogue(I) of the starting bromide from its IR spectrum (absence of band at 880 cm^{-1}) and PMR spectrum (Fig.2)(disappearance of exocyclic methylene protons at 4.77 and 4.47 ppm and also emergence of a quaternary methyl signal at 0.87 ppm).



I

The component of retention time 252 seconds displays, in it PMR spectrum(Fig.3),a quaternary methyl signal at 1.10 ppm; this value is 0.03 ppm higher than that for the quaternary methyl in 9-bromomethyl camphene. The fact that no skeletal rearrangement has taken place is revealed by its PMR spectrum in which the bridge-head protons at 2.68 and 2.10 ppm and the exocyclic methylene protons at ~4.8 and ~4.5 ppm remain unchanged. Because <u>exo-</u>

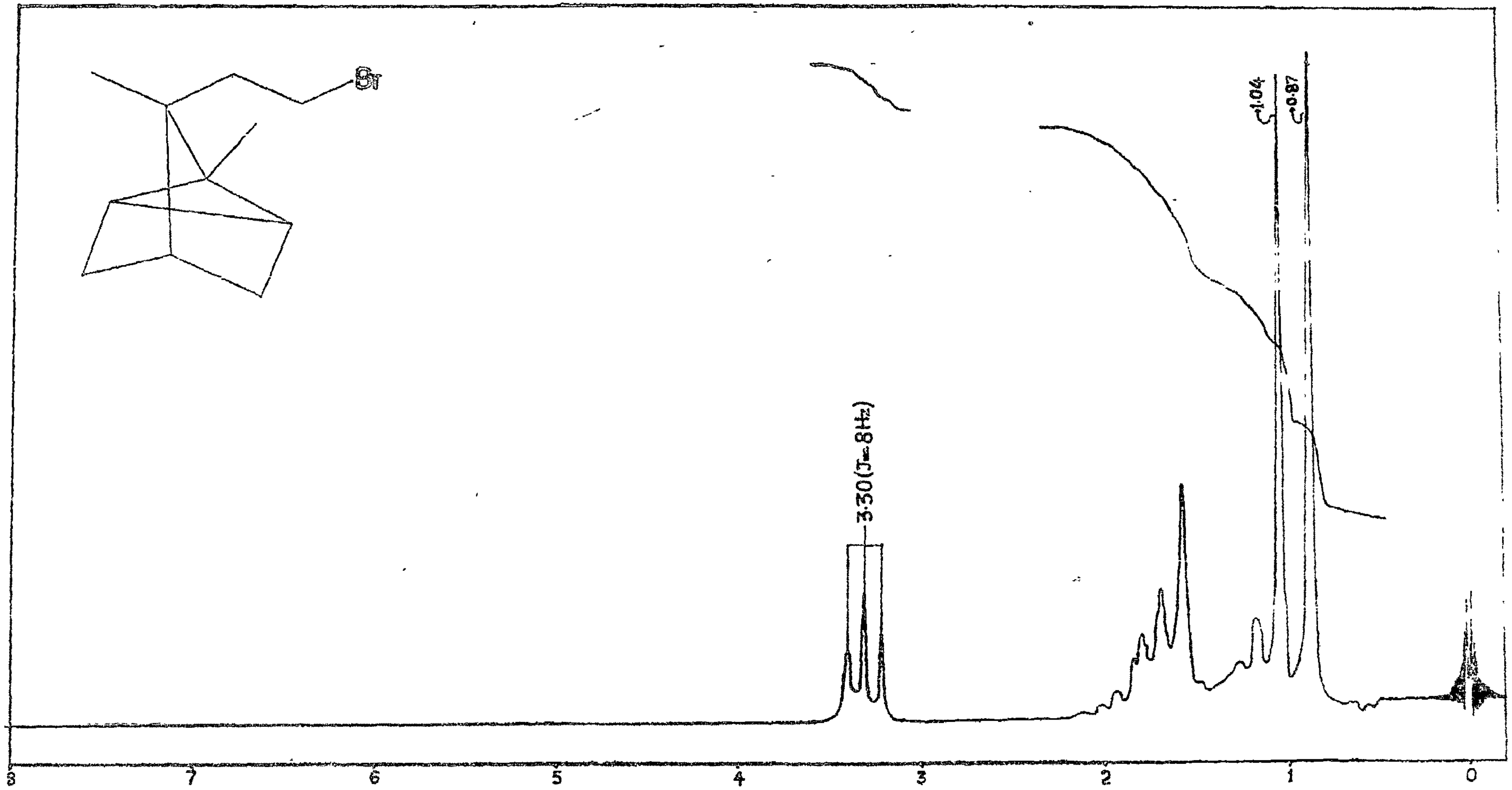


FIG.2: PMR SPECTRUM OF THE TRICYCLIC BROMIDE(I)

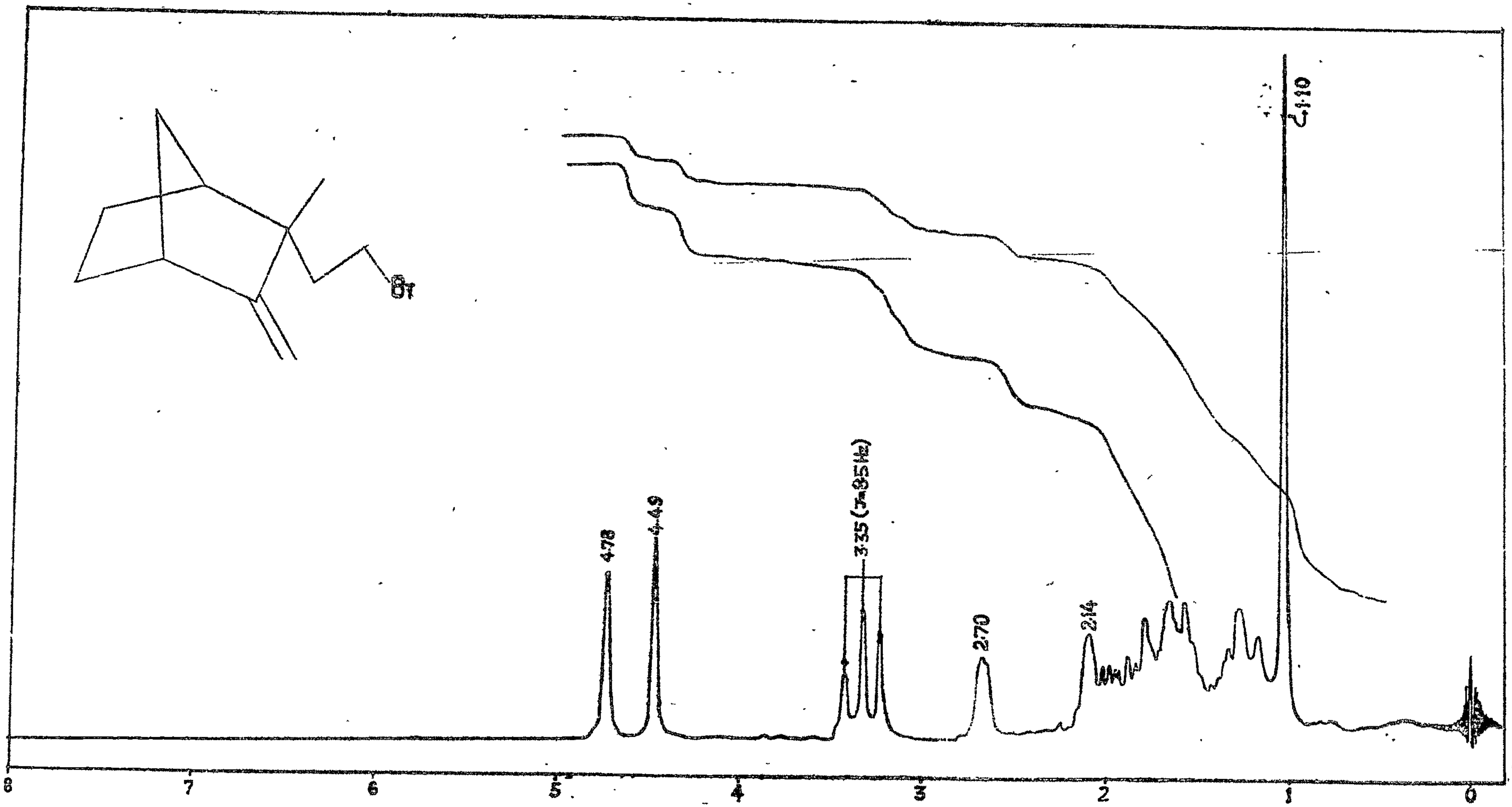
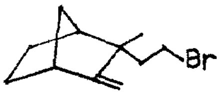


