COMMIPHORA MUKUL

CHAPTER-1

ALIPHATIC TETROLS, POSSIBLE IONOPHORES, FROM COMMIPHORA MUKUL

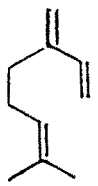
INTRODUCTION

Guggulu (Sanskrit) is the gum-resin exudate from the tree Commiphora mukul (Hook, ex stocks) Engl. (Syn. Balsamodendron mukul Hook, ex stocks) and is an article of commerce in India.[1] C. mukul belongs to the genus Commiphora of the family Burseraceae. This tree is endemic to India and grows wild in the semi-arid regions of Rajasthan, Gujarat and Karnataka. In its natural setting, the tree remains essentially denuded of its foliage for most of the year. Its bark is ash-coloured and comes off in rough flakes, exposing the underbark which also peels off. On injury, the plant exudes a yellowish gum-resin, which quickly solidifies to an agglomerate of tears or stalactitic pieces. The dried resin has a balsamic odour. The trees are tapped commercially, during winter. Average yield of gum-resin per tree is around ~700-900 g. per year.

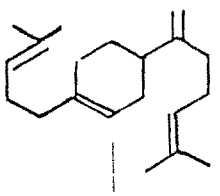
Chemistry

The gum-resin is known to furnish[2] an essential oil (0.4%) consisting chiefly of myrcene (1) and camphorene (2). Bose and Gupta[3] reported separation of the gum-resin into alcohol-soluble resin and an insoluble carbohydrate gum; the latter was subjected to detailed study for structure elucidation

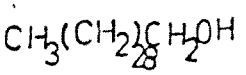
Ali et al.,[4] partitioned the alcohol extract of C. mukul gum-resin between water and diethylether and isolated mericyl alcohol (3) and β-sitosterol (4) from the unsaponifiable residue of ether extract. From the aq. portion, the amino acids–cystine, histidine, lycine, arginine, aspartic acid, serine, glutamic acid, threonine, alanine, proline, tyrosine, tryptophane, valine, leucine and isoleucine were detected.



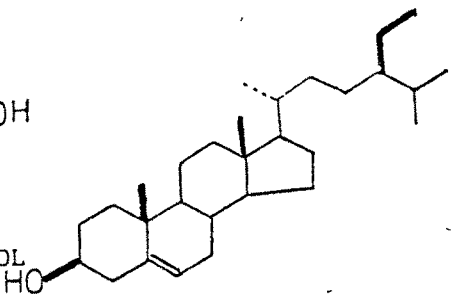
(1)MYRCENE



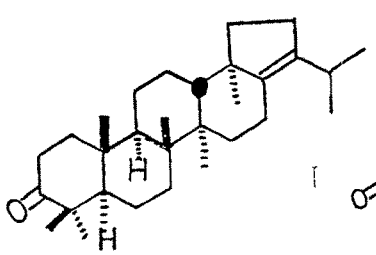
(2)CAMPHORENE



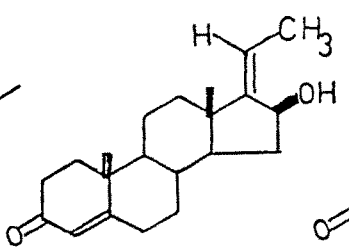
MERICYL ALCOHOL
(3)



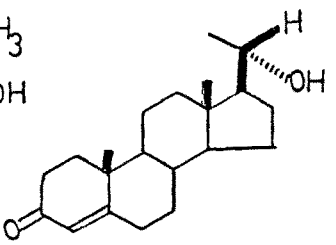
(4)β-SITOSTEROL



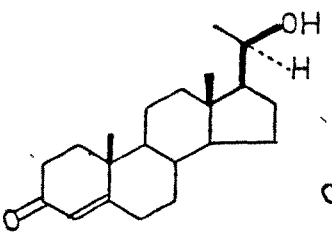
(5)HOPENONE-1



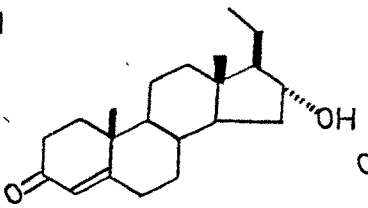
(6)Z-GUGGULSTEROL



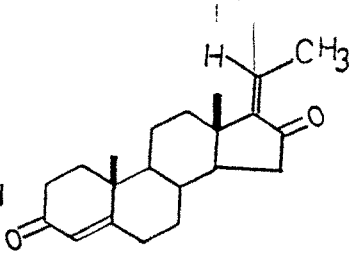
(7)(20S)-20-HYDROXY-4-PREGNENE--3-ONE



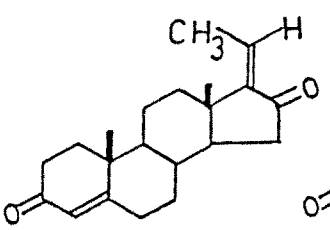
(20R)-20-HYDROXY-4-PREGNENE--3-ONE
(8)



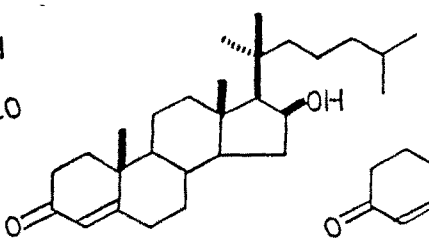
(9)GUGGULSTEROL-VI



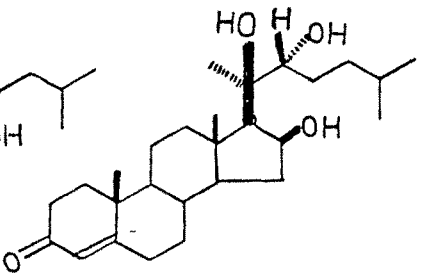
(10)Z-GUGGULSTERONE



(11)E-GUGGULSTERONE.



(12)GUGGULSTEROL-III



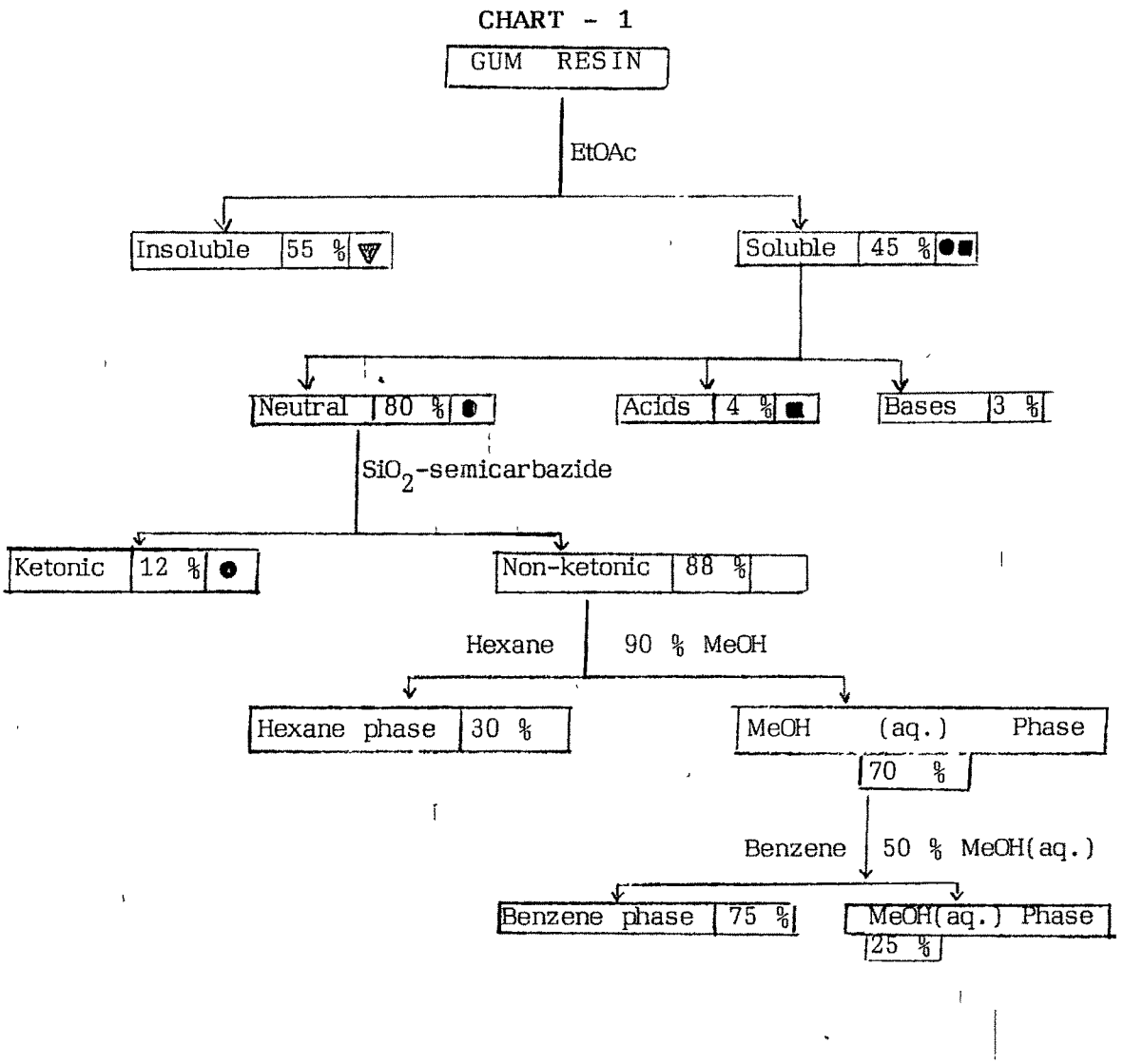
(13)GUGGULSTEROL -I

Sukh Dev and co-workers in collaboration with the pharmacological group of Dr. Nityanand (CDRI, Lucknow) reported important results regarding the chemistry and pharmacological activity[5-11,27,28] of guggulu. Chart-1 depicts the separation[10] scheme for the isolation of constituents.

Compounds reported from the ketonic extract are hopenone-1 (5)[11], Z-guggulsterol (6)[12], (20 S)-20-hydroxy-4-pregnen-3-one (7)[12], (20 R) -20-hydroxy-4-pregnen-3-one (8)[12], guggulsterol-VI (9)[12], Z-guggulsterone (10)[5a], E-guggulsterone (11)[5a], guggulsterol-III (12)[5a,12] and guggulsterol-1 (13)[5a,12]

A diterpene hydrocarbon cembrene-A (14)[5b], its related alcohols mukulol (15)[5b,6] and cholesterol (26)[5a] were isolated from the hexane phase material.

From benzene phase, four crystalline substances, all lignans and a waxy solid were isolated. Lignans isolated are sesamin (16)[5a] pluviatilol (17)[12], gugguligan-I (18) and gugguligan-II (19)[12,20]. The waxy solid was a mixture of long-chain polyol esters. These esters are derived from homologus polyols and ferulic acid (20)[12]. The polyols were recognized as tetrols of general structure (21) in which C_{20} and C_{18} compounds predominated[5c]. Configuration of these polyols has been established by synthesis starting with D-glyceraldehyde[13]. These polyols which have been given the generic name 'guggultetrol' have all been found to have the D-xylo configuration, 22 is a typical member of ester and 23 is a typical guggultetrