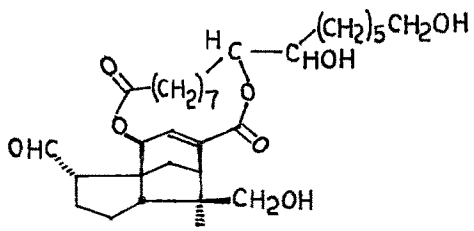
CHAPTER - II

NEUTRAL COMPONENT OF LAC RESIN

INTRODUCTION

While carrying out the separation of 'Palas' seed lac into 'hard' and 'soft' resin fractions, Sukh Dev and co-workers[1] isolated a neutral material for which a structure(1) was suggested[2] by them. These authors also reported[2] isolation of laccijalaric ester-I(2), jalaric ester-I(3), laccijalaric ester-II(4) and jalaric ester-II(5) from 'soft' resin fraction.



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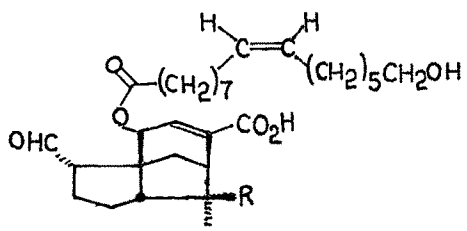
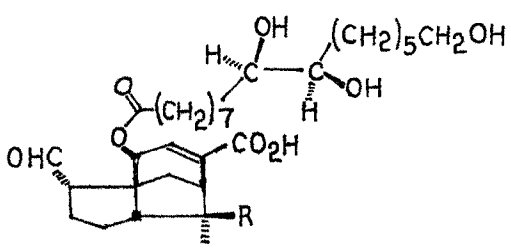
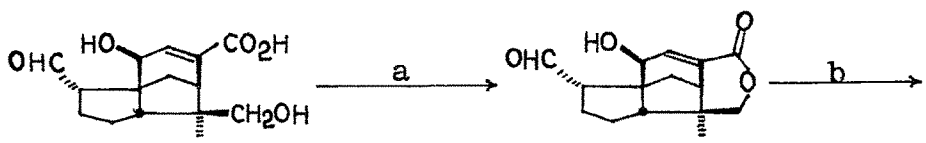


2. R=CH_3
3. R=CH_2OH



4. R=CH_3
5. R=CH_2OH

From the comparison of structures(1) and (3), it becomes clear that jalaric ester-I(3) can be elaborated to (1)-the neutral fraction of lac resin. Jalaric ester-I (3) has earlier been synthesized by Sukh Dev et al[3] by carrying out selective condensation of jalaric acid(6) with 16-hydroxy-(Z)-9-hexadecenoic acid(the scheme shown in Fig.1).



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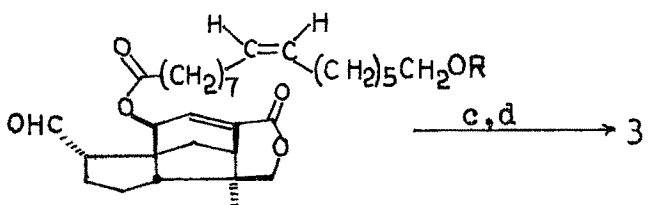


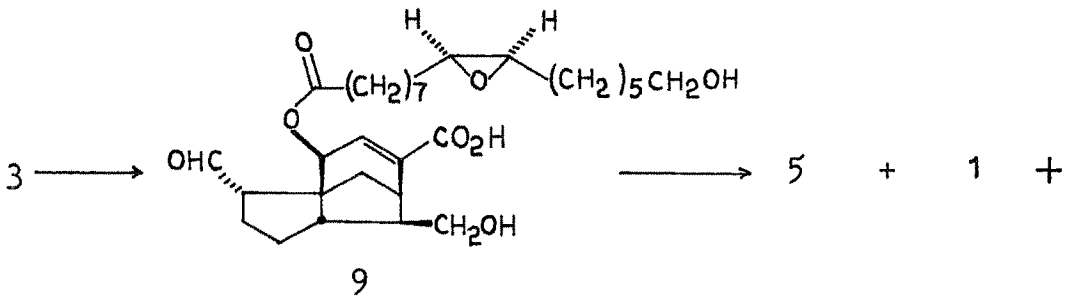
8 (R=HCO)

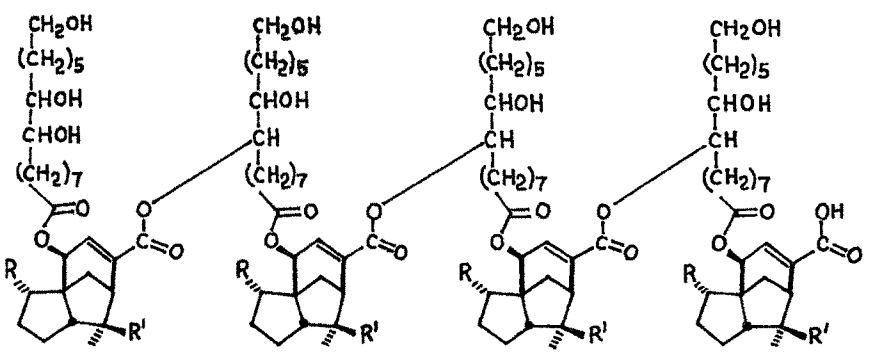
Reagents: (a) $Ac_2O/NaOAc$ (b) $ClCO(CH_2)_7CH=CH(CH_2)_5CH_2OCHO$

(c) $NaHCO_3$ (d) H_3^+O

FIG.1: SYNTHESIS OF JALARIC ESTER-I(3)

Conceptually, jalaric ester-I(3) on epoxidation should furnish oxirane(9), which on hydrolysis would give jalaric ester-II(5) in which aleuritic acid moiety will have the required, <u>threo</u> configuration, or it can undergo intramolecular epoxide opening by the carboxyl function to generate(1), or it can lead to polyesters of type(10) resulting from intermolecular oxirane ring-cleavage(Fig 2). Attempted transformations as conceived above form, in part, the subject matter of the present investigation.





10 : R = CHO/COOH

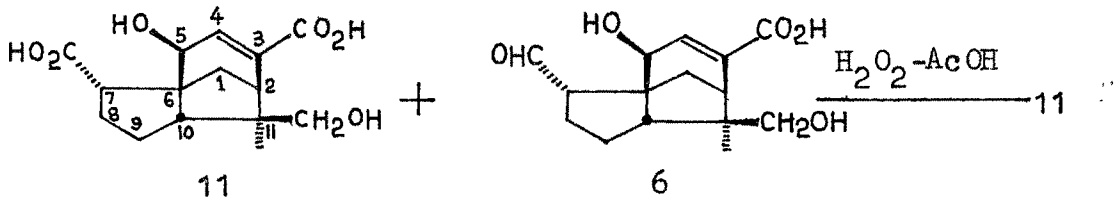
R = CH_2OH

FIG.2: CONCEIVED TRANSFORMATIONS

For doing this, we required sufficient quantity of jalaric acid(6) as the starting material. Jalaric acid is highly susceptible to air-oxidation and its content in lac resin varies depending upon the degree of exposure ; the oxidation product being epishellolic acid(11). While collecting jalaric acid by a hydrolytic procedure[4] of isolation, it was observed that jalaric acid is invariably accompanied by considerable quantity(20-25%) of epishellolic acid(11). At this juncture, it was thought that it would be convenient if epishellolic acid could be converted into jalaric acid δ-lactone(7), which is an intermediate in the proposed synthesis of the neutral component(1),starting from jalaric acid.

CONVERSION OF EPISHELLOLIC ACID TO JALARIC ACID DERIVATIVE(15)

In some isolation experiments, we got mixture of epishellolic acid(~ 87%) and jalaric acid(~13%). The mixture was subjected to a known H_2O_3-AcOH oxidation[4] whereby jalaric acid(present in the mixture) got oxidized to epishellolic acid. This crude epishellolic acid(TLC: homogeneous; no spot on 2,4-DNP spray, PMR: absence of signal at 9.7 ppm for aldehydic proton) was used without further purification for the next step(lactonization).



In order to carry out selective Rosenmund reduction of the carboxyl function at C-7, it is necessary to protect (a)the other carboxyl function a t C-3 and (b) the two hydroxyl groups. This has been readily achieved by making lactone linkage involving the primary -OH and the C_5-COOH function. The allylic-OH group has been protected as its acetate.

Epishellolic acid(11) was treated with Ac_2O-NaOAc in benzene at reflux temperature for 30 minutes and the product, thus obtained, reacted with Ac_2O-pyridine at 30° for 16 hours. The product, which mainly consisted of two compounds of R_f values 0.63 and

0.56(tlc, solvent system:benzene/EtOAc/AcOH=6:30:1) in a ratio of 1:3(PMR), respectively, was chromatographed over SiO_2 gel/IIA and eluted with benzene containing increasing proportions of EtOAc. 14% EtOAc in benzene eluted the compound of R_f 0.63 (homogeneous to tlc) which, from its IR spectrum(Fig 3)(1710-1760 cm^{-1}, δ-lactone, -OAc and -COOH; 1635 cm^{-1}, trisubstituted double bond), U.V. absorption spectrum(λ_{max}^{EtOH} 237 nm, $\epsilon = 3.2 \times 10^3$) and PMR spectrum (Fig 4) ($-OCOCH_3$: s,3H,2.12 ppm; $-CH_2OCO-$:s, 2H, 4.14 ppm; >C=C(H)-C(H)OAc:m, 2H, 5.95 ppm), was characterized as the acetate(12) of epishellolic acid δ-lactone.

16% EtOAc in benzene eluted the compound of R_f 0.56(homogeneous to tlc). This was, from its IR spectrum (Fig.5) (1700-1750 cm^{-1}, -OAc and -COOH; 1640 cm^{-1}, trisubstituted double bond), U.V. absorption spectrum(λ_{max}^{EtOH} 226 nm, $\epsilon = 7.8 \times 10^3$) and PMR spectrum (Fig.6)($-CH_2OCOCH_3$:s,3H, 2.04 ppm;$-CH_2OAc$: q, 2H, 3.9 ppm, J=11.5 Hz; >C=C-C-$OCOCH_3$: s,3H, 2.15 ppm; >C=C(H)-C(H)OAc:d, 1H,5.98 ppm,J= 2Hz and >C=C(H)-C-: d, 1H, 6.75 ppm, J= 2Hz), soon characterized as the diacetate(13) of epishellolic acid.

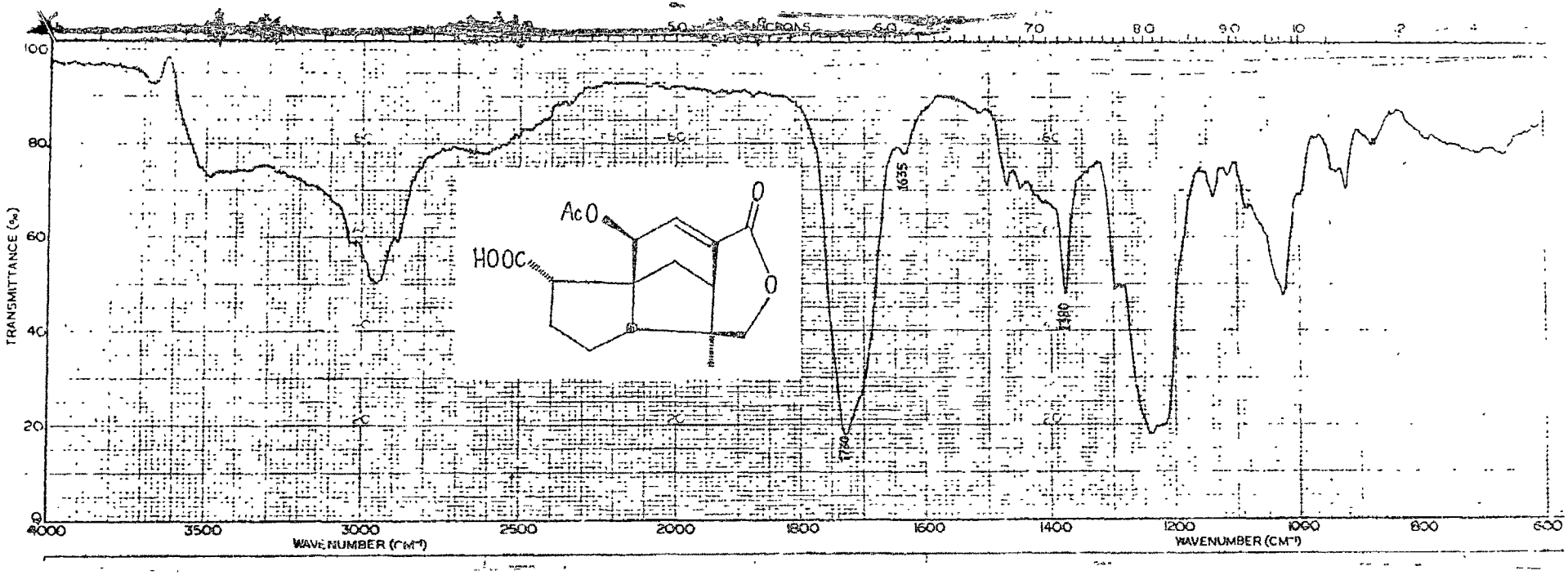


FIG.3: IR SPECTRUM OF THE ACETATE OF EPISHELLOLIC ACID-δ-LACTONE(12)

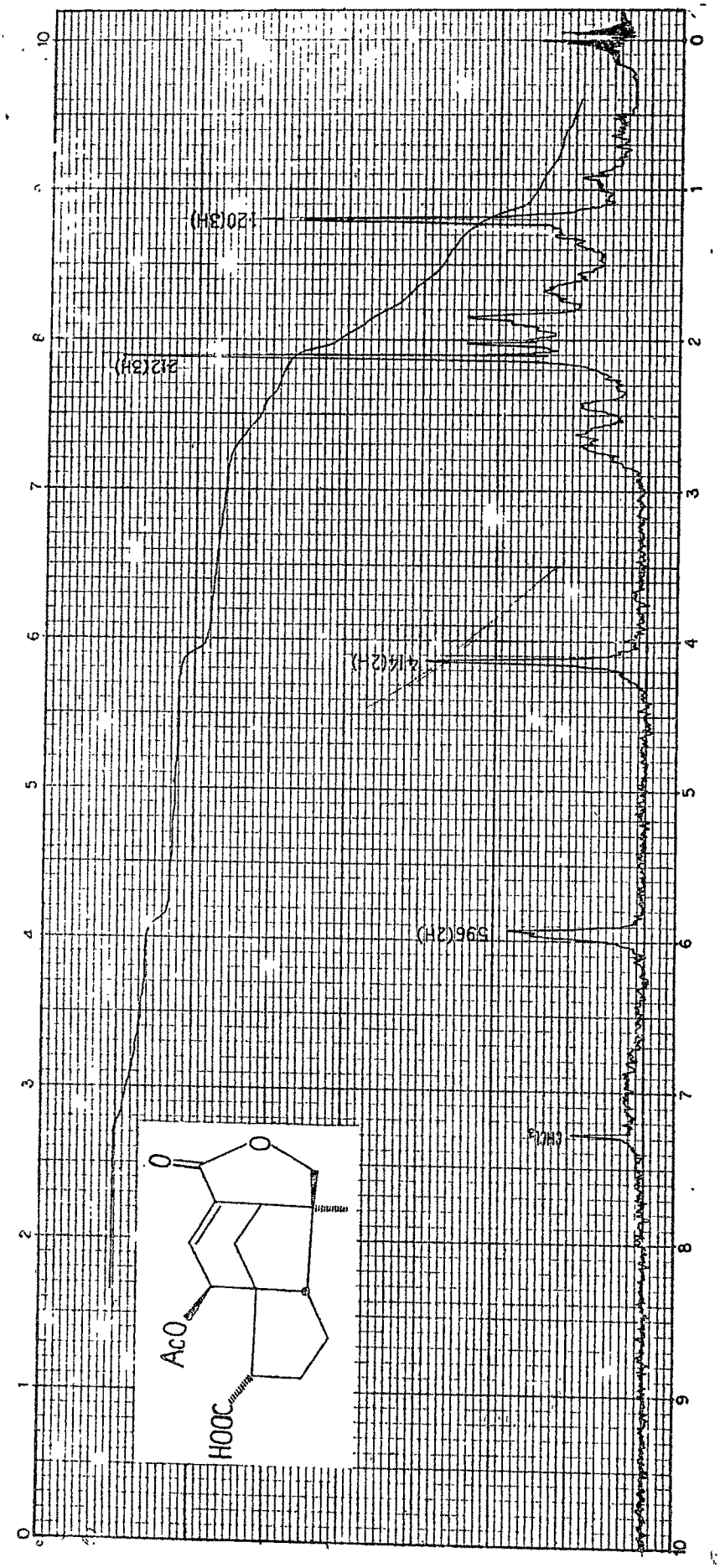


FIG.4: PMR SPECTRUM OF THE ACETATE OF EPISHELLOLIC-δ-LACTONE(12)

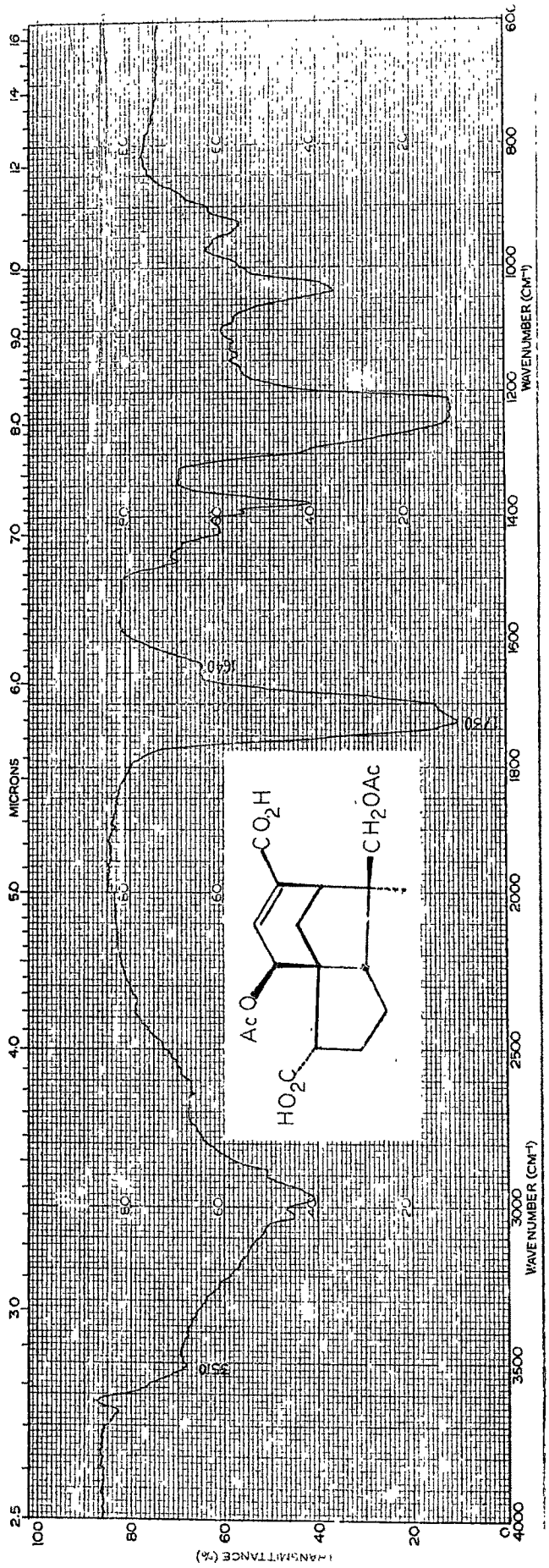


FIG.5: IR SPECTRUM OF EPISHELLOLIC ACID-DIACETATE(13)

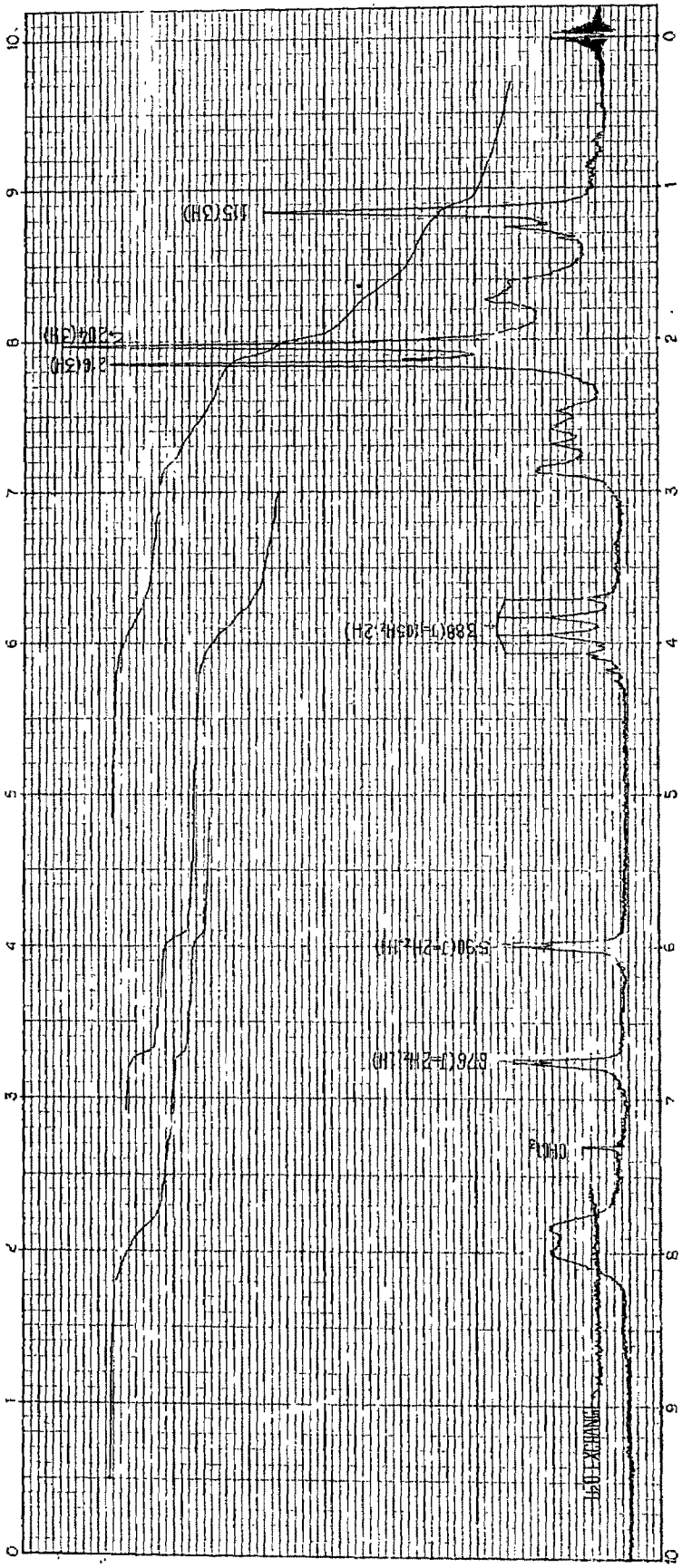
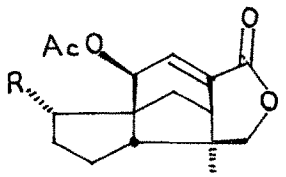
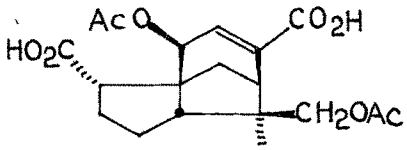


FIG.6: PMR SPECTRUM OF EPISHELLOLIC ACID-DIACETATE(13)



12 : R=CO_2H
14 : R=COCl
15 : R=CHO



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Now, Rosenmund reduction[5] of the acid chloride(14) may give rise to the targetted compound(15). This acid chloride(14) can be prepared from the acid(12) by treating it with either oxalyl chloride or thionyl chloride. Because phosphours impurities, which are often present in oxalyl chloride, completely inhibit Rosenmund reduction, we preferred to use thionyl chloride.

The acid(12) was refluxed for one hour with one molar excess of freshly distilled thionyl chloride(b.p.75-76°) and the residue left after removal of excess thionyl chloride was subjected to the aforesaid Rosenmund reduction using xylene as solvent, 5% $Pd/BaSO_4$ as catalyst and quinoline-S for partial poisoning of the catalyst. The product, after usual work-up, was separated into acidic and neutral parts. The acidic part was composed of epishellolic acid(TLC,PMR). The neutral part, which was homogeneous to tlc(solvent system: benzene/EtOAc/AcOH=6:30:1) and gave a yellow spot with 2,4-DNP spray, was the required aldehyde(15)(PMR, >CHCHO: d,1H, 9.77 ppm; $-OCOCH_3$: s, 3H, 2.17 ppm; $-CH_2O-CO-$: s,2H,4.17 ppm; >C=C(H)-C(H)-OAc:m, 2H, 5.9 ppm; identical with the reported PMR[2]).

For further establishing the identity of this compound, an authentic sample of jalaric acid δ-lactone(7) was prepared by lactonization of jalaric acid according to the reported method[2] and converting this lactone(7) into the corresponding acetate(15) by Ac_2O-pyridine method. The comparison of physical and spectral (TLC,IR,PMR) data revealed that both the compounds were identical.

Thus, this completes the conversion of epishellolic acid into jalaric acid derivative(15).

ATTEMPTED SYNTHESIS OF THE NEUTRAL PART

Keeping in view the smoothness with which the -CHO group in jalaric acid and its derivatives undergoes air-oxidation and also the Cannizarro reaction which it would undergo[6,7,8] under the alkaline conditions to be used in the conceived reaction sequence, it is necessary to protect this aldehyde group first. Since a very convenient preparation of jalaric acid δ-lactone(7) from jalaric acid was known in literature[2], we decided to use it for the protection of -CHO group and then go ahead with the scheme at hand.

PROTECTION OF -CHO GROUP OF JALARIC ACID δ-LACTONE(7)

Jalaric acid δ-lactone(7) was refluxed[9] with excess of MeOH and catalylic amount of NH_4Cl for 1.5 hours. The product was isolated in 96% yield by removing the excess of methanol, adding water to the residue and extracting with EtOAc. This product, from its IR spectrum (Fig.7) (3450 cm^{-1}, OH; 1690-1730, carbonyl group; 1630 cm^{-1}, tri-substituted double bond) and PMR spectrum (Fig.8) ($CH(\underline{OMe})_2$: bs, 6H, 3.33 ppm; $-COO\underline{Me}$: s, 3H, 3.78 ppm; $>C=C(H)-\overset{1}{C}(\underline{H})OH$; d, 1H, 4.77 ppm, J=2Hz and $>C=C(\underline{H})-$: d, 1H, 6.67 ppm, J= 2 Hz), was characterized as dimethylacetal of methyl ester of jalaric acid(16). This was further confirmed from its

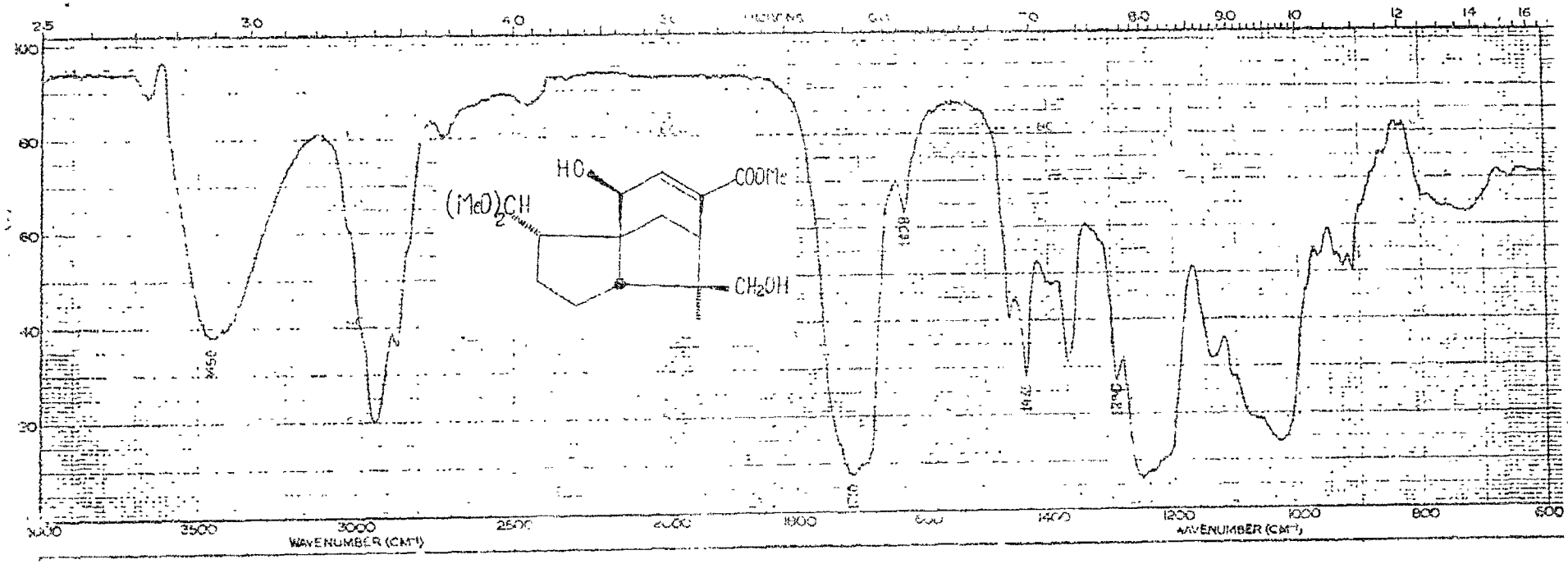


FIG.7: IR SPECTRUM OF DIMETHYL ACETAL OF METHYL ESTER OF JALARIC ACID(16)

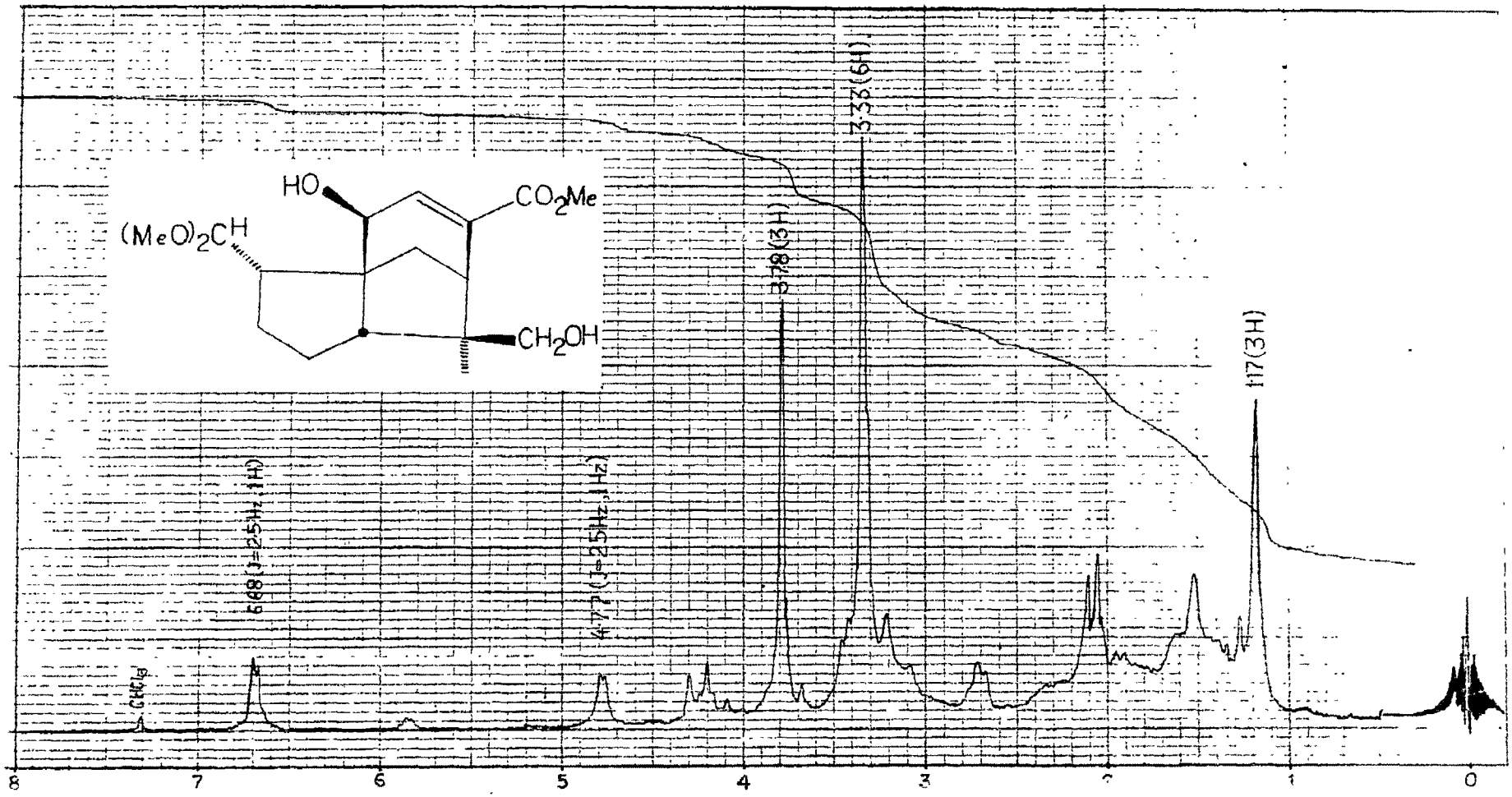
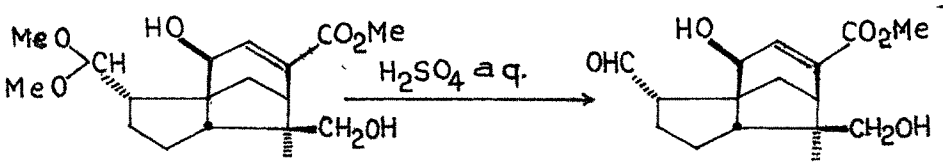


FIG.8: PMR SPECTRUM OF DIMETHYL ACETAL OF METHYL ESTER OF JALARIC ACID(16)

product of hydrolysis(10% H_2SO_4 aqueous), which from its PMR spectrum(Fig 9)(-CH_2OH: bd, 2H, 3.3 ppm; -CO_2Me: s, 3H, 3.8 ppm; >C=C(H)-C(H)OH: d, 1H, 4.75 ppm, J= 2.5 Hz, >C=C(H)-: d, 1H, 6.72 ppm and -CHO: d, 1H, 9.78 ppm) was the expected methyl ester(17) of jalaric acid.



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Transketalization[10] of jalaric acid δ-lactone with 1,3-dioxolan of butan-2-one using p-toluene sulphonic acid as catalyst resulted in opening up of the lactone ring(PMR: disappearance of -CH_2OCO signal at 4.16 ppm). Also, when jalaric acid δ-lactone was treated with $HSCH_2CH_2SH$-BF_3.Et_2O[11] the lactone ring was found open.