FIG.3: PMR SPECTRUM OF 10-BROMOMETHYL CAMPHENE(II)

methyls appear ~ 0.03 ppm downfield as compared to <u>endo</u>-methyls(cf. β-santalene and epi- β-santalene)[24], this compound must be the C-3 epimer, i.e. 10-bromomethyl camphene (II), of 9-bromomethyl camphene.

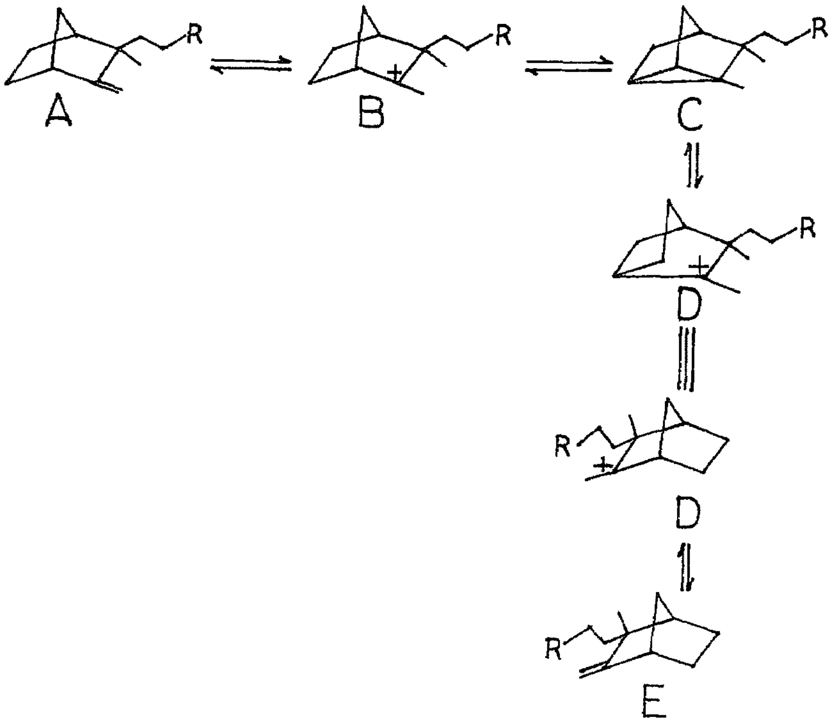


II

(iii) Isomerization of 9-cyanomethyl Camphene

This has been discussed in detail in the preceding chapter. However, 9-cyanomethyl camphene behaves exactly like 9-bromomethyl camphene.

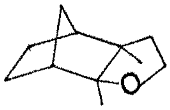
We propose the following mechanism for the formation of 10-substituted camphenes from 9-substituted analogues.



Protonation of the double bond in A followed by 2,6-hydride shift gives the tricyclic analogue C(A→B→C). Breaking of one of the cyclopropane bonds in C gives the tertiary carbonium ion D which, when deprotonated, furnishes the C-3 epimer (E) of A. Because these isomerizations reach an equilibrium stage, all the steps must be reversible.

(iv) Isomerization of 9-Hydroxymethyl Camphene

In this case, a single product was formed which was, from its IR spectrum(Fig.4) (1075 cm^{-1}, ether), PMR spectrum (Fig.5)(two quaternary methyls at 0.94 and 1.00 ppm and a multiplet for 2H at 3.47 ppm), and Mass spectrum(Fig.6) m/e 151(M^+-15), characterized as a 5-membered cyclic ether(III).



