C H A P T E R - 2

SYNTHESIS OF (+)-CARVONE FROM (+)-CAR-3-ENE

Abstract

This Chapter describes the stereospecific conversion of (+)-car-3-ene into (+)-carvone, an important flavouring agent, by two different routes. The key reaction in this transformation is the sigmatropic rearrangement of car-2-ene and its derivative. This conversion provides the basis for an industrial process for the preparation of (+)-carvone from (+)-car-3-ene.

SYNTHESIS OF (+)-CARVONE FROM (+)-CAR-3-ENE

INTRODUCTION

(+)-Carvone (9) is valued as a flavouring component for its warm-herbaceous, breadlike, spicy and slightly floral odour.[1] Its commercial production is essentially based on its isolation from caraway seed oil[2] (Carum carvi L.) or dill seed oil[2] (Anethum graveolens L.). Practically all the (+)-carvone (9) used is obtained from these natural sources, though the commercial synthetic method for its antipode (-)-carvone from (+)-limonene,[3] in principle, can be exploited for the production of (+)-carvone (9), starting from (-)-limonene. Certain uncommon pine species, carrot seed oil, a great number of oils from Labiatae etc. are rich in (-)-limonene but the isolation of this terpene from these essential oils is generally not economically feasible.[4] This rare and irregular availability of (-)-limonene is a severe limitation on synthetic production of (+)-carvone (9) from (-)-limonene and only small quantities are said to be produced by (-)-carvone producers.[5] Syntheses of (+)-carvone (9) from (-)-limonene[6] as well as from (-)-carvone[7] have been described. Attempts have also been made by several groups[7] for a stereospecific conversion of (-)-carvone to (+)-carvone (9),

but the yields are generally low. (+)-Carvone (9) is used as a flavouring agent in bread, pickles, spices etc., and is rather expensive (70$/lb.).

PRESENT WORK

In view of the higher cost of natural (+)-carvone (9) it appears worthwhile to develoo a synthetic route for (+)-carvone (9) from a readily available natural source. The abundance of (+)-car-3-ene (1) in Indian turoentine oil (55-65%) which has the required chirality at C_6, makes it an attractive starting material for (+)-carvone (9). We now report on its preparation from the abundantly available (+)-car-3-ene (1) by two different schemes, which are shown in Fig. 1. The key reaction in each case is the well-established[8] stereospecific (1,5)-sigmatropic rearrangement[9], (Fig. 2) of a car-2-en derivative under thermal treatment.

(+)-3α,4α-Epoxycarane (2), readily obtainable[10,11] from (+)-car-3-ene (1) is the starting point for both the schemes.

SCHEME -1

Isomerisation of (+)-3α,4α-epoxycarane (2) to car-2-en-4-ol(3).

For the transformation of epoxides to allylic alcohols, various

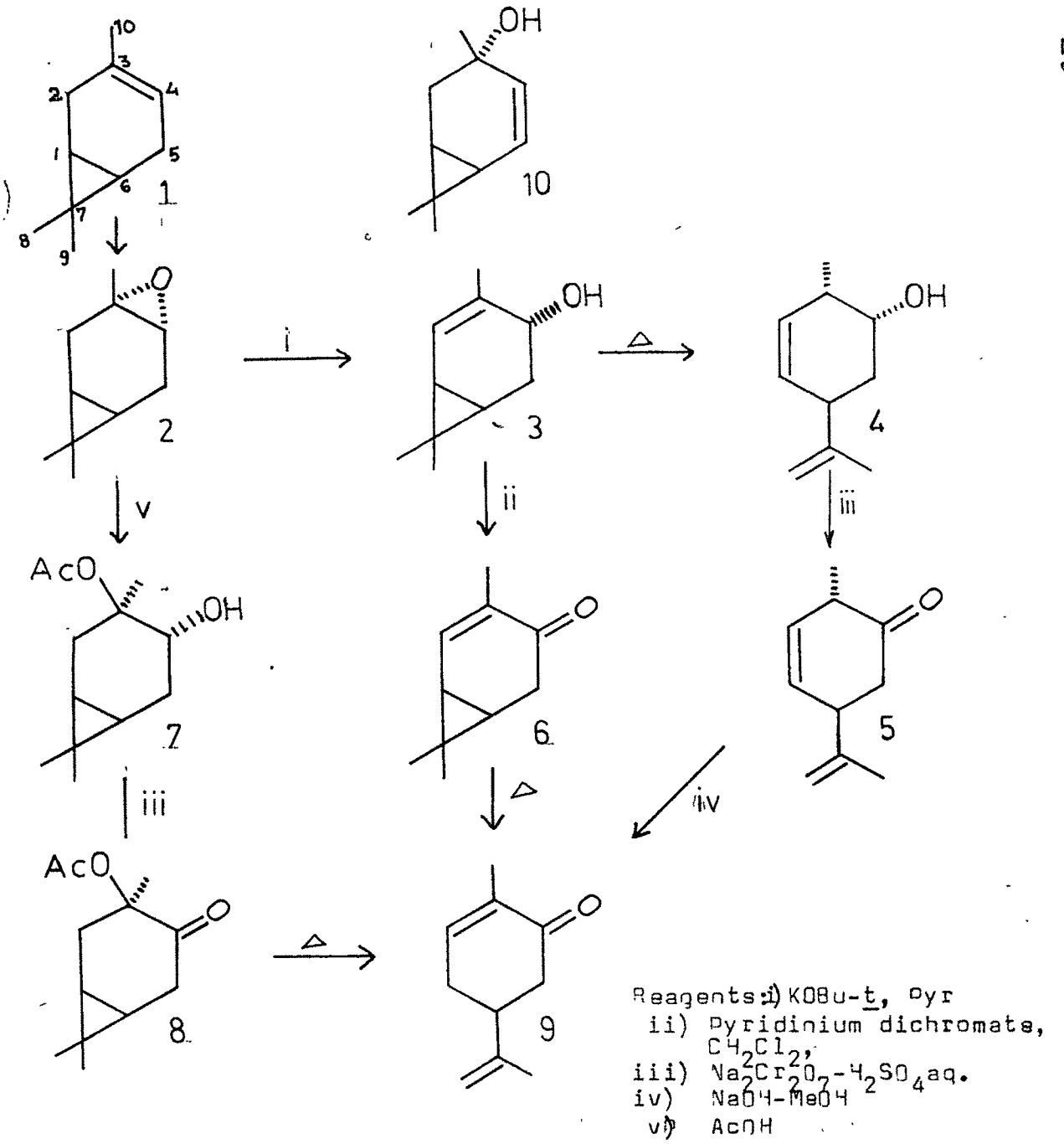


Fig. 1. Transformation of (+)-car-3-ene into (+)-Carvone

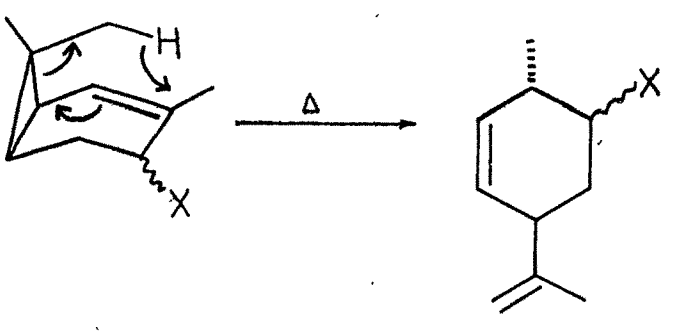


Fig. 2. Thermal rearrangement of car-2-ene and its derivatives.

reagents are well-documented in literature (described in Chapter 1 of this Part). The conversion of (+)-3α, 4α-epoxycarane (2) to the desired car-2-en-4-ol (3)[12], under the influence of KOBu-t in pyridine has been reported earlier[13], and 3 has been claimed as the only product of this reaction. However, in our hands, both the desired alcohol 3 and the allylic tertiary alcohol (10)[12] were obtained in an approximate ratio of 1 : 1.3 ; changing the amount of base relative to the epoxide (0.2 - 4.4 mol. equiv. of base per one mol. equiv. of epoxide) had little effect on the product composition, though rate of isomerization decreased significantly with lower proportions of the base. These results are not surprizing if one concedes that the C-5 methylene protons, being next to the cyclopropane ring can effectively[15] compete with the C-10-methyl hydrogens for reaction with the base, notwithstanding the greater propensity of a methyl group for carbanion formation in such reactions.[14] Also, the presence of some unchanged epoxide (10%) which was attributed to the change of an aprotic medium to partly protic medium as the reaction progresses, appear to be in error. In order to varify the claim, the isomerisation of 2 was carried out with KOBu-t in totally protic medium like t-BuOH. The isomerisation was sluggish

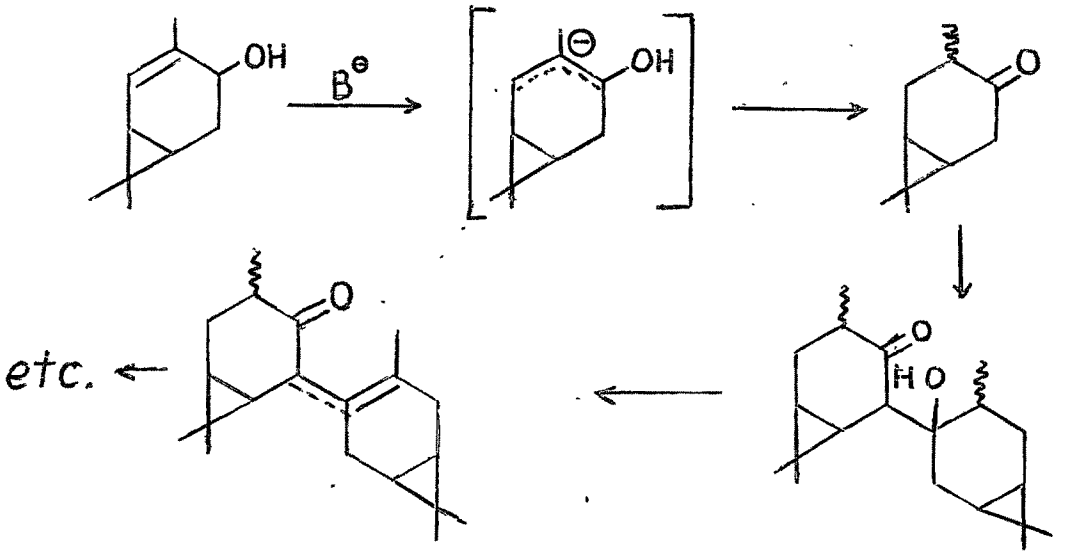
as expected, because KOBu-t in a protic solvent like t-BuOH is expected to be less basic as compared with KOBu-t in aprotic solvent like pyridine.[13] The product composition was nearly the same except for the presence of car-3(10)-en-4-ol (3% by ^{1}H-NMR) and the most amazing observation was that even under total protic conditions the isomerisation did go to 88% conversion.

The allylic alcohol (10) is known to undergo rearrangement with traces of acid[16] and hence fractionation was achieved in presence of solid Na_2CO_3[17] (0.33% w/w) on spinning-band column (45 theoritical plates) to furnish car-4-en-3-ol (10) practically pure (^{1}H-NMR) in 50% yield and car-2-en-4-ol (3) of 90% purity (GC, ^{1}H-NMR) in 33% yield, based on (+)-3α,4α-epoxycarane (2). The identity of 3 and 10 was established by comparison of the physical constants (B.P., $[\alpha]_D$, n_D)[17] and spectral data (IR[17], ^{1}H-NMR 3[18], 10[19]).

In an attempt to simplify and economize on the existing procedure for isomerisation of (+)-3α,4α-epoxycarane (2) to car-2-en-4-ol (3) many methods were tried, and these are briefly mentioned below.

Isomerisation of 2 to afford 3 was also attempted on high-surface-sodium-on-alumina which is known to have

basicity comparable to that of KOBu-t[20]. The isomerisation was carried out with or without solvent. With solvents like toluene or xylene, the isomerisation was incomplete and an attempt to push the isomerisation to completion by prolonged stirring at reflux temperature resulted in more residue formation besides incomplete conversion. The isomerisation without solvent on $NaAl_2O_3$ did go to completion but residue formation to the tune of 18-23% was observed which was possibly formed at the cost of desired alcohol 3 by base catalyzed[21] rearrangement as depicted below, followed by aldol condensation and dehydration at high temperature. Also formed were minor



quantities of o-and m-cymenes besides small quantities of unidentified compounds. The isolable yield of desired

car-2-en-4-ol (3) and by-product car-4-en-3-ol (10) was of the order of 21% and 33% respectively, quite low as compared to K-OBut-t-pyridine method.

Isomerization of 2 with a catalytic amount of sodium salt of allylic alcohol (3) prepared either *via* an exchange with sodium methoxide or by direct addition of sodium to 3, does effect the desired isomerisation but only at comparatively higher temperatures resulting in side-product formation. It was therefore pursued with pyridine as solvent to increase its basicity, to effect the isomerisation at comparatively lower temperature and to avoid side-product formation. Dilution of epoxide (2) and the alkoxide in pyridine to 1: 0.5 parts w/v appears to be optimum to keep the reaction mixture homogeneous, and to achieve an optimum temperature of 139-140^{o}C which is necessary for complete isomerisation within 5 to 5.5 hours. The isomerisation product was considerably cleaner than the Na-Al_2O_3 product and gave 33% and 36% isolated yield of 3 and 10 respectively with just 6-8% of residue. Though the isolated yield of both 3 and 10 by this method was found to be better than Na-Al_2O_3 method, yet again low as comoared to KOBu-t-pyridine method.

In the course of isomerisation, it was discovered that sodium salt of allylic alcohols (3 and 10) gave similar results as that of pure 2^{o}-alcohol (3) alkoxide. Secondly, the presence of NaOMe, due to incomplete exchange, did not gave any contamination of normal SN_2 opening product of NaOMe. In fact, NaOMe in methanol on prolonged heating gave the SN_2 addition product, i.e., 3-hydroxy-4-methoxycarane. It was conceived that NaOMe-Pyridine possibly behaves as a strong base and a weak nucleophile. The isomerisation procedure has been further simplified by avoiding a cumbersome secondary allylic alcohol exchange with NaOMe. Finally, repeating the isomerisation of (+)-3α,4α-epoxycarane (2) with NaOMe in pyridine as a base did support the intuition and gave comparable results to KOBu-t-pyridine method, yielding 3 and 10 in 31-35% and 39-42% isolated yields respectively. Recovery of methanol and pyridine was almost quantitative and were found satisfactory for its reuse.

From the data available in literature on isomerisation of epoxides in general and (+)-3α,4α-epoxycarane in particular , it is possible to generalise three different mechanistic pathways:

1. Acid catalyzed isomerisation in general leads to rearrangement products (carbonyl compounds) besides dehydration to form hydrocarbons.

2. Strong base-catalyzed isomerisation proceeds *via* abstraction of proton from C-2, C-10 and C-5 followed by C-O bond cleavage.

3. Organometallic compounds (base) and alumina proceeds by co-ordination of metal with oxirane followed by C-O bond cleavage with simultaneous abstraction of proton from C_{10} methyl.

The third mechanistic pathway avoids rearrangement and formation of 3^{o}-allylic alcohol (10) (described in Chapter 1 of this Part).

Pyrolysis of car-2-en-4-ol (3) to *p*-mentha-5,8-dien-2-ol(4).

The car-2-en-4-ol(3) was pyrolysed by a known[8] method with or without traces of pyridine at 215± 5^{o}C to afford *p*-mentha-5,8-dien-2-ol (4) in 93% yield. The reaction is quite clean and the only complication was due to the acid-sensitive nature of 3, which in the absence of base-(pyridine) undergoes dehydration and rearrangement forming considerable low boiling hydrocarbons, which are not only

responsible for a lower yield of 4 but also for lowering the temoerature in the pot leading to poorer conversions. Using pyridine, pyrolysis was considerably sluggish but gave a comparatively cleaner product. For analytical purpose it was purified by chromatography on silver nitrate impregnated silica gel[22] to yield pure p-mentha-5,8-dien-2-ol (4) as a colourless mobile liquid. Structure 4 is in full accord with its spectral characteristics.

Brown's oxidation of p-mentha-5,8-dien-2-ol (4) to p-mentha-5,8-dien-2-one (5). Brown's oxidation[23] of 4 (with $Na_2Cr_2O_7$-H_2SO_4 aq. in two phase system) in EtOAc as well as in diethyl ether furnished the corresponding ketone (5)[24] in 60% yield. This ketone (5) was quite labile, attempts to purify it by inverted dry column chromatography[25] on silvernitrate SiO_2-gel[22] resulted partly in isomerization of the double bond and epimerization at C-1. Preparative Glc on 20% CW on Chromosorb W NAW 45-60 mesh, 3/8' x 12', at 220° also resulted in isomerization of the double bond to a minor extent. Structure 5 was in full accord with the spectral characteristics.

Isomerization of p-mentha-5,8-dien-2-one (5) to (+)-carvone (9). The equilibration of α, β and β-γ-olefinic ketones is normally very facile and α,β-unsaturated ketone is invariably favoured unless the γ-position is substituted with alkyl groups. The desired isomerisation can be

brought about either by trace of mild acid or base or even by thermal treatment. In a situation like the one present in 5, where the α-position is substituted with methyl, the isomerisation is expected to be extremely facile and favours the formation of α,β-unsaturated ketone. Exposure of 5 to methanolic NaOH (1 hr, reflux) resulted in its isomerisation to the desired (+)-carvone (9) in quantitative yields. The identity of (+)-carvone (9) was established by comparison of physical constants (B.P., n_D^{25}, $[\alpha]_D$) and spectral characteristics (IR, ^{1}H-NMR, UV) with the authentic sample of (+)-carvone.

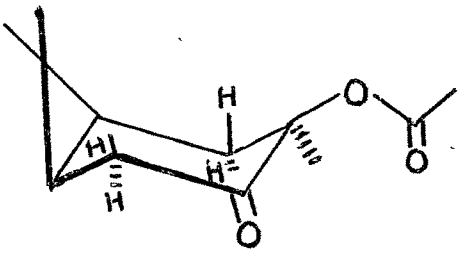
Oxidation and *in situ* isomerisation of p-metha-5,8-dien-2-ol (4) to (+)-carvone (9). In another varient of this sequence, p-mentha-5,8-dien-2-ol (4) was converted into (+)-carvone (9) in over 80% yield by one-pot oxidation

and *in situ* isomerisation with N-chlorosuccinimide-dimethyl sulphide[26] and triethyl amine as the base.

SCHEME-2

Conversion of (+)-3α,4α-epoxycarane (2) to 3β-acetoxy-caran-4α-ol (7). In the second approach, (+)-3α,4α-epoxycarane (2) was exposed to AcOH (25°, 72 hr) to get a complex reaction product, from which the known[29] hydroxy acetate (7) could be isolated in 83% purity[30] in a yield of 40%. 3β-Acetoxycaran-4α-ol (7) was obtained by Cocker and co-workers by opening 2, either with NaOAc buffered AcOH (R.T., 72 hr)[29] or with Ac_2O-H_2O_2 in AcOH (R.T., 96 hr)[29]. The use of buffer media (NaOAc or Ac_2O-H_2O_2) has been observed to offer no advantage over plain acetic acid medium in our hands. The identity of 7 was established by comparison of spectral data (IR, ^{1}H-NMR) with reported values[29]. It is also a labile compound, which undergoes isomerisation to 4α-acetoxycaran-3β-ol on exposure to hot AcOH and to some extent on SiO_2-gel column.[29]

Oxidation of 3β-acetoxycaran-4α-ol(7) to 3β-acetoxy-caran-4-one (8). Oxidation of 7 to the acetoxy ketone (8) could be successfully manipulated by oxidation with Brown's reagent[31] at 0-5°, using the inverse addition technique to afford the hitherto unknown 3β-acetoxy-caran-4-one (8) in 64% isolated yield. It was purified by chromatography on SiO_2-gel to afford oure 8 as a mobile colourless liquid. Insoection of molecular model for 3β-acetoxycaran-4-one (8) reveals that, of the four possible conformations, two boats and two half chairs, the boat conformations need not be considered because of steric interactions similar to the one present in 4-caranone and 4-isocaranone.[32] This leaves only two half chair conformations namely (11) and (12) for 8. Apparently 12 has the least steric interaction and should



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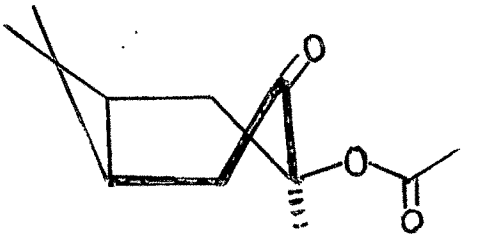

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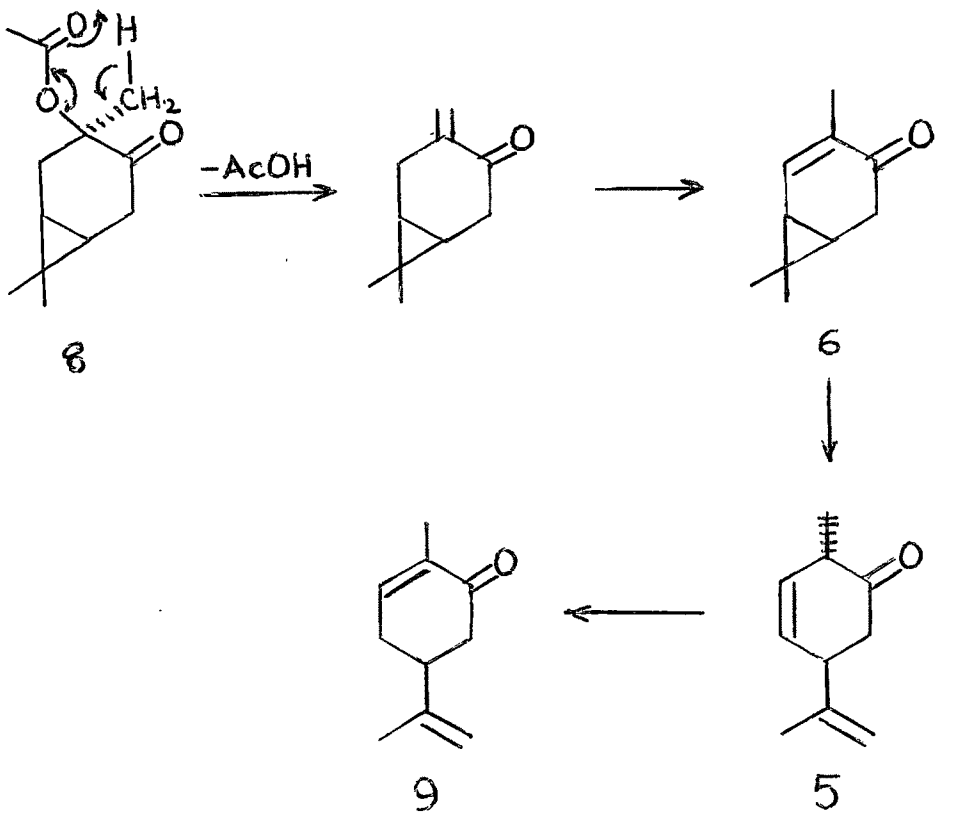
be favoured over 11, but this would mean shielding of C_8-Me because of a diamagnetic anisotropy of carbonyl. In fact in the PMR spectrum of 8, the C_8 and C_9-Mes come as a 6H singlet at 1.11 opm, suggesting the conformation of 8 as 11 and not 12. As there is practically no shift in the C_{10}-Me position (1.42 ppm) on passing from CCl_4 to benzene as a solvent[32,33] in recording the ^{1}H-NMR, this indicates the equitorial nature of C_{10}-Me and supoort the conformation of 11 for 8.

Pyrolysis of 3β-acetoxycaran-4-one (7) to (+)-carvone (9).

Pure 8 on pyrolysis (200°) yielded a complex mixture of products, from which pure (+)-carvone (9) was isolated by chromatography (SiO_2 gel) in a yield of 25%. ^{1}H-NMR monitoring of the reaction showed that the conversion proceeds by way of car-3(10)-en-4-one to 6 → 5 → 9 as depicted below. The formation of car-3(10)-en-4-one* as the primary product was apparent from the aliquot which in its ^{1}H-NMR shows the olefinic signal at 6.24 ppm which subsequently disappears with corresponding increase of

*The intermediacy of this ketone was studied only in the mixture and was not confirmed by isolating it in pure form (from the aliquot).



the 6.7 ppm signal. Also, GC showed a peak at RRT 1.33 which on further cooking disappears with concomitant increase in a signal at RRT 1.78 corresponding to (+)-carvone (9). The car-3(10)-en-4-one under pyrolytic conditions isomerised to a more stable car-2-en-4-one (6), which as expected opened up *in situ* to (5) by a (1,5)-sigmatropic rearrangement, well-known in the carane system with a double bond at C_2.[8,9] The $\beta\gamma$-unsaturated ketone (5) *in situ* got isomerised to afford (+)-carvone (9) as a final product.

Oxidation of car-2-en-4α-ol (3) to car-2-en-4-one (6).

In order to firmly establish the intermediacy of car-2-en-4-one (6) and p-mentha-5,8-dien-2-one (5), a samole of 6 was prepared. The oxidation of car-2-en-4-ol (3) is known[35]

to furnish 6 in 92% yield via Brown's oxidation. Repetition of Brown's oxidation using ether and Et-OAc as solvent gave 57% and 50% yield of desired ketone (6). Oxidation using pyridinium chromate on SiO_2[36] in benzene was extremely sluggish at room temperature (at high temp., by-product formation was observed) and gave only 32.8% yield of ketone (6). Oxidation of car-2-en-4-ol (3) was best carried out by pyridinium dichromate[27] in CH_2Cl_2 to furnish 6 (70% yield), earlier described[28] as a minor oxidation product of car-3-ene (1) with permanganate. The identity of this ketone (6) was established by comparison of IR and ^{1}H-NMR with reported values[34].

Pyrolysis of car-2-en-4-one (6) to (+)-carvone (9). When this ketone (6) was heated to 200° (N_2) for some 5 hr, it smoothly got transferred into the required (+)-carvone (9)*. ^{1}H-NMR monitoring of the reaction clearly established the intermediacy of p-mentha-5,8-dien-2-one (5) showing a singlet at 5.72 ppm, $-\underset{H}{C}=\underset{4}{C}-$, which keto on reducing with

*Pyrolysis was also carried out in presence of catalytic amount of pyridine but it did not show any advantage over pyrolysis without pyridine. Presence of trace of acid was found deleterious and leads to carvacrol formation.

time and vanished comoletely in 5 hrs with concomitant increase in olefinic signal at 6.66 oom and vinylic methyl at 1.75 opm, belonging to (+)-carvone (9). The yield of (+)-carvone (9), based on GC, was 81%. The identity of 9 was established by isolating oure 9 by column chromatography (SiO_2-gel) and comparing its physical constants and spectral data as in the case of route-1.

EXPERIMENTAL

All b.ps are uncorrected. Light petroleum refers to fractions b.p. 60-80°. 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° for 6 hr and standardised.[38] TLC was carried out on silica gel layers (0.25 mm) containing 15% gypsum and activated at 110-115° (2 hr.); spray reagent, 1% vanillin in 50% H_3PO_4 aq.

The following instruments were used for spectral/ analytical data: Schmidt + Haensh Polarimeter model Polatronic 1; Perkin Elmer model 402 Ultraviolet Spectrophotometer; Perkin-Elmer model 267 Infrared spectrophotomer; Perkin-Elmer model R32 (90 MHz) NMR Spectrometer; Varian Mat CH7 Mass spectrometer (70 eV, direct inlet system); Hewlett-Packard 5712A and 7624A Gas Chromatographs (Al columns, 180 cm x 0.6 cm, unless stated otherwise; support 60-80 mesh chromosorb 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), t (triplet), q (quartet), m (multiplet), b (broad). While summarising mass spectral data, besides the molecular ion, nine most abundant ions (m/z) are reported with their relative intensities.

(+)-Car-2-en-4α-ol (3) and (-)-car-4-en-3α-ol (10)

(a) Using t-BuOK/pyridine. In a 1 ltr. three-necked round bottom flask equipped with a distillation condenser, a receiver (1 ltr., rbf), a thermowell, and a nitrogen inlet, dried with free-flame and allowed to cool to room temperature under N_2-flow, was taken dry t-BuOH (750 ml)* and potassium metal (41 g, 1.052 mole) was added to it in portions while stirring under Nitrogen blanket. The potassium dissolved during 3 hrs and then contents were slightly warmed (50-60°). t-BuOH (500 ml, bath 90-100°C, 3.5 hr) was distilled off at atmospheric pressure and the last traces were removed under suction (120 mm, 0.5 hr). Vaccum was released with N_2 and the distillation condenser was replaced with reflux condenser under N_2 atmosphere. To t-BuOK, anhydrous pyridine+ (300 ml) was added, under dry

*Dry t-BuOH was prepared by refluxing commercial t-BuOH over sodium 4 g/100 ml and then distilled it from sodium under anhydrous conditions, b.p. 80-81°C.

+Dry pyridine was prepared by refluxing pyridine over NaOH 50 g/200 ml for 3 hrs and distilled under anhydrous conditions, b.p. 113-115°C.

inert gas (N_2). After stirring for 20 min. to dissolve t-BuOK, 3α,4α-epoxycarane (304 g, 2.0 moles) was introduced and the reaction mixture refluxed (bath temo. 125-130°) with stirring for 2.5 hr, when TLC (solvent: 15% EtOAc in light pet.) indicated essentially complete conversion. During the next 3 hr, bulk of pyridine and t-BuOH (450 ml) were collected by distillation, and the residue cooled, diluted with ice-water (500ml) and the product taken up in light pet. (150 ml x 4). After usual work-up, 285 g of a liquid product, shown by GLC (Glass column, 5% Carbowax 20M, 110°) to consist of 3 (40%, RRT = 2.26) and 10 (52%, RRT = 1.00) with some other products (not investigated) was obtained. Fractionation of this material (166 g), using a spinning-band column (45 theoritical plates) in presence of small amount of Na_2CO_3 furnished car-4-en-3α-ol (10; 75.3g, b.p. 82-83/7 mm, 95% pure by GLC) and car-2-en-4α-ol (3; 55 g, b.p. 92-95°/6 mm, 90% pure by GLC).

Pure samples had the following characteristics.

Car-4-en-3α-ol (10)

n_D^{25} 1.4818,

$[\alpha]_D$ - 287.3° (C_6H_6, c 5.4%). (Lit.[10], n_D^{20} 1.4853, $[\alpha]_D^{26}$ -289° in C_6H_6, c 3.6%).

IR (liq.): 3400, 1645, 1224, 1173, 1115, 1076, 995, 943, 912, 860 and 742 cm^{-1}

^{1}H-NMR: Me-C (3H, singlets at 0.88 and 1.15 ppm), Me-C-O(3H, s, 1.15 ppm); CH=CH (2H,s, 5.77 ppm).

Car-2-en-4α-ol (3):

n_D^{26} 1.4958, $[\alpha]_D$ + 190.0° (C_6H_6, c 5.0%).
(Lit.[10], n_D^{20} 1.4978, $[\alpha]_D^{22}$ + 203.8° in C_6H_6, c 3.2%).
IR (liq.): 3360, 1650, 1200, 1140, 1070, 1040, 1000, 875 and 845 cm^{-1}.

^{1}H-NMR: Me-C (3H, singlets at 0.82 and 1.10 ppm), Me-C=C (3H, s, 1.78 ppm), CHOH (1H, t, 3.62 ppm, J = 5 Hz), C=CH (1H, bs, 5.53 ppm).

(b) Using Na-Al_2O_3: (i) Preparation of the catalyst: Commercial alumina (80-300 mesh; 2.46 kg) was stirred with 10%HNO_3 (4L) at 60-80°C for 45 mins., the acid layer decanted and alumina washed with water (tap water; 10 washings) and finally with D.M. Water. The held up water was sucked under industrial suction (120 mm) as far as possible and the alumina was dried in hot sun, activated at 450-500°C for 16 hrs, and finally was transferred hot into a conical flask, stoppred tightly and allowed to cool to room temp.

The activated alumina (690 g) was transferred into a predried (free flame with N_2 flow), 3 ltr. three-necked r.b.f. (fitted with N_2 inlet, addition funnel, condenser with drying tube, a thermowell and a Harsh burg stirrer) and heated to 200°C for 2 hrs. It was cooled to 160°C and sodium (69 g 3 moles) was added in pieces under N_2 blanket during 30 mins and heated to 160-180°C for 2 hr while stirring.

(ii) Isomerization of epoxide: The black finely oowdered catalyst was cooled to 110°C and 3α,4α-epoxycarane (1.52 kg, 10 moles) was added slowly. Initial epoxide addition raised the temp. to 180°C which subsequently subsided to 80°C. The hetrogeneous reaction mixture was then heated to 120-135°C for 12 hr with vigorous stirring, when TLC (15% EtOAc in toluene) indicated essentially complete conversion. At this stage the sodium salt and the catalyst was decomposed with water (160 ml) and stirred for 10 min. The liquid layer was filtered through sintered funnel and the alumina was washed with light pet. (250 ml x 9). Aq. layer was back extracted with light oet. (250 ml) and the combined layers were washed with 50% brine (250 ml x 8) till neutral. Removal of solvent furnished crude product (1.487 kg, 97.8%) which on careful fractionation using a 6' x 1" column packed with glass helices (35 theoritical olates) furnished car-4-en-3α-ol (10; 505.3g, 33.25%) and

car-2-en-4α-ol (3, 323.18 g, 21.26%) and residue (352.65 g, 23.2%).