An efficient ketal formation from aldehydes by using $HC(OMe)_3$ and lanthanoide salts as catalyst is reported[12]. Also, these conditions are reported to be suitable for acid sensitive molecules. With hydrated cerrous chloride as catalyst, our system(7) behaved, once again, differently

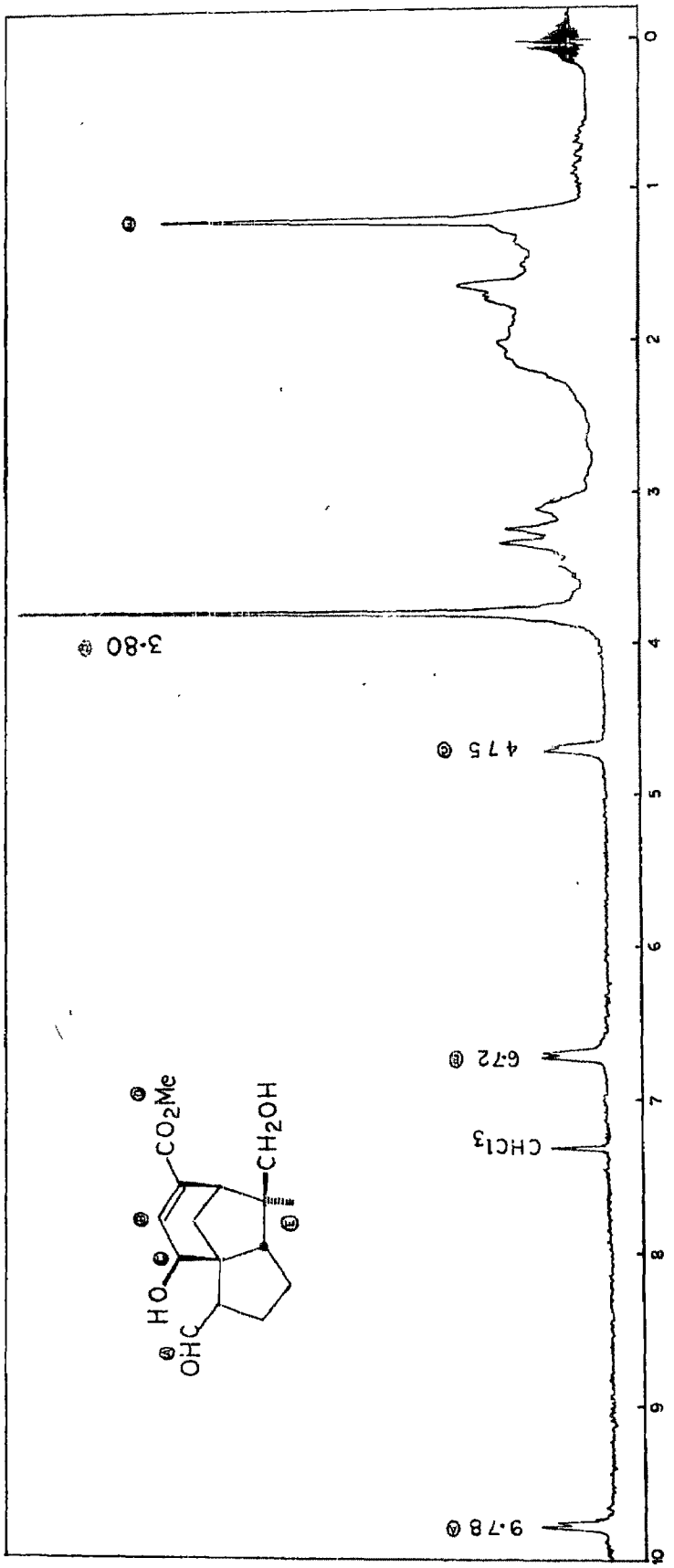


FIG.9: PMR SPECTRUM OF METHYL ESTER OF JALARIC ACID(17)

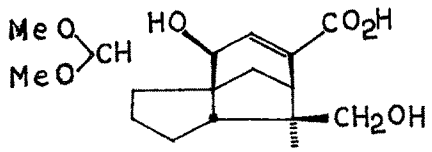
and the reaction was found to be almost equivalent to using MeOH-NH_4Cl. MeOH-$HC(OMe)_3$-$CeCl_3.XH_2O$ combination was, however, found superior to MeOH-NH_4Cl in the sense that with the former the protection reaction was much faster than the opening up of the lactone ring (PMR). Analysis by PMR of aliquots taken at different intervals revealed that with passage of time the signal for $-CO_2\underline{Me}$ at 3.8 ppm appears at the expense of the signal for $-\underline{CH_2}OCO$ at 4.16 ppm. A reaction time of 10 minutes gave complete protection of -CHO function, but ~ 75% of the lactone ring had cleaved(PMR). Complete cleavage of the lactone ring was observed(PMR) after 30 minutes.

From above, it is clear that the δ-lactone ring of jalaric acid δ-lactone(7) is extremely labile under even very mild acidic conditions and an absolutely neutral condition is desired to achieve the above -CHO protection while keeping the lactone moiety fully intact. Such conditions we could not find in the literature. In view of this defficulty, we decided to protect the aldehyde group first and then bring about the lactonization.

PROTECTION OF -CHO OF JALARIC ACID

Jalaric acid was treated with MeOH-NH_4Cl[9] for 1.5 hours at reflux temperature. Usual work-up gave, in ~95% yield, a product which from its IR spectrum (Fig 10)(3400 cm^{-1}, OH;

2500-2700 and 1680 cm^{-1}, COOH), U.V. absorption spectrum (λ_{max}^{EtOH} 2.33 nm, ϵ=7.97 x 10^3) and PMR spectrum(Fig.11) (disappearance of aldehydic signal at 9.7 ppm and appearance of a signal at 3.24 ppm for 6H) was the desired jalaric acid dimethyl acetal(18).



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LACTONIZATION OF DIMETHYL ACETAL(18)

Now, having got the -CHO group protected as its dimethyl acetal, one can not use acidic conditions generally used for lactonization, as under these conditions the acetal would cleave back to the starting aldehyde(6). Basic conditions also obviously cannot be used. Hence, we require neutral conditions to bring about the lactonization.

2,2'-Dipyridyl disulphide-triphenylphosphine, a neutral reagent used for lactonization, is known to act through activation of -COOH group by converting it into its thio-ester

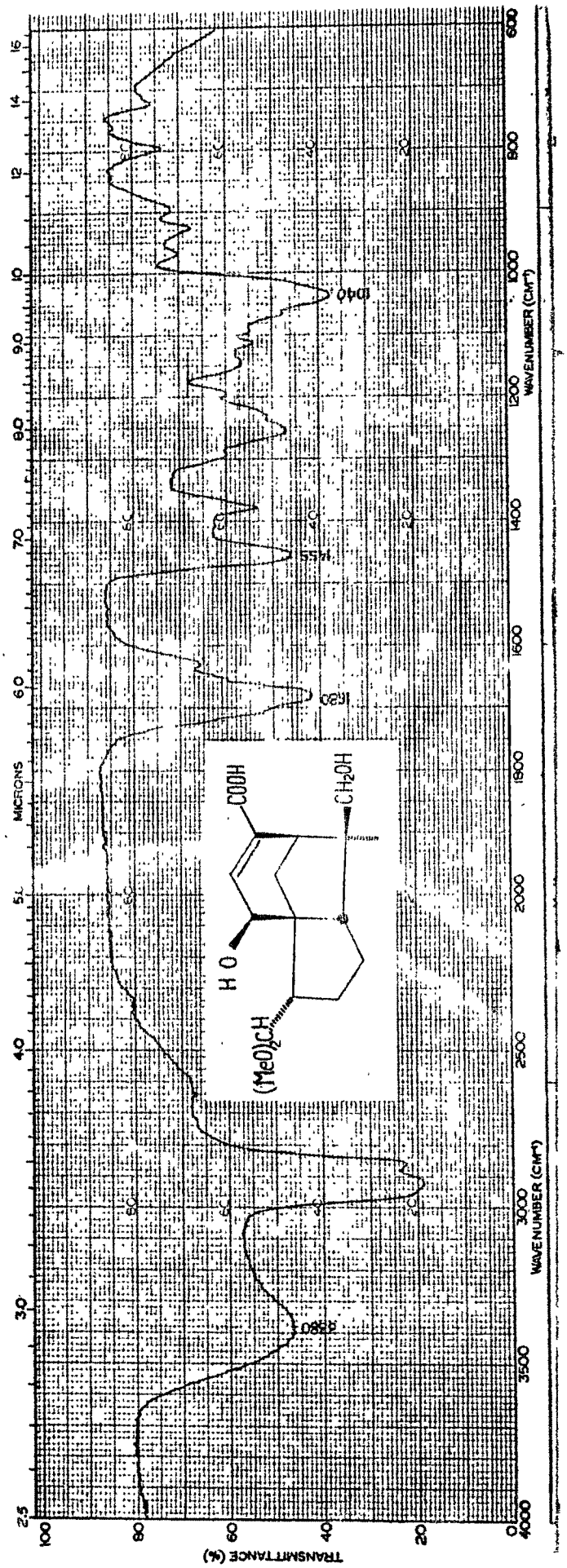


FIG.10: IR SPECTRUM OF JALARIC ACID-DIMETHYL ACETAL(18)

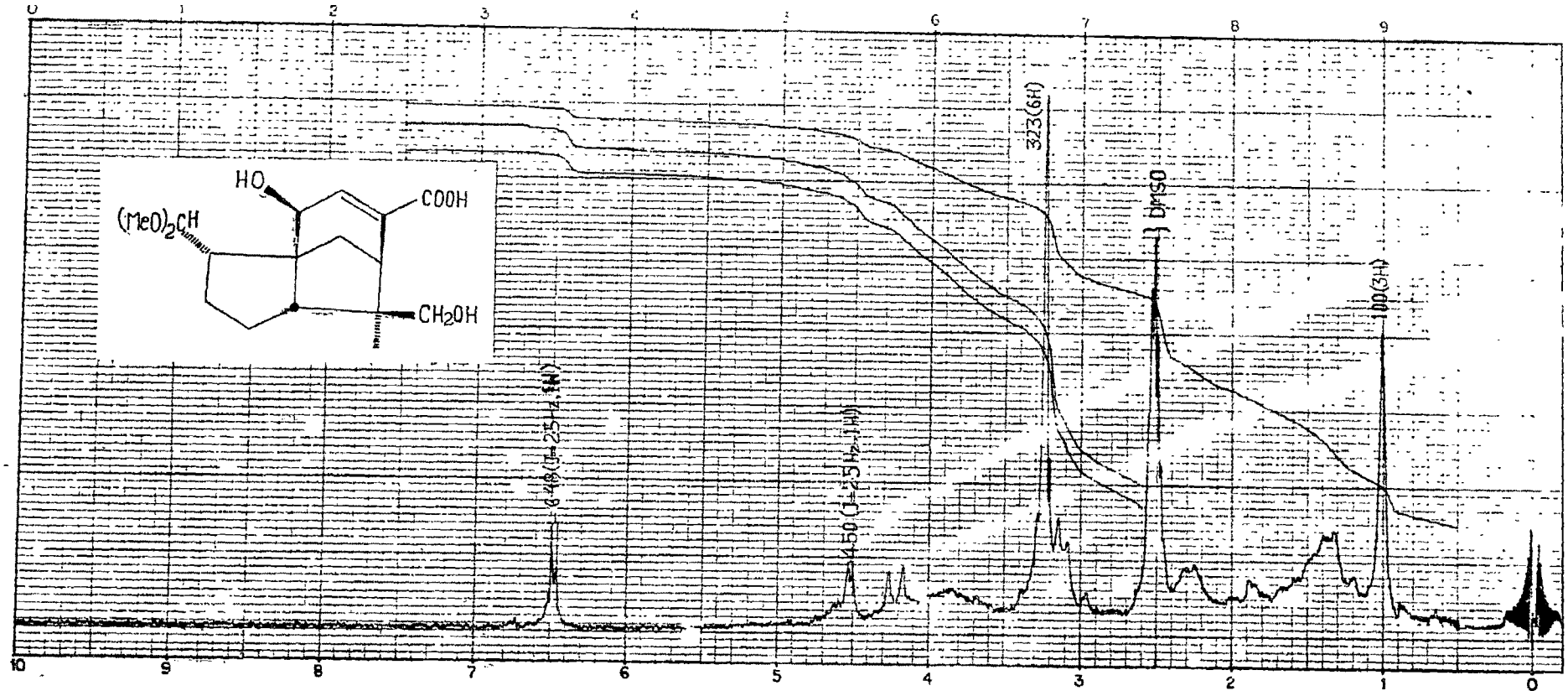
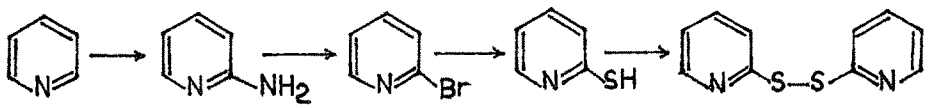


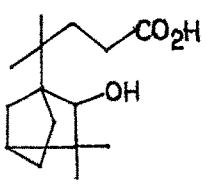
FIG.11: PMR SPECTRUM OF JALARIC ACID-DIMETHYL ACETAL(18)

which then can be subjected to lactonization[13]. 2,2'-Dipyridyldisulphide(DPDS) was prepared from pyridine by using the following scheme. Of the several procedures



available[14-18] for the preparation of 2-bromopyridine, the one followed by us was essentially that of Craig[14,15].

As a model reaction, we wanted to try this reagent first with the hydroxy acid(19) which can be readily obtained from the lactone(20), a material available in our lab.



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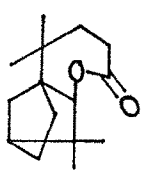

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Lactone(20) was hydrolyzed with ethanolic KOH. Usual work-up gave a product which, from its IR spectrum(Fig.12) (3500 cm^{-1}, OH; 2500-2700 and 1710 cm^{-1}, COOH) and PMR spectrum (Fig.13) ( )C(H)OH: s,1H, 3.73 ppm; $-\underline{CH_2}CO_2H$: t,

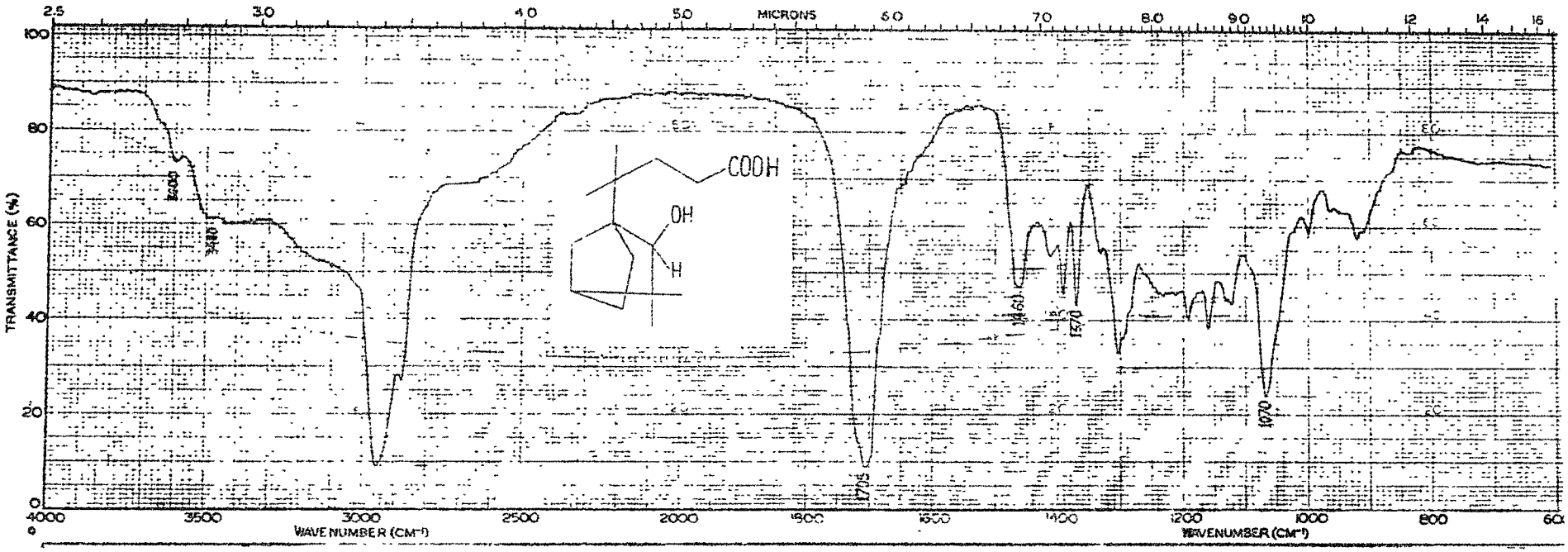


FIG.12: IR SPECTRUM OF THE HYDROXY ACID(19)

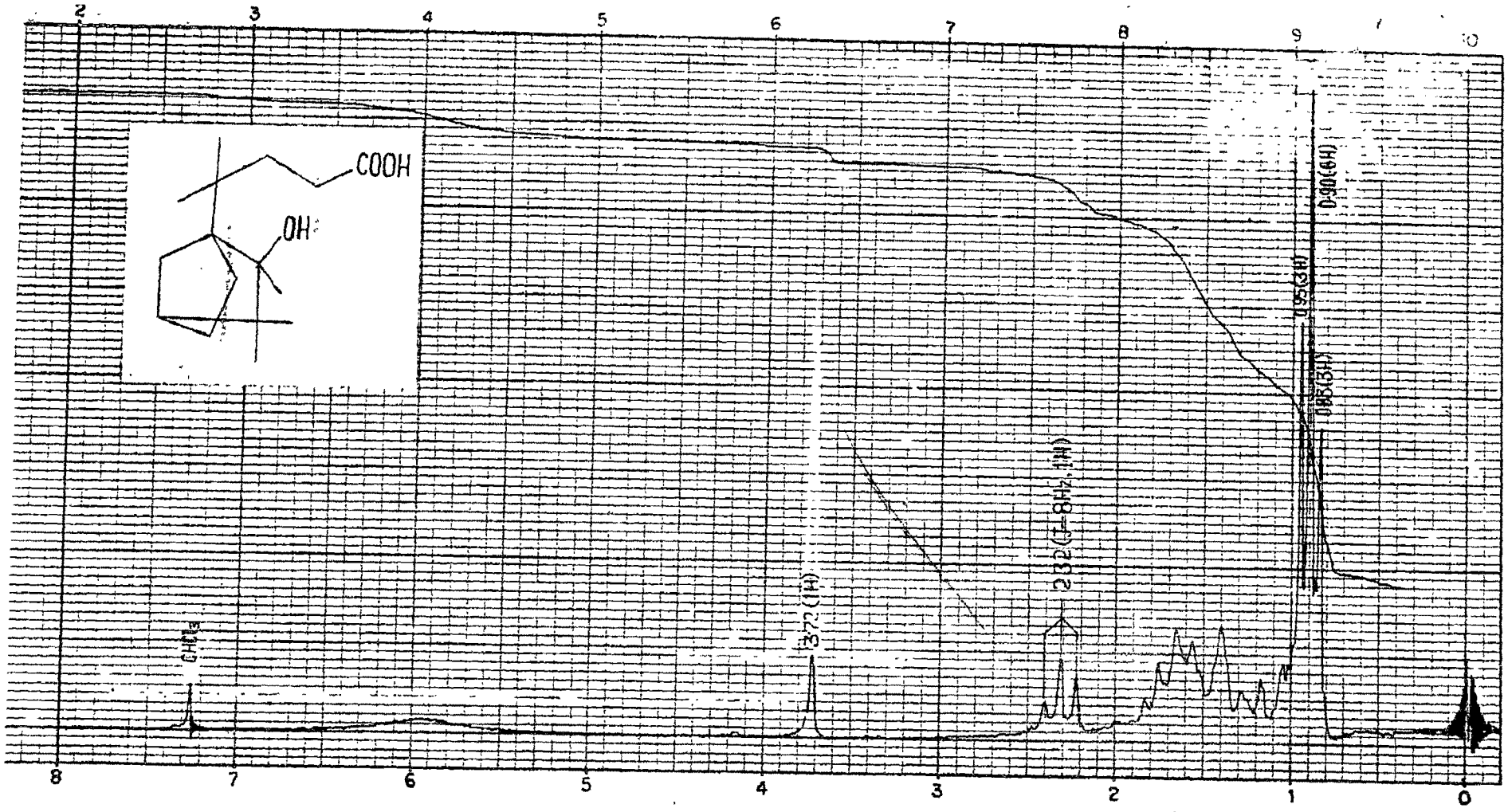


FIG.13: PMR SPECTRUM OF THE HYDROXY ACID(19)

2H, 2.31 ppm), was the desired acid(19). This(19) was treated with equimolar amounts of ϕ_3P and DPDS in xylene at ~ 30° for 5 hours and the resulting turbid solution added slowly(10 hrs) to a large volume of refluxing xylene. After an additional reflux for 5 hours, xylene was removed under reduced pressure and the product obtained in ~ 90% yield, after chromatography over SiO_2/IIB(eluted with benzene), was identical in all respects with the lactone(20)(PMR, >C<u>H</u>OCO:s,1H,4.18 ppm and IR, 1720 cm^{-1}, lactone).

Under the above conditions, no lactonization of jalaric acid-dimethyl acetal was observed. The reaction was followed by PMR analysis of the crude product.

The lactonization of jalaric acid-dimethyl acetal(18) was finally achieved by using N,N'-dicyclohexylcarbodiimide(DCC), another neutral reagent used for lactonization[19] and esterification[20]. The acetal(18) was treated with equimolar quantity of DCC in dry and pure EtOAc for 4 hours at ~ 30° under continuous flow of nitrogen. The product, after usual work-up(~ 95% yield), was, from its PMR spectrum(Fig.14)(-<u>CH_2</u>OCO-:s,2H,4.16 ppm. and -CH(<u>OMe</u>)$_2$: bs, 6H, 3.32 ppm), the desired lactone-acetal(21).

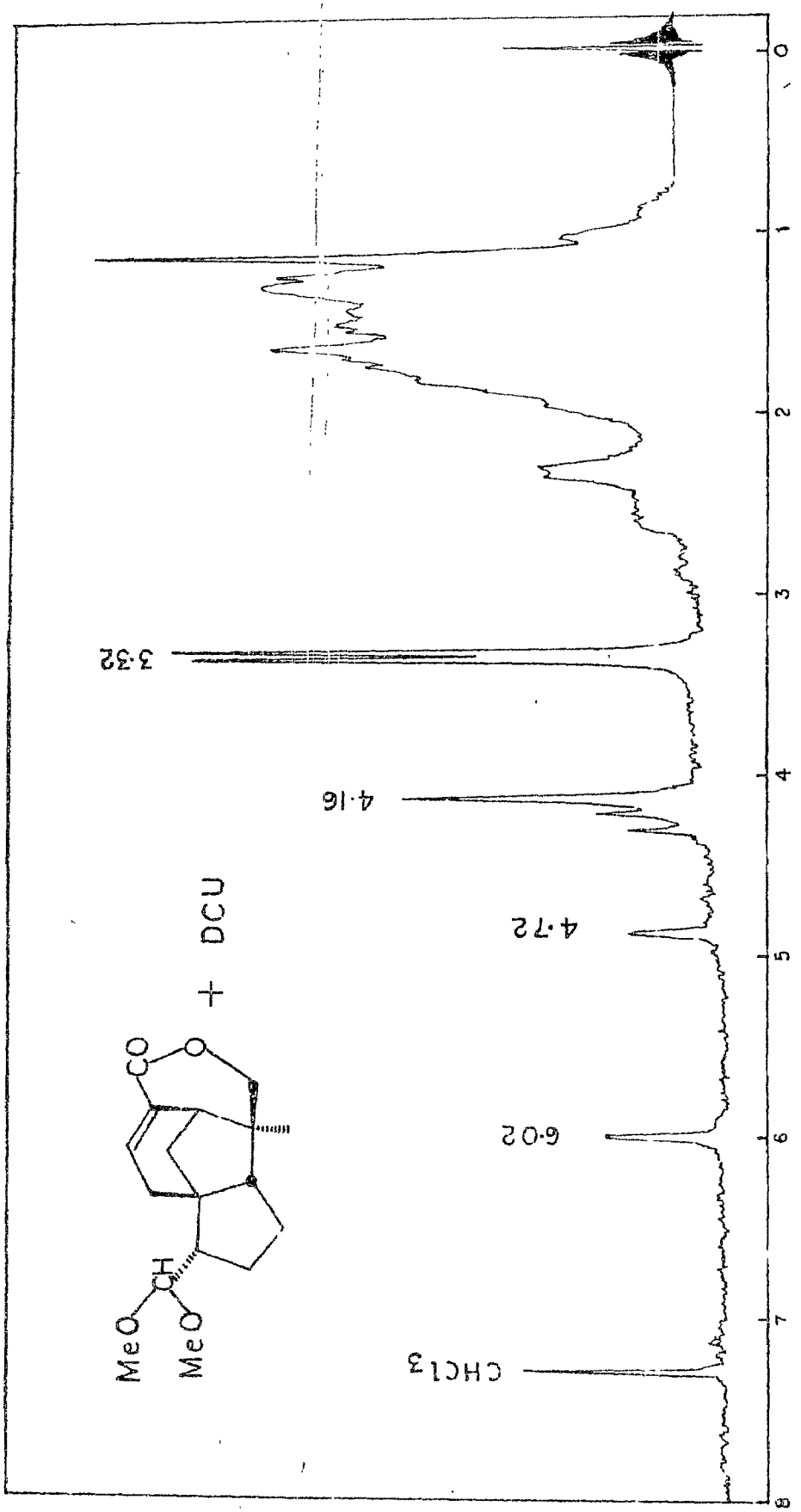
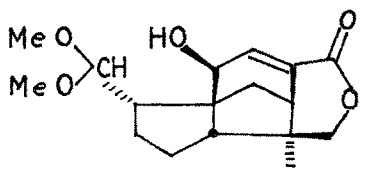


FIG.14: PMR SPECTRUM OF JALARIC ACID δ-LACTONE-DIMETHYL ACETAL(21) + DCU



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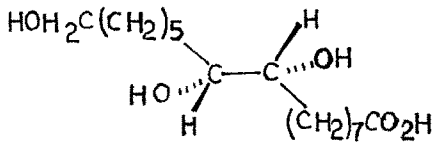
This acetal lactone(21) is the key compound which is to be condensed with the formate of 16-hydroxy(Z)-9-hexadecenoic acid(26). This acid(26) has been synthesized from threo-aleuritic acid(22, natural, m.p. 100-101°C) by following a reported method[3].

16-HYDROXY-(Z)-9-HEXADECENOIC ACID(26)

The threo-acid(22) was first converted, in 94% yield, into a trans-acid(24) by treating it first with $HC(OEt)_3$-ØCOOH and then with alcoholic alkali. This trans acid(24) gave, on trans-hydroxylation with H_2O_2-HCOOH, erythro-aleuritic acid(23) (92% yield), which when subjected to the conditions outlined for the preparation of (24) above, furnished a viscous liquid essentially containing(25). This(25) was passed through a column of SiO_2gel/IIA using 25% EtOAc in benzene as eluant to give pure 16-hydroxy-(Z)-9-hexadecenoic acid(25) in 90% yield.



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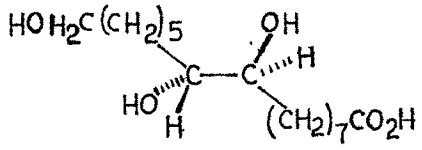

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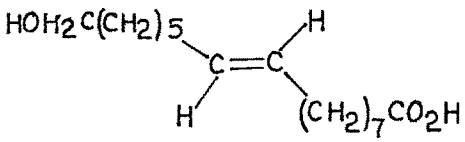

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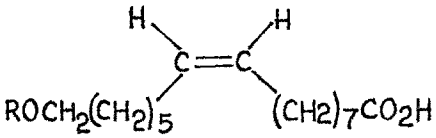


25 : R═H

26 : R═HCO

FORMATE OF (26)

Sukh Dev and co-workers[3] have prepared this formate by treating the hydroxy-acid(25) with acetic-formic anhydride for 24 hours at 25-30°C. Obtaining anhydrous formic acid for the preparation of acetic-formic anhydride is a laborious job. Also, the preparation of acetic-formic anhydride from CH_3COCl and HCOONa is time consuming(6-8 hours). We have simplified their procedure as it was found that cis acid(25) on refluxing with 80% HCOOH for 5 hours followed by removal of the excess HCOOH under reduced pressure and usual work-up including purification(passing through a column of SiO_2 gel/IIA using 20% EtOAc in benzene as eluant) results in the pure(26)

(PMR, IR). Under almost the same conditions, cholic acid has earlier been converted into its triformyl derivative by Cortese and Bauman[21].

ATTEMPTED CONDENSATION VIA ACID CHLORIDE FROM(26)

Esterification of an acid with an alcohol via the acid chloride from the former is well known and a commonly used reaction. This procedure has been followed by Sukh Dev and co-workers[3] for esterifying the cis acid(26) with the alcohol (7, i.e. jalaric acid δ-lactone). Here also, we used the same procedure for esterifying the acid(26) with the alcohol(21). The product was separated into acidic and neutral parts. The acidic part was composed of the cis acid(26) (IR,PMR). PMR analysis of the neutral part revealed cleavage of the acetal function with the esterification/condensation reaction going alright. The pyridinium hydrochloride formed during the course of the reaction is believed to be responsible for the undesired cleavage of the acetal function.

ATTEMPTED CONDENSATION USING DCC

Esterification of acids with alcohols using N,N'-dicyclohexyl-carbodimide(DCC) is also a well known reaction[20]. After the failure of condensation via acid chloride method above, we thought of using DCC for the above-said condensation without isolating the alcohol(21) in the lactonization step.

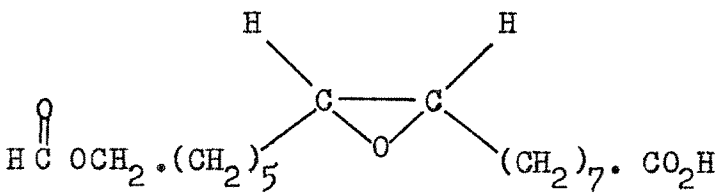
After the lactonization reaction was over, equimolar amounts of DCC and the acid(26) were added and the mixture stirred at room temp. for 5 hours. Product(s) was/were isolated by filtering off the precipitated N,N'-dicyclohexyl-urea(DCU), followed by removal of the solvent under diminished pressure(250 torr). From the PMR spectra of the compounds(7), (12), and (21), it is clear that once the -OH group of(21) is esterified the signal for the proton on carbon bearing this -OH in(21) should move downfield to ~6 ppm and also the region from 4.5 to 5.0 ppm should be completely devoid of any signal. Moreover, as the olefinic proton of(21) also appears at ~6 ppm, the ratio of the area of the signal at ~6 ppm to that of one at 5.37 ppm(a triplet for the two olefinic protons in the acid 26) should be 1:1. We analyzed the PMR spectrum of the above product in these terms and found that no esterification had taken place. To confirm it further, we chromatographed this product(containing the slight excess of DCC and the unprecipitated DCU) over SiO_2gel/IV using benzene containing increasing proportions of EtOAc as eluant and isolated the two components, (21) and (26), separately (PMR). In place of EtOAc, we have used other solvents like THF, dioxan, and benzene and refluxed the reaction mixture(16 hours) but with no fruitful avail.

FUTURE PROSPECTS

It was soon realized that when a 1:1 mixture of (21) and (26) was treated in benzene with 0.01 molar excess of tert-butylhydroperoxide[22] and catalytic amount of molybdenum stearate followed by reflux(5 hours) and work-up(benzene and excess of the reagent were distilled off, the product taken up in benzene and washed with water) it resulted in,contrary to our expectations, faster epoxidation of the double bond in (21) than the one in (26) (PMR). So, one has to have selective epoxidation of the double bond in the acid part (26) over the one in the alcohol part(21) by using some other selective epoxidation reagent, if one wants to carry out this epoxidation after the condensation/esterification step. Bearing in mind that here one is dealing with a material (21) having an acetal group(labile to acidic conditions) and also a δ-lactone ring(susceptible to basic conditions), the epoxidation reagent, hence, should be perfectly neutral.

We preferred epoxidation prior to esterification. Epoxidation of the cis acid(26) has been easily carried out by refluxing (5 hours) it in benzene with tert-butyl hydroperoxide and catalytic amount of molybdenum stearate. The residue,left after removal of the solvent and the excess reagent, was passed through a short column of SiO_2 gel/IIA using 20% EtOAc in benzene as eluant. The product, from its IR spectrum

(Fig.15)(1715,2500-2700 cm^{-1}, COOH; 1730 cm^{-1}, -OCHO) and PMR spectrum (Fig.16) (absence of olefinic protons at 5.27 ppm), was characterized as the epoxide(27).



27

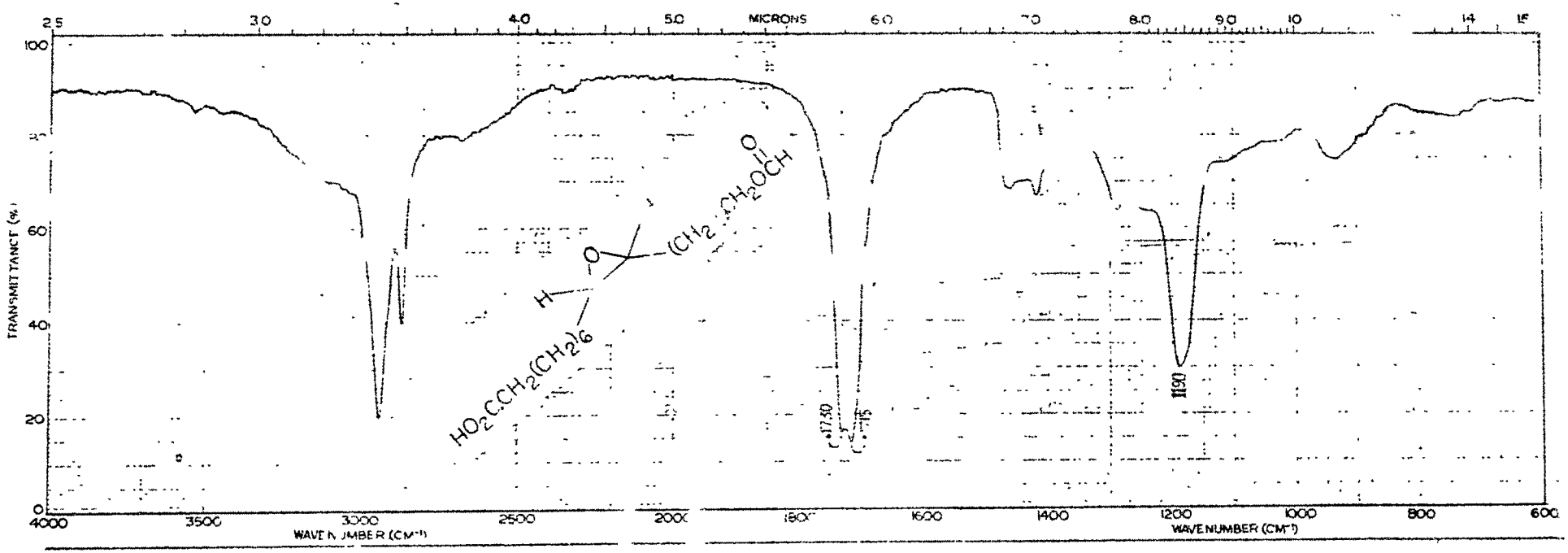


FIG.15: IR SPECTRUM OF THE EPOXY-ACID(27)

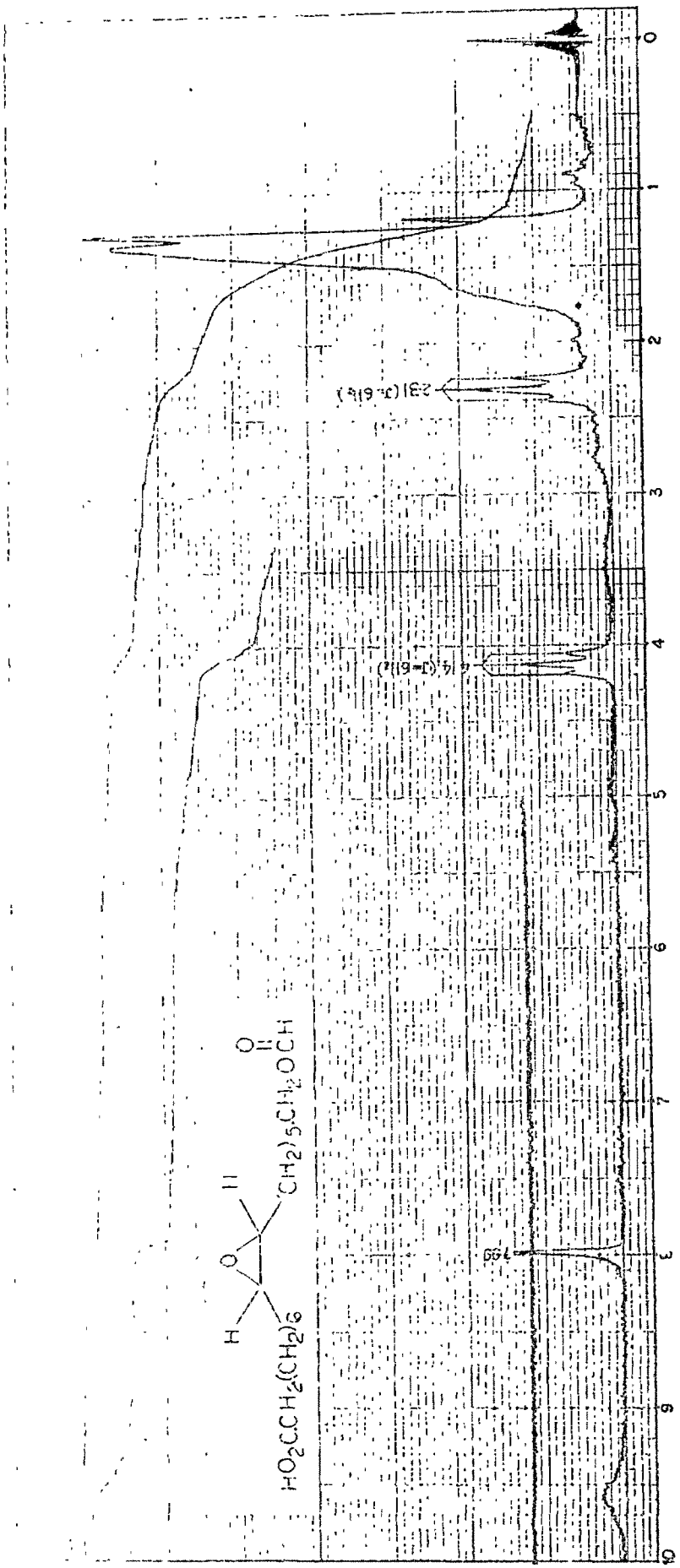


FIG.16: PMR SPECTRUM OF THE EPOXY-ACID(27)

EXPERIMENTAL

For general remarks, see PART A- CHAPTER-II under experimental.

OXIDATION OF JALARIC ACID TO EPISHELLOLIC ACID(11)

20 ml of a mixture of H_2O_2(6.9 ml, 30%) and AcOH(21 ml) was added with shaking to a mixture(3.2 g) of epishellolic acid (~87%) and jalaric acid(~13%). It was warmed for 20 minutes at water bath temperature and the material kept at ~30°C for 20 hours. Water(7 ml) was added to it and the product freed from AcOH in vaccuo(30 mm) to yield white powder (~3.2 g, yield = ~100%). PMR(no signal for aldehydic proton at 9.7 ppm) of the product showed complete oxidation of jalaric acid (present in the mixture) to epishellolic acid.

ACETATE OF EPISHELLOLIC ACID δ-LACTONE(12)

Crude epishellolic acid(0.108 g, as obtained above), Ac_2O(0.4 ml), and NaOAc (0.026 g) were refluxed in benzene (8.5 ml) for 20 minutes. The reaction was quenched by pouring the mixture into water (10 ml). It was stirred and let stand for an hour to complete conversion of Ac_2O to AcOH, The benzene layer was separated and the aqueous phase extracted with EtOAc(5 ml x 3). The combined extract was washed with water(8 ml x 2) and brine(8 ml x 1). Drying and solvent removal gave a material(0.093 g) which was dissolved in pyridine(1 ml) and Ac_2O(0.5 ml) and kept at ~30° for 18 hours. Most of the

pyridine and excess of Ac_2O were removed under vacuum(15 mm) at ~ 40°C. Water(10 ml) was added to the residue (0.105 g) and extracted with EtOAc (5 ml x 3). The combined extract was successively washed with 10% HCl aqueous(5 ml x 3), water(5 ml x 3) and brine(5 ml x 1). Solvent removal gave a crude product (0.091 g) which showed two spots on TLC (R_f= 0.63 and 0.56, solvent-system: benzene/EtOAc/AcOH=6:3:1)

The above mixture(0.090 g) was chromatographed over SiO_2 gel/ IIA(7 g, 21 x 1.0 cm) and eluted with benzene containing increasing proportions of EtOAc. 14% EtOAc in benzene eluted δ-lactone acetate(12) as a foamy solid (0.025 g, R_f= 0.63). IR Spectrum: 1710-1760 cm^{-1}(carbonyl groups) and 1635 cm^{-1} (trisubstituted double bond). U.V.absorption spectrum: λ_{max}^{EtOH} 237 nm, ϵ 3.2 x 10^3. PMR spectrum: $-OCOCH_3$(s,3H,2.12 ppm), $-CH_2OCO$ (s,2H, 4.14 ppm), >C=C(H)—C(H)OAc(m, 2H, 5.95 ppm) and a quaternary methyl(s, 3H, 1.2 ppm).

16% EtOAc in benzene eluted epishellolic acid di-acetate (13, 0.035 g, foam, R_f = 0.56). IR spectrum: 1700-1750 cm^{-1}, carbonyl groups and 1640 cm^{-1}, trisubstituted double bond. U.V.absorption spectrum: λ_{max}^{EtOH} 226 nm, ϵ 7.8 x 10^3). PMR spectrum: $-CH_2OCOCH_3$(s, 3H, 2.04 ppm), >C=C-C(H)$OCOCH_3$(s,3H, 2.15 ppm), $-CH_2OAc$(bq, 2H, 3.9 ppm, J= 11.5 Hz), >C=C-C(H)OAc(d,1H,5.98 ppm, J=2Hz), >C=C(H) (d,1H,6.75 ppm,J=2Hz) and a quaternary methyl(s,3H, 1.15 ppm).

ACETATE OF JALARIC ACID δ-LACTONE (15): ROSENMOND REDUCTION

Epishellolic acid δ-lactone acetate(12, 300 mg) and thionyl chloride (0.2 ml) were heated to mild reflux(1 hour) under anhydrous conditions. The excess thionyl chloride was removed at room temperature(30°C) under vacuum to give the corresponding acid chloride(14, 335 mg, yield=~99%). 5% Pd/$BaSO_4$(40 mg), quinoline-S (4 mg) and dry ortho-xylene(15 ml) were placed in a 25 ml three necked r.b.flask which was equipped with a reflux condenser, magnetic stirring and a gas bubbler. The reflux condenser jacket was left empty and, while a slow stream of hydrogen was passed through the stirred catalyst-suspension, this was heated to distill off ~5 ml of the solvent (xylene) through the condenser to ensure anhydrous condition. Heating was interrupted, the water circulation through the condenser started and the above acid chloride(335 mg, dissolved in 2 ml of xylene) added. Hydrogen flow was increased(100 bubbles per minute) and the content of the flask refluxed for 6 hours. Xylene was removed under reduced pressure(10-20 mm) at 40-50°C, water(10 ml) was added to the residue(280 mg) and this was extracted with EtOAc(5 ml x 3). The combined EtOAc extract was successively washed with cold 5% $NaHCO_3$ aqueous (5 ml x 2), water(5 ml x 2) and brine(5 ml x 2). Drying and solvent removal under reduced pressure(200 mm) at ~40°C gave jalaric acid δ-lactone acetate(15, foamy solid, 0.22 g, 70% yield).

IR spectrum: 1710-1760 cm^{-1} (carbonyl groups).PMR spectrum: $OCOCH_3$(s, 3H, 2.17 ppm), $-CH_2OCO$(s,2H, 4.17 ppm), >C=C(H)-C(H)OAc(m, 2H, 5.9 ppm), >CH-CHO(d,1H, 9.77 ppm, J= 1.5 Hz) and a quaternary methyl (s,3H, 1.23 ppm). These data are in complete agreement with the reported values[2].

JALARIC ACID δ -LACTONE(7) AND ITS ACETATE(15) FROM JALARIC ACID

Jalaric acid(2.2 g), Ac_2O(8 ml) and NaOAc (0.50g) were refluxed in benzene(170 ml) for 20 minutes. The reaction was quenched by pouring the reaction mixture into water(200 ml). It was stirred and let stand for an hour to convert Ac_2O into AcOH. The benzene layer was separated and the aqueous part extracted with EtOAc(60 ml x 3). The combined organic extract was separated into acidic(0.78 g) and neutral (1.5 g) parts using cold 5% $NaHCO_3$ aqueous(50 ml x3). This neutral material on TLC showed two spots of R_f 0.72 (minor) and 0.60(major) (solvent system: benzene/EtOAc/AcOH=6:30:1)which have earlier been identified[2] as (15) and (7), respectively. In our hands, the content of (15) in the neutral part has been varying, in several experiments, from 10 to 15% (PMR).

DIMETHYL ACETAL OF METHYL ESTER OF JALARIC ACID(16)

(a) NH_4Cl CATALYSED CLEAVAGE OF δ -LACTONE

NH_4Cl(5 mg) was added to a solution of jalaric acid δ -lactone (7, 50 mg) in dry methanol (2 ml). A vigorous reaction resulted which was allowed to subside by itself (20 minutes). Reaction contents were heated at reflux for 1.5 hrs.

Excess methanol was distilled off and water(5 ml) added to the residue. It was extracted with EtOAc(5 mlx3) and the combined extract washed successively with cold 5% $NaHCO_3$ aqueous(5 ml x 2), water(5 ml x2) and brine(5 ml x1). Drying and solvent removal gave the title compound (16, 55 mg, 85% yield).

IR spectrum: 3450 cm^{-1}(OH), 1690-1730 cm^{-1}(-C=O) and 1630 cm^{-1}(trisubstituted olefinic bond). UV absorption spectrum: λ_{max}^{EtOH} 235 nm, ϵ =1.6 x 10^3. PMR spectrum: $-CH(OMe)(OMe)$ (bs, 6H, 3.33 ppm), -COOMe(s, 3H, 3.78 ppm), >C=C-C-C(H)OH(d,1H, 4.77 ppm, J=2 Hz), >C=C(H)- (d,1H, 6.67 ppm, J=2 Hz) and a quaternary methyl(s, 3H, 1.17 ppm).

METHYL ESTER OF JALARIC ACID(17)

10% H_2SO_4 aq(3 ml) was added to a solution of the above dimethyl acetal of methyl ester of jalaric acid(16, 55 mg) in benzene(3 ml). This was gently refluxed(6 hours) under nitrogen. Benzene was removed under reduced pressure(100-150 mm) at water bath temperature and the residue diluted with water(5 ml). It was extracted with EtOAc (5ml x2) and the combined extract washed successively with 5% $NaHCO_3$ aq(4 ml x 2), water(4mlx2) and brine(4 ml x 1). Drying and solvent removal under reduced pressure(150-200 mm) at water bath temperature gave methyl ester of jalaric acid(16, 40 mg, 83% yield).

PMR spectrum: -$\underline{CH_2}$OH(bd, 2H, 3.3 ppm, J=8.5 Hz), -COO$\underline{Me}$ (s, 3H, 3.8 ppm), >C=C-C($\underline{H}$)OH (d, 1H, 4.7 ppm, J= 2.5 Hz), >C=C($\underline{H}$)(d,1H, 6.72 ppm, J= 2.5 Hz), >CH-C$\underline{H}$O (d, 1H, 9.78 ppm, J= 2.5 Hz) and a quaternary methyl (s, 3H, 1.2 ppm).

(b) $\underline{CeCl_3}$ CATALYZED CLEAVAGE OF δ-LACTONE

Trimethyl orthoformate(0.7 ml) was added to a solution of jalaric acid δ-lactone(7, 56 mg) in 0.4 M methanolic solution of $CeCl_3 \cdot 7H_2O$ (0.5 ml). The solution was kept at room temperature(~30°C) for 10 minutes and then poured into cold $NaHCO_3$ aq(10 ml, 5%, at 0-5°C). It was extracted with EtOAc (5 ml x 3) and the combined extract washed with water(5 ml x2) and brine(5 ml x 1). Drying and solvent removal gave a material (0.056 g) which consisted of 21(~25%) and 16(~75%)(PMR). This mixture (56 mg) was again dissolved in 0.4 M methanolic solution of $CeCl_3 \cdot 7H_2O$ (0.5 ml) and trimethyl orthoformate(0.7 ml) was added to it. This was kept at ~30°C for 30 minutes. The work-up(as described above) gave a material (60 mg, 83% yield) which,from its PMR spectrum,was (16), the dimethyl acetal of methyl ester of jalaric acid.

$\underline{\text{JALARIC ACID DIMETHYL ACETAL(18)}}$.

NH_4Cl(0.15 g) was added to a solution of jalaric acid(1.0 g) in MeOH(15 ml). After the vigorous and exothermic reaction subsided(30 minutes), the solution was heated at reflux for

1.5 hours. Excess methanol was distilled off and water(20 ml) added to the residue. It was extracted with EtOAc(10 ml x3) and the combined extract washed with water(10 ml x2) and brine (10 ml x 1). Removal of the solvent at water bath temperature gave jalaric acid dimethyl acetal(18; 1.04 g, 88.5% yield).

IR spectrum: 3400 cm^{-1}(OH), 2500-2700 cm^{-1} and 1680 cm^{-1} (COOH) and 1630 cm^{-1}(trisubstituted double bond). U.V.absorption spectrum: λ_{max}^{EtOH} 233 nm, $\epsilon = 7.99 \times 10^3$. PMR spectrum: $CH<^{\underline{OMe}}_{\underline{OMe}}$ (bs, 6H, 3.24 ppm), $>CH\ C\underline{H}(OMe)_2$ (d,1H, 4.22 ppm, J = 8 Hz), $>C=C-C(\underline{H})OH$(d, 1H, 4.51 ppm, J = 2.5 Hz), $>C=C(\underline{H})-$(d,1H,6.47 ppm, J=2.5 Hz), and a quaternary methyl(s, 3H, 1.0 ppm).

ATTEMPTED DPDS INDUCED LACTONIZATION OF (18)

Jalaric acid dimethyl acetal(18, 0.16 g, 1 m mole),triphenyl phosphine (0.20 g, 1 m mole) and 2,2'-dipyridyldisulphide(0.11 g, 1 m mole) were taken in dry xylene (5 ml) and stirred at $\sim 30^{\circ}C$ for 5 hours under a slow stream of dry nitrogen. The resulting turbid solution was diluted with xylene(10 ml) and added slowly at 10 minutes intervals extending over 15 hours to refluxing xylene(100 ml) under a slow nitrogen current. Refluxing was continued for another 10 hours when xylene was removed under reduced pressure(10-15 nm) to furnish a crude product(0.47 g) which,from its PMR spectrum,was the starting material(jalaric acid dimethyl acetal; 18) only.

PREPARATION OF THE HYDROXY ACID(19)

A solution of the lactone(20;4 g) in 20% ethanolic KOH (2.5 ml) was kept at ~30° for 20 hours. The alkaline solution was freed from EtOH on water bath under reduced pressure(150 mm) and the aqueous residue diluted with water(50 ml). It was extracted with ether(20 ml x 2) to remove the unreacted lactone, if any. The aqueous portion was acidified(20% HCl, 17 ml) to pH 6 and extracted with ether (25 ml x 2). The combined ether extract was washed neutral and dried. Solvent removal gave the hydroxy acid(19; 3.98 g, ~93% yield).

IR spectrum: 3500 cm^{-1}(OH) and 2500-2700 and 1710 cm^{-1}(COOH). PMR spectrum: >C(H)OH(s, 1H, 3.73 ppm), $-CH_2COOH$(t,2H,2.31 ppm, J= 8 Hz) and four quaternary methyls(3s, 0.83 ppm for 3H, 0.9 ppm for 6H and 0.95 ppm for 3H).

DCC INDUCED LACTONIZATION OF (18): PREPARATION OF (21)

Jalaric acid dimethyl acetal (18, 65 mg, 0.2 m mole) and N,N'-dicyclohexylcarbodimide(46 mg, 0.22 m mole) were taken in purified EtOAc (5 ml) and the solution stirred at ~30°C for 4.5 hours. The precipitated N,N'-dicyclohexyl urea was filtered off and the filtrate freed of the solvent, under reduced pressure(200 mm). Redissolution in EtOAc(2 ml) and filtration removed a further small quantity (10 mg) of dicyclo hexyl urea. PMR of the product (80 mg*),obtained after solvent removal,showed it to consist of (21) and dicyclohexyl urea.

* Dicyclohexyl urea could not be removed completely.

PMR spectrum: $-CH\begin{matrix}OMe\\OMe\end{matrix}$ (s, 6H, 3.32 ppm), $-\underline{CH_2}-OCO$(s, 2H, 4.16 ppm), $>C=C-\overset{|}{C}(\underline{H})OH$(bs, 1H, 4.72 ppm), $>C=C(\underline{H})-$(ill-resolved d, 1H, 6.02 ppm), a quaternary methyl(s, 3H, 1.1 ppm) and signals for dicyclohexyl urea.

FORMYLATION OF 25(26)

A solution of 16-hydroxy-(Z)-9-hexadecenoic acid(25; 1.08 g, 4 m moles) in 80% HCOOH aq(8 ml) was refluxed for 5 hours. The excess HCOOH was removed under reduced pressure(100 mm). Water (10 ml) was added to the residue(1.40 g) and extracted with EtOAc(10 ml x 2). The combined extract was washed with water (5 ml x 2). The crude product(1.30 g),obtained after removal of the solvent,was passed through a column of SiO_2 gel/IIA(10 g, 5 x 2.2 cm) using benzene containing increasing proportions of EtOAc. The pure product (1.18 g, 99% yield),which eluted with 20% EtOAc in benzene(20 ml x 5),was the formate (26).

IR spectrum: 3400 cm^{-1} (OH), 1710 and 2500-2700 cm^{-1}(COOH). PMR spectrum:$\underline{CH_2}CO_2H$(t,2H,2.3 ppm, J= 6.5 Hz), $-\underline{CH_2}OCHO$ (t, 2H, 4.12 ppm, J= 6.5 Hz), $-C(\underline{H})=C(\underline{H})$ (t,2H, 5.3 ppm, J= 5 Hz) and $-CH_2OC\underline{H}O$(s, 1H, 7.97 ppm).

PREPARATION OF THE EPOXIDE(27)

A solution of the olefin(26; 1.0 g) and molybdenum stearate (0.10 g) in benzene(15 ml) was refluxed for 5 hours. Benzene and excess of the reagent were removed by distillation under reduced pressure(100 mm) and the residue(1.12 g) was filtered through a column of SiO_2gel/IIA(10 g, 10 x 1.5 cm) using benzene containing increasing proportions of EtOAc. 20% EtOAc in benzene(20 ml x 5) eluted the epoxide(27; 0.98 g, 98% yield).

IR spectrum: 1710 and 2500-2700 cm^{-1}(COOH) and 1730 cm^{-1} (-OCHO). PMR spectrum: -OC<u>H</u>O(s, 1H, 7.98 ppm), -<u>CH_2</u>OCHO(t, 2H, 4.13 ppm, J = 6 Hz) and -<u>CH_2</u>COOH(t, 2H, 2.31 ppm, J= 6 Hz).

REFERENCES

1. R.G.Khurana, A.N.Singh, A.B.Upadhye, V.V.Mhaskar, and Sukh Dev, Tetrahedron, 26 4167(1970).
2. A.N.Singh, A.B.Upadhye, V.V.Mhaskar, and Sukh Dev,Tetrahedron, 30 867(1974).
3. A.N.Singh,V.V.Mhaskar,and Sukh Dev, Tetrahedron,34 595(1978).
4. A.N.Singh, A.B.Upadhye, M.S.Wadia,V.V.Mhaskar, and Sukh Dev, Tetrahedron, 25 3855(1969); M.S.Wadia, R.G.Kurana,V.V. Mhaskar, and Sukh Dev, Tetrahedron, 25 3841(1969).
5. Org. Reactions Vols IV and VIII.
6. T.A.Geissman in Organic Reactions(Editor,R.Adams),Vol.II pp. 94-113, John Wiley, New York(1946).
7. U.R.Nayak and Sukh Dev, Tetrahedron, 19 2298 (1963).
8. G.W.K.Cavill and D.L.Ford, Austral.J.Chem., 13 296(1960).
9. J.I.Degraw, L.Goodman, and B.R.Baker, J.Org. Chem, 26 1156(1961).
10. H.J.Dauben, B.Loken and H.J.Ringold, J.Am.Chem.Soc.,76 1359(1954).
11. L.F.Fieser, J.Am.Chem.Soc., 76 1945(1954); E.J.Corey and R.B.Mitra, J.Am.Chem.Soc. 84 2938(1962).
12. J.L.Luche and A.L.Gemal, J.Chem.Soc.(Chem. Commun.) 976(1978).
13. E.J.Corey and K.C.Nicolaou, J.Am.Chem.Soc., 96 5614(1974); E.J.Corey, K.C.Nicolaou and L.S.Melvin, J.Am.Chem.Soc.,97 653(1975); E.J.Corey, K.C.Nicolaou and Takeshi Toru, J.Am.

Chem. Soc., 97 2287(1975); H.Gerlach and A.Thalmann, Helv.Chim.Acta., 57 2661(1974).

14. Org. Synthesis, Coll.Vol III.
15. Craig, J.Am.Chem.Soc., 56 232(1934).
16. Wibaut and DenHertog, Rec. trav.chim, 51, 358(1932).
17. McElvain and Goese, J.Am.Chem.Soc., 65 2230(1943).
18. M.S.Newman and W.S.Jones, J.Am.Chem.Soc., 69 1221(1947).
19. R.B.Woodward, F.E.Bader, H.Bickel, A.J.Fray, and R.W. Kierstead, Tetrahedron, 2 1(1958).
20. S.Neelakantan, R.Padmasani, and T.R.Seshadri, Tetrahedron, 21 3531(1965).
21. F.Cortese and L.Bauman, J.Am.Chem.Soc., 57 1393(1935).
22. M.N.Sheng and J.G.Zajacek, J.Org.Chem., 35 1839(1970).