III

It is believed that the moment the carbonium ion B is formed, it is trapped by the incipient -OH group and, thus, the further reaction is completely inhibited.

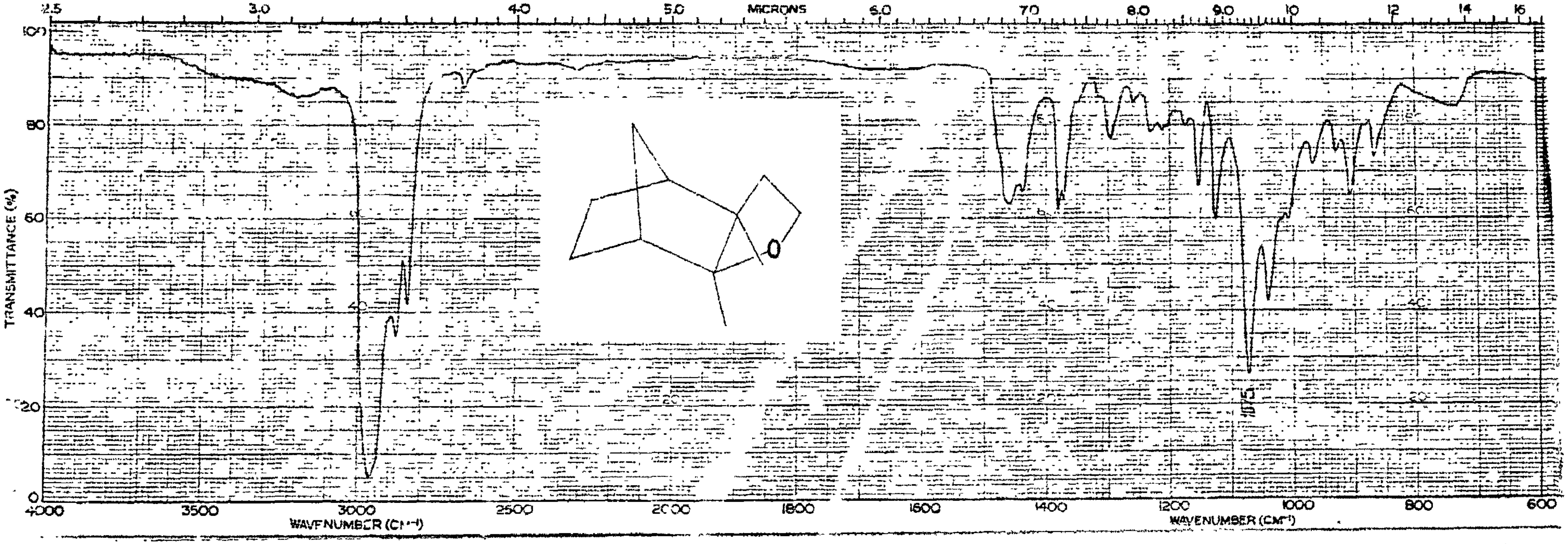


FIG.4: IR SPECTRUM OF THE CYCLIC ETHER(III)

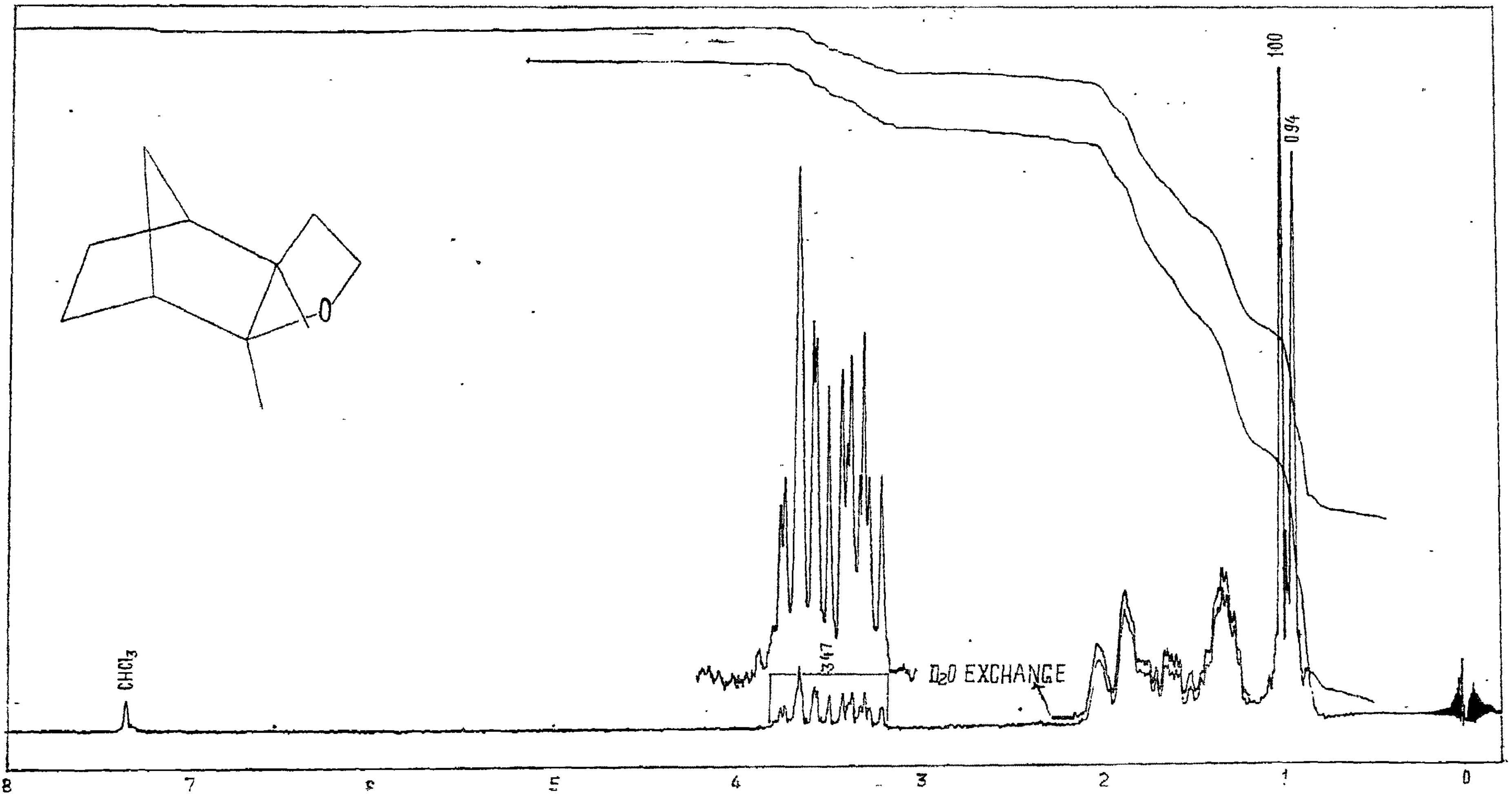


FIG.5: PMR SPECTRUM OF THE CYCLIC ETHER(III)

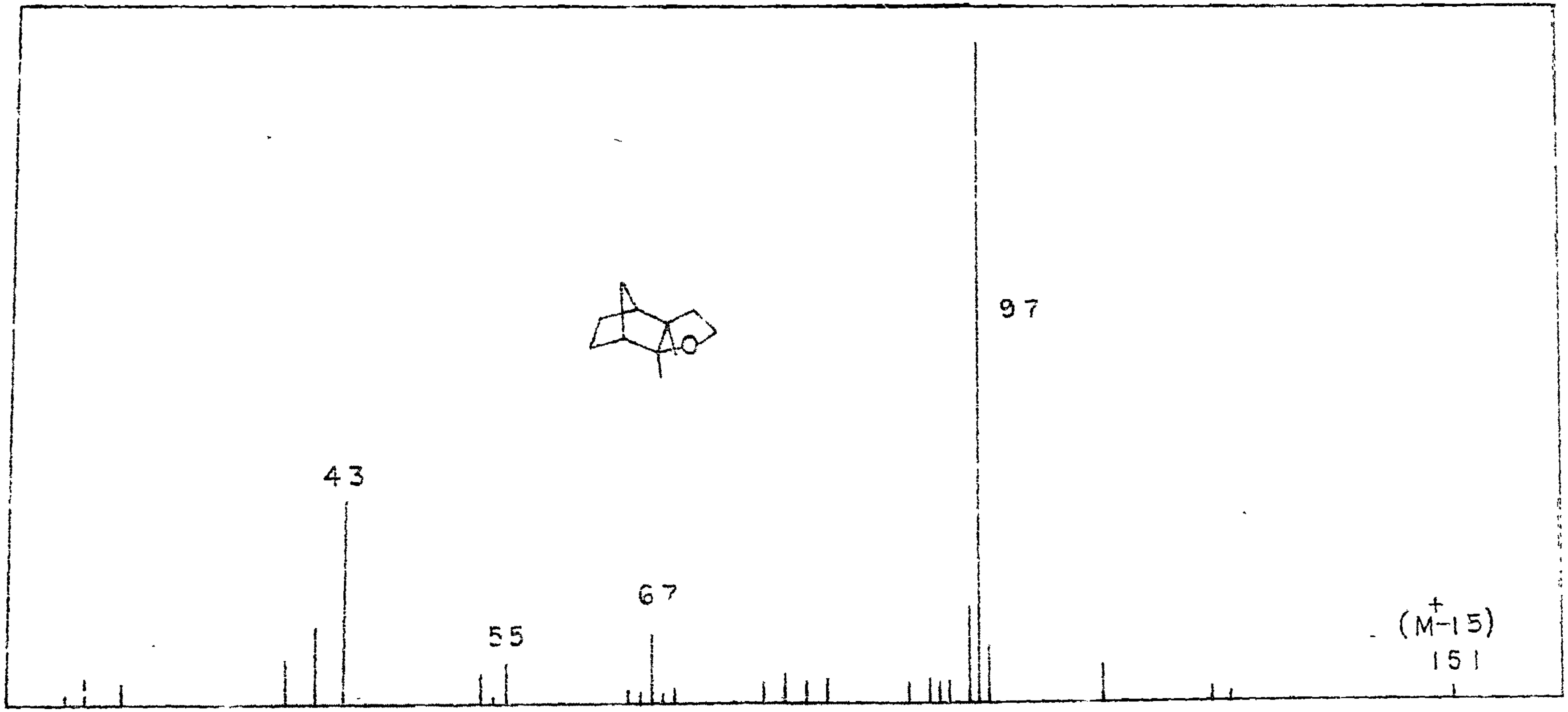


FIG.6 : MASS SPECTRUM OF THE CYCLIC ETHER(III)

EXPERIMENTAL

For general remarks, see the 'experimental' of PART A-CHAPTER-II.

AcOH CATALYZED ISOMERIZATION

(a) OF LONGIFOLENE

A solution of longifolene(0.5 g, 2.45 m moles) in AcOH (10 ml) was refluxed under anhydrous conditions for 24 hours. It was allowed to cool to room temperature (~30°C) and was diluted with water(40 ml) and extracted with ether(15 ml x 3). The combined extract was washed with water(15 ml x 2) and the residue(0.49g, 98% yield), left after evaporation of the solvent, was distilled. The distillate(0.475 g, 95% yield, b.p.$_{bath}$ 95-100°C/1.5 torr) was shown by glc analysis(10% DEGS column, 12', 150°C) to be a mixture of isolongifolene(10.92%),longicyclene(22.12%), the unreacted starting material(57.76%), and some other minor products(9.20%; not investigated). In different experiments where inorganic acetates were used, these were added to the above reaction mixture before heating to reflux. The results of these are given in Table 1.

(b) OF CAMPHENE

Camphene(0.33 g, 2.45 m moles) was dissolved in AcOH(10 ml) and the solution was refluxed for 24 hours. The work-up, as described above for longifolene, gave a product mixture(0.324 g, 98.2% yield) which contained (glc:10% CW, 170°), besides the unreacted camphene (35.68%), tricyclene(6.26%) and isobornyl acetate(58.06%). Here also, the experiments using inorganic acetates were performed in a manner as described above for longifolene. The results of these are given in Table 2.

10% H_3PO_4 IN DIOXAN CATALYZED ISOMERIZATION

(a) OF LONGIFOLENE

A solution of longifolene(0.50 g; 2.45 m moles) in 10% H_3PO_4 in dioxan(10 ml) was refluxed and the reaction was monitored by withdrawing aliquots(~1 ml at a time) at different intervals. Each aliquot was diluted with water(5 ml) and extracted with ether(5 ml x 2). The combined ether extract was washed with water(5 ml x 2). Product mixture, obtained by distillation of the residue left after solvent removal, was analyzed by gas liquid chromatography(10% DEGS, 12', 150°). One such reaction for 12 hours gave a product mixture(0.490 g; 99% yield) which was composed of longicyclene(19.82%) and longifolene (80.18%). These results are given in Table 4.

(b) OF CAMPHENE

A solution of camphene(0.33g, 2.45 m moles) in 10% H_3PO_4 in dioxan(10 ml) was refluxed for 28 hours. It was allowed to cool to room temperature(~30°C) and was diluted with water (40 ml) and extracted with ether(15 ml x 2). The residue (0.318 g; 96.4% yield), left after solvent evaporation, was distilled. The distillate (0.310 g; 95% yield, b.p.$_{bath}$ 90-95°C/60 torr) was, by glc(10% C.W.,100°C), a mixture of tricyclene(21.51%) and the unreacted camphene (78.49%).

(c) OF β-SANTALENE

A solution of β-santalene(0.50g, 2.45 m moles) in 10% H_3PO_4 in dioxan(10 ml) was refluxed for 29 hours under anhydrous conditions. The reaction mixture was dumped in water(40 ml) and extracted with ether (15 ml x 3). The extract was washed with water (15 ml x 2). Solvent removal gave a residue(0.50 g) which was distilled to give a product mixture(0.49 g; 98% yield, b.p.$_{bath}$ 100-115°/1.5 torr)consisting of, besides the unreacted β-santalene(26%), α-santalene (~14%) and three/four new products(60%; not characterized).

(d) OF 9-BROMOMETHYL CAMPHENE

A solution of 9-bromomethyl camphene(0.56 g; 2.45 m moles) in 10 ml of 10% H_3PO_4 in dioxan was refluxed for 29 hours. The work-up as described above for β-santalene followed by distillation of the residue, left after solvent removal, gave the product mixture(0.540 g; 96.4% yield, b.p.$_{bath}$85-105°/0.5 torr) whose composition from glc analysis(10% C.W.,12',170°C) was: 9-bromomethyl camphene(31.5%), 10-bromomethyl camphene(31.83%), tricyclic analogue of 9-bromomethyl camphene(16.48%), and some other minor products (~20.18%; not investigated).

(e) OF 9-CYANOMETHYL CAMPHENE

A solution of 9-cyanomethyl camphene(0.424 g, 2.45 m moles) in 10 ml of 10% H_3PO_4 in dioxan was refluxed for 29 hours. The work-up as described above for 9-bromomethyl camphene gave a product mixture (0.410 g; 96.7% yield, b.p.$_{bath}$105-110°C/0.3 torr) which, on glc analysis (10% C.W., 12', 190°C) was found to be a mixture of 9-cyanomethyl camphene(46.25%), 10-cyanomethyl camphene(34.4%), and the tricyclic analogue of 9-cyanomethyl camphene(19.35%).

(f) OF 9-HYDROXYMETHYL CAMPHENE

A solution of 9-hydroxymethyl camphene(0.407 g; 2.45 m moles) in 10 ml of 10% H_3PO_4 in dioxan was refluxed for 29 hours. The work-up as described above for 9-cyanomethyl camphene gave a product(0.390 g; 96% yield, b.p.$_{bath}$ 110-115^{o}C/0.3 torr) which was characterized, from its IR spectrum (Fig. 4) and PMR spectrum(Fig. 5), as the 5-membered cyclic ether(III).

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