(c) Using sodium salt of car-2-en-4-ol (3). In a 500 ml three-necked r.b.f. equipped with thermowell, nitrogen inlet, addition funnel and 9" vigreux column with Perkin triangle (the whole assembly being dried with free-flame with a gentle dry N_2 flow), was taken dry MeOH (50 ml) and sodium (3.8 g, 0.1644 g atoms) and was added slowly at 20°C. It was allowed to dissolve while stirring magnetically (0.5 hr). Excess of MeOH (34 ml) was distilled at pot temp. 80-100°C. To the dry sodium methoxide, was then added 2°-alcohol (25 gr, 82%) at 100°C pot temp. in one lot (10 min) and MeOH (5 ml) was distilled off at 120-130° bath temp. (25 min). To this sodium salt of allylic alcohol was added dry pyridine (75 ml) and stirred well at 110-120°C till it dissolves. α-Epoxide (2, 125 g., 0.82 mole, 95% pure) was added, the exit was closed with N_2 system. It was then stirred at 135-142°C (5-5.5 hr) when TLC (15% EtOAc in light pet.) indicated essentially complete conversion. Pyridine (72 ml) was distilled off (pot 100-105°C, press. 120-30 mm, 0.5 hr) and the residue was cooled, diluted with ice water (100 ml) and the product taken up in light pet. (100 ml x 2). After usual work-up 148 g of crude product

was distilled to furnished distillate (133.87 g, 89.2%, b.p. 78-79°/5 mm) and residue (12.65 g, 8.4%). Fractionation of this material (133.87 g), using a spinning-band column (45 theoretical plates) furnished car-4-en-3α-ol (10; 45 g, b.p. 72-76°/5 mm, pure) and car-2-en-4α-ol (3; 41.62 g, b.p. 90-96°/5 mm, pure).

(d) Using MeONa/pyridine. To the MeONa (Na; 15.2 gm, 0.66 mole in 200 ml dry MeOH) prepared as described earlier (Method 'c'), anhydrous pyridine (250 ml) was added, under dry inert gas (N_2) conditions. After stirring for 20 min to dissolve MeONa at 110-120°C, 3α,4α-epoxy carane (500 gm, 3.29 mole) was introduced and the reaction mixture stirred (pot. 138-139°) for 8-10 hr while removing low boilers (traces of Me-OH and pyridine, 90 ml) when TLC (solvent: 15% EtOAc, in light pet.) indicated essentially complete conversions. During the next 1 hr, the bulk of pyridine (210 ml) was collected by distillation, and the residue cooled, diluted with ice water (250 ml) and the product taken up in light pet. (100 ml x 3). After usual work-up, 482 gr (96.38%) of crude product was distilled to furnish distillate (408.3, 81.6%, b.p. 75-84/5) and residue (65 gm, 13%). Fractionation of this material (408.3 gr), using a spinning-band column (45 theoritical

plates) furnished car-4-en-3α-ol (10, 195 gm, 39%, b.p. 72-76/5 mm, pure) and car-2en-4α-ol (3, 155-52 gm, 31.1%, b.o. 90-96/5 mm, pure).

(+)-trans-p-Mentha-5,8-dien-2-ol (4)

Car-2-en-4α-ol (3, 53.72 g, 0.354 mole) and pyridine (0.6 ml) were refluxed (bath temp. 215-220°) under N_2 for a total of 11½ hr, when TLC (10% $AgNO_3$-SiO_2 gel ; solvent, 15% EtOAc in toluene) established disappearance of 3. The reaction mixture was distilled to get the required p-mentha-dienol 4: b.p. 84-86°/ 5 mm, 51.4 g (GLC purity 95%; GLC: 360 cm x 0.6 cm Al.column, 10% Carbowax 20M, 170°). An analytically pure sample was obtained by Inverse-Dry-Column-Chromatography[25] using 15% $AgNO_3$-SiO_2 gel (28.5 cm x 7.5 cm, solvent, 25% EtOAc in toluene; 4 charged, 3.9 g); b.p. 86°/5 mm, n_D^{25} 1.4911, $[\alpha]_D^{25}$ + 242.2° ($CHCl_3$, 4.3%) (Lit.[8b], $[\alpha]_D^{20}$ + 232.4°). IR (liq.): 3400, 1649, 1070, 1050, 1000, 897, 790 cm^{-1}. ^{1}H-NMR: Me CH (3H, d, 1.03 ppm, J = 7 Hz), 7 Hz),

Me-C=CH_2 (3H, s, 1.75 ppm),

CHOH (1H, b sig., 3.88 ppm, W_H = 11 Hz),

Me-C=CH_2 (2H, s, 4.74 ppm),

CH-CH=CH-CH (2H, bs, 5.5 ppm).

(+)-trans-p-Mentha-5,8-dien-2-one (5)

To a soln of above alcohol (50.53 g, 0.33 mole) in EtOAc (150 ml) cooled to 10 ± 2°, Brown's reagent[31] (495 ml, 0.33 mole; 100 g $Na_2Cr_2O_7 . 2H_2O$ + 300 ml H_2O + 136 g 97% H_2SO_4 - made to 500 ml) was added (1½ hr) while stirring at 25 ± 3°. Stirring was continued at this temp. for an additional 4 hr, 20 min, when absence of starting alcohol was indicated by TLC (solvent, 5% EtOAc in toluene). EtOAc layer was separated, aq. part extracted with EtOAc (150 ml x 4). The combined EtOAc extracts was washed with 10% $NaHCO_3$ aq. (25 ml x 5), water (25 ml), brine (25 ml x 2) and dried. Removal of solvent and fractionation of residue furnished 5 as a colourless liquid (28-32 g), b.p. 80-85°/5 mm (GLC purity 95%), n_D^{25} 1.4830, $[\alpha]_D^{25}$ + 192° (neat). IR (liq.): 1725, 1650, 1320, 1230, 1150, 905, 805 cm^{-1}. ^1H-NMR:

Me-CH (3H, d, 1.15 ppm, J = 7.5 Hz),
Me-C=CH_2 (3H, s, 1.75 ppm),
Me-C=CH_2 (2H, s, 4.78 ppm),
CH-CH=CH-CH (2H, s, 5.72 ppm)

3β-Aceloxycaran-4-one (8)

3α,4α-Epoxycaran (62 g, 0.41 mole) was mixed with gl.AcOH (250 ml) and the soln. left aside at room temp. (25°)

for 72 hr, when TLC (solvent, 15% EtOAc in toluene) showed only traces of epoxide. The reaction mixture was diluted with water (250 ml) and the product taken up in light pet. (100 ml x 4). The combined extracts were washed with 10% $NaHCO_3$ aq. (30 ml x 3), water (30 ml) and brine (30 ml). Solvent was flashed off and the residue distilled to collect a fraction (28.0 g), b.p. 100-103°/1 mm containing 83% of required 3β-acetoxycaran-4α-ol (7) (GLC; 10% carbowax 20M, 360 cm x 0.6 cm, 200°). Structure 7 was clear from comparison of its IR and ^{1}H-NMR spectra with the values reported in the literature.[29]

To Brown's reagent[31] (225 ml ≡ 0.15 mole $Na_2Cr_2O_7 \cdot 2H_2O$) and EtOAc (50 ml), cooled to 0°, the above product (27.0 g, 83%, GLC purity) in EtOAc (40 ml) was slowly introduced, with stirring during 1 hr at 0-5°. Stirring was continued at 10 ± 5° for additional 1.5 hr with TLC monitoring (solvent, 10% EtOAc in light pet.). Usual work-up furnished a product (26 g) which was distilled to get a material (19.7 g), b.p. 122-123°/3-4 mm, containing 72% required ketone 8 by GLC (10% SE30, 150°). This was purified by column chromatography, over SiO_2 gel/IIA (2.5 cm x 110.7 cm); 5% EtOAc in light pet. (100 ml x 3) eluted GLC pure

ketone 8 (14.5 g) : b.p. 122-123°/3.5 mm, n_D^{25} 1.4690, $[\alpha]_D$ + 222.8° (neat).

IR (liq.) (Fig. 3): 1740, 1725, 1460, 1370, 1255, 1145, 1095, 1065, 1024, 970, 870, 820 and 750 cm^{-1}.

^1H-NMR (Fig. 4): Me-C (6H, s, 1.12 ppm).
Me-C-O (3H, s, 1.44 ppm)
CH_3-COO (3H, s, 1.95 ppm),
CH_2-CO (2H, m. 2.40 ppm).

Mass. m/z 210 (M^+, 0.5%), 43 (100%), 107 (40%), 150 (30%), 108 (30%), 82 (30%), 67 (22%), 135 (13%).

(Found: C, 69.05; H, 8.24. $C_{12}H_{18}O_3$ requires: C, 68.54; H, 8.63%).

(+)-Car-2-en-4-one (6)

To a soln of 3 (10 g, 0.666 mole) in CH_2Cl_2 (100 ml), powdered pyridinium dichromate[27] (30 g, 0.08 mole) was added with stirring during 10 min and the mixture stirred at room temp. (30°) till TLC (solvent, 10% EtOAc in light pet.) showed absence of the starting alcohol (7 hr). At this stage the reaction mixture was filtered through a short column of neutral Al_2O_3 (grade III; 120 g), the column

washed with EtOAc (100 ml x 3), and the combined filtrate and washings washed with 10% $NaHCO_3$ aq (70 ml x 1), brine (70 ml x 1) and dried. Removal of solvent furnished a residue (9.5 g), which was distilled to get a pale yellow product (8.3 g), b.p. 60-70°/2.5 mm. This product (68.0 g) which was only 75% pure by GLC (10% Carbowax 20M, 170°) was further purified by fractional distillation on a high-performance spinningband column (80 theoritical plates)[39] to get over 90% pure (GLC) carenone (6) as a colourless liquid, b.p. 95°/10 mm, n_D^{27} 1.5270,

$[\alpha]_D$ + 5.34° (neat).

IR (liq. (Fig. 5): 1660, 1640(sh), 1456, 1409, 1380, 1312, 1259, 1140, 1084, 1048, 1010, 927, 850 cm^{-1}.

^{1}H-NMR (Fig. 6): Me-C (3H, singlets at 0.83 and 1.20 ppm), Me-C=C (3H, s, 1.75 ppm) CH_2CO (2H, m. 2.48 ppm), C=CH (1H, m. 6.69 ppm).

Mass: m/z 150 (M^+, 60%), 107 (100%), 108 (75%), 91 (40%), 79 (38%), 77 (26%), 135 (25%), 93 (24%).

(Found: C, 79.48; H, 9.65. $C_{10}H_{14}O$ requires: C, 79.95; H, 9.39%).

(+)-Carvone (9)

(a) From (+)-car-2-en-4-one (6). Ketone 6 (7.76 g; 85% pure) was heated at 205 ± 2° (bath temp. 220 ± 5°), under reflux (N_2), for 5 hr. At this stage GLC (10% Carbowax 20M, 170°) showed absence of both 6 or 5. Distillation of the product furnished a distillate (6.82 g) containing 80% carvone (GLC: 10% Carbowax 20M, 170°). A part (2.0 g) of this product was chromatographed (SiO_2 gel/IIA, 1.5 cm x 40 cm) to get pure carvone (1.3 g, eluted with 5% EtOAc in light pet.): colourless liquid with a clean caraway odour; b.p. 95°/7 mm, n_D^{25} 1.4955, $[\alpha]_D^{25}$ + 62.21°. λ_{max}^{EtOH} (Fig. 7): 235 nm (ε10630). IR (liq.) (Fig. 8): 1675, 1645, 1250, 1110, 995 cm^{-1}. ^{1}H-NMR (Fig. 9): Me-C=C (6H, bs, 1.76 ppm), C=CH_2 (2H, bs, 4.76 ppm), C = CH (1H, b sig., 6.67 ppm, W_H = 10 Hz). (Lit.[40]: $[\alpha]_D$ + 62.3°, UV, IR, ^{1}H-NMR).

(b) From (+)-trans-p-mentha-5,8-dien-2-one (5). Exposure of this ketone (22.5 g, 0.15 mole) to NaOH (0.9 g, 0.022 mole) dissolved in MeOH (90 ml) at reflux for 1 hr (N_2) effected its smooth, essentially quantitative isomerisation to (+)-carvone,

which was recovered, after usual work-up followed by distillation, b.p. 92-95°/7 mm, yield 20.52 g (GLC purity, 97%).

(c) From (+)-trans-p-mentha-5,8-dien-2-ol (4). To a suspension of N-chlorosuccinimide (6.95 g, 0.052 mole) in dry dichloroethane (40 ml), cooled to 0°, anhydrous dimethyl sulphide (4 ml, 0.054 mole) was introduced with stirring under strictly anhydrous conditions (N_2). To the complex, thus obtained, alcohol 4 (5.0 g, 0.032 mole) dissolved in dichloroethane (10 ml) was added slowly (10 min) while stirring and maintaining temp. at -10 to -8°. After stirring at this temp. for 2.5 hr, dry triethylamine (8.0 ml, 0.057 mole) was slowly introduced. The reaction mixture was stirred for another 5 min, cold bath removed to permit the reaction mixture to attain room temp. when it was heated at 70° for 1 hr. The reaction mixture was made acidic (H_2SO_4 aq.), the solvent layer separated, washed with water (20 ml x 2), 5% Na_2CO_3 aq. (5 ml), water (20 ml x 2), brine (20 ml) and dried. Usual work-up furnished after distillation, a product (4.13 g), b.p. 75-88°/5 mm containing 97% carvone (GLC), but having an undesirable odour.

(d) From (+)-3β-acetoxycaran-4-one (8). Pure 8 (2.86 g) was heated under reflux (N_2; bath temp. 240 $\pm$ 5°, pot temp. 180-190°) for 4 hr and worked up with EtOAc (50 ml), which was washed with 10% Na_2CO_3 aq (5 ml x 2), water and brine and dried. Removal of solvent gave a product (1.95 g), which was now free from AcOH. This material (0.7 g) was again heated as before (bath temp. 240 $\pm$ 5°, pot temp. 210 $\pm$ 5°) for 3 hr and worked up. The product was chromatographed on SiO_2-gel/IIA (1.5 cm x 24.0 cm), when 5% EtOAc in light pet.(10 ml x 2) eluted 0.2 g of pure (+)-carvone (GLC, PMR).

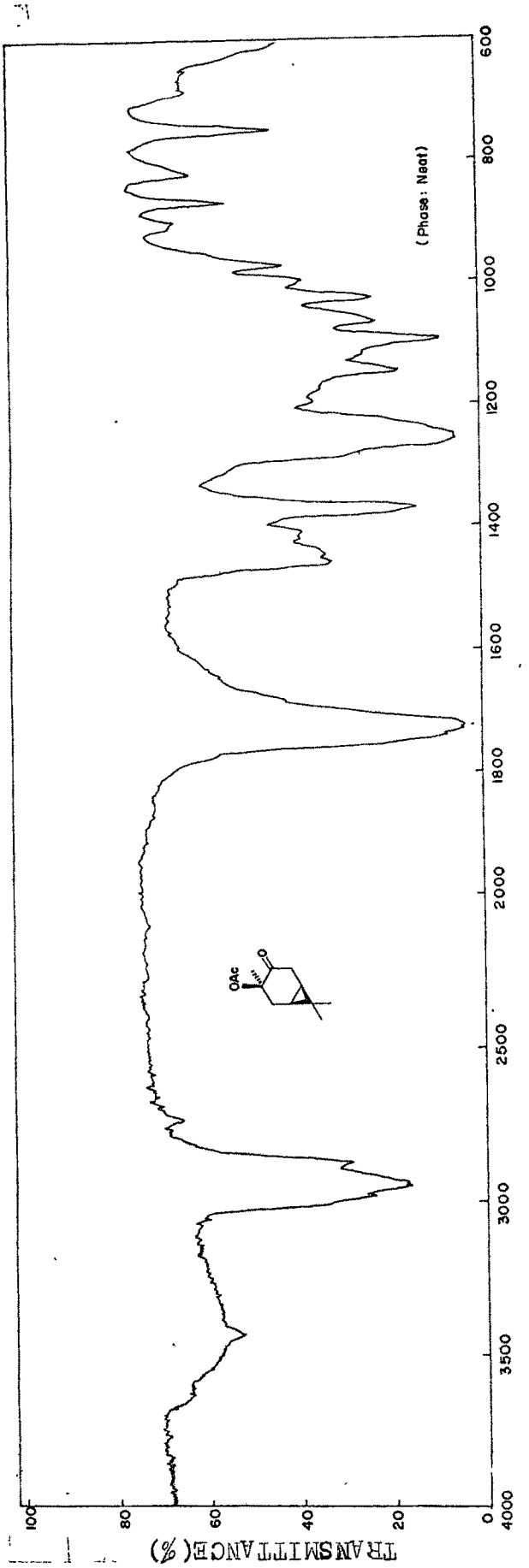


FIG.3 : IR SPECTRUM OF 3 -ACETOXYCARAN-4-ONE(8)

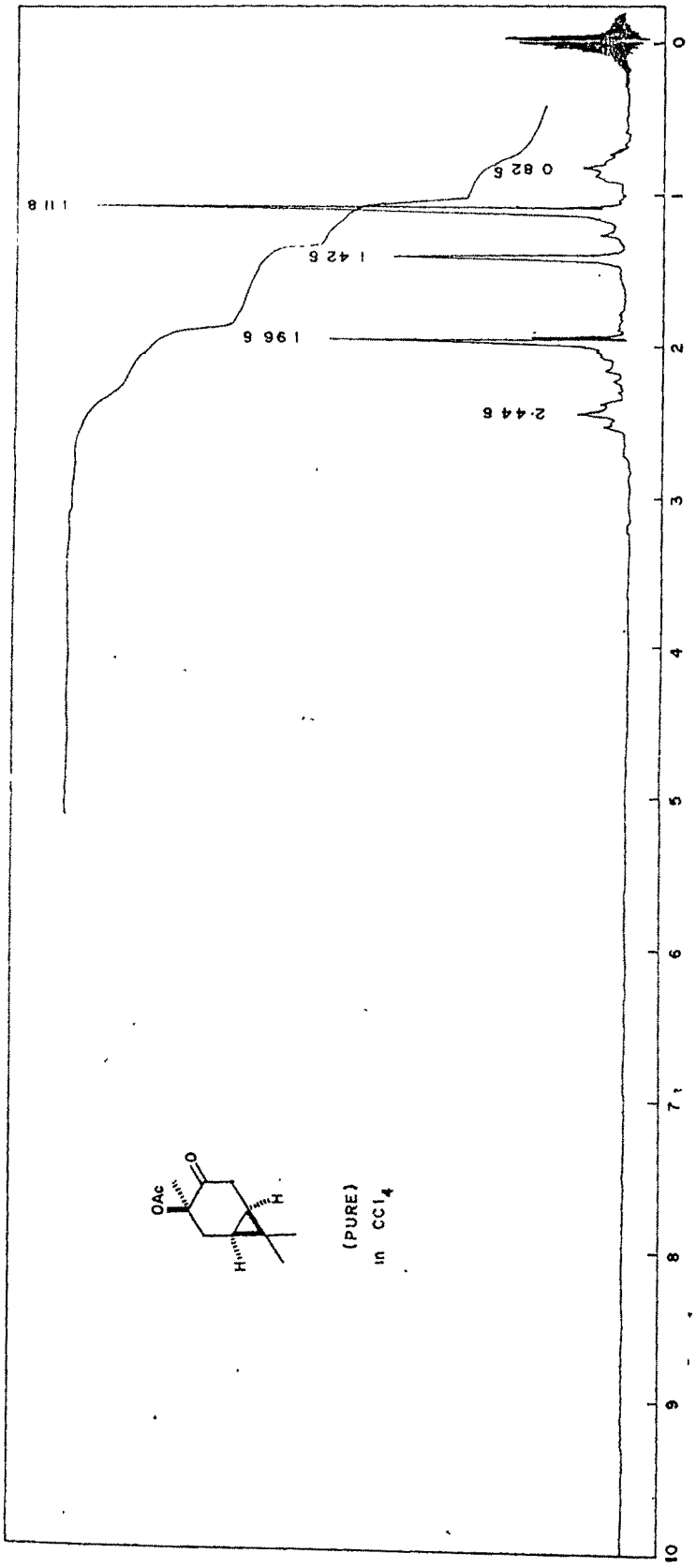


FIG.4 : ^{1}H-NMR SPECTRUM OF 3β-ACETOXYCARAN-4-ONE(8)

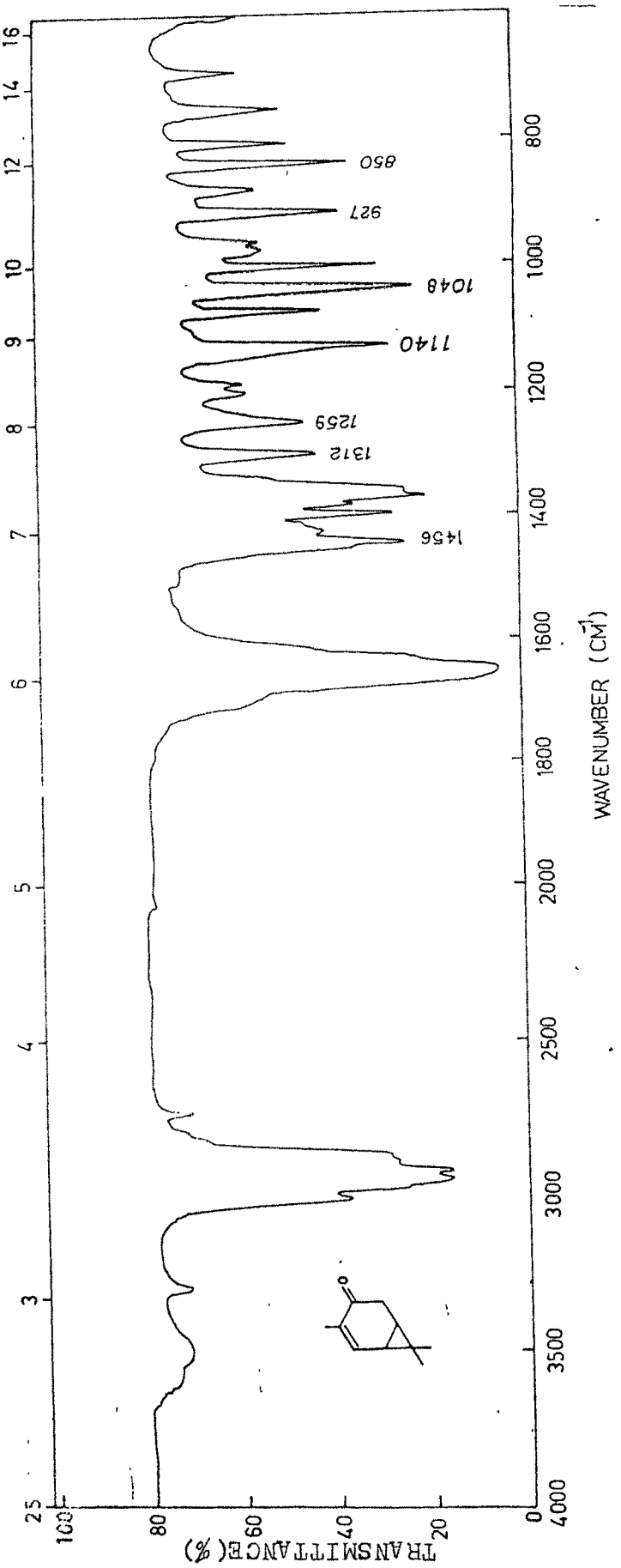


FIG. 5 : IR SPECTRUM OF (+)-car-2-en-4-one(6)

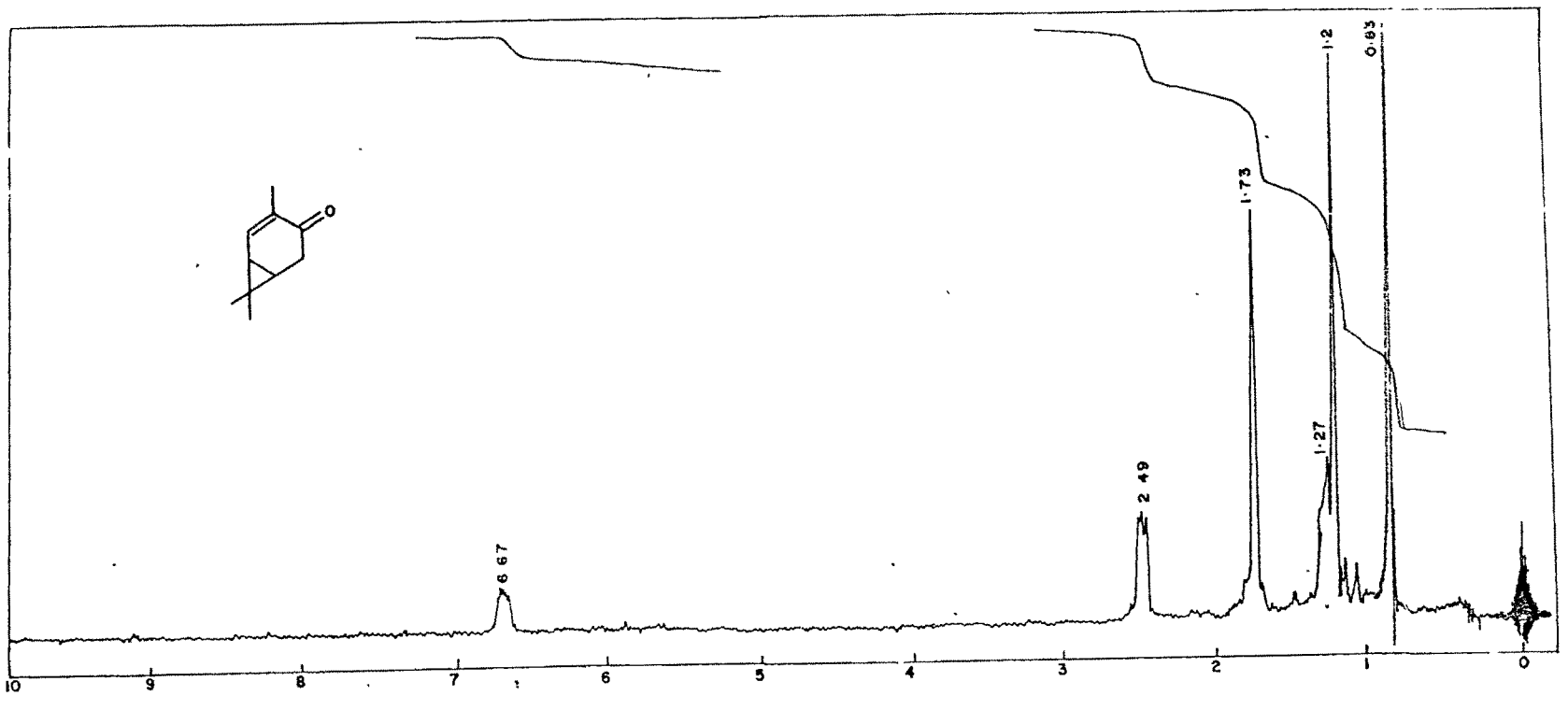


FIG.6 : ^{1}H-NMR SPECTRUM OF (+)-car-2-en-4-one(6)

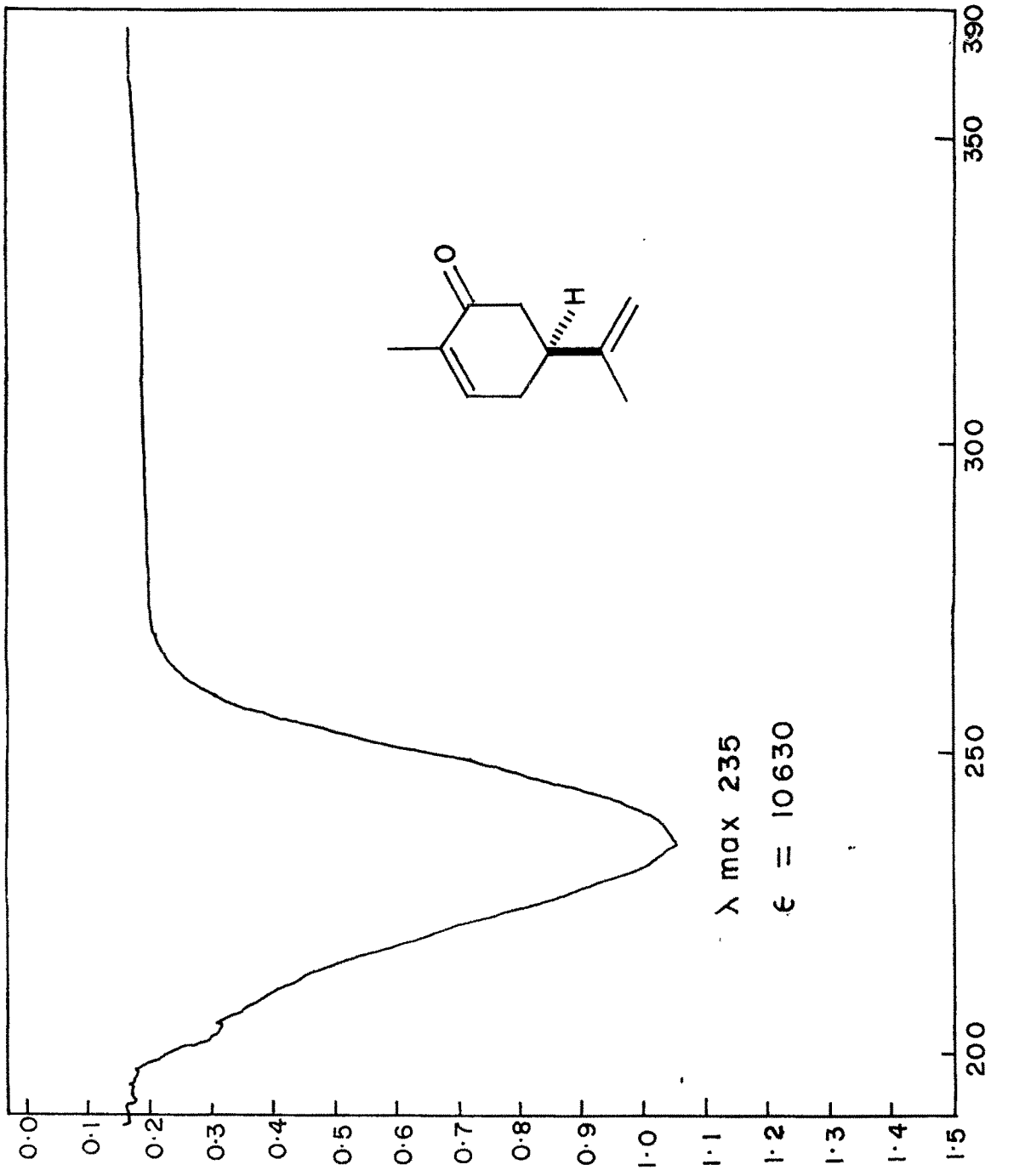


Fig. 7. UV OF d-CARVONE

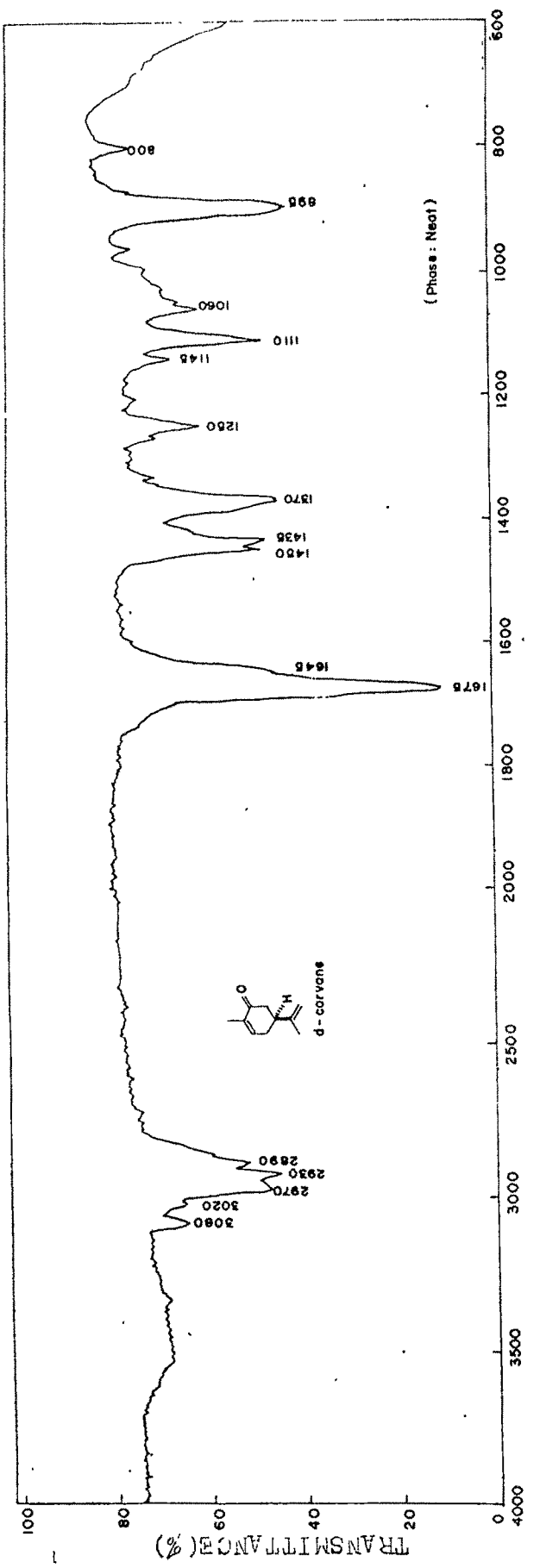


FIG.8 : IR SPECTRUM OF d-Carvone(9)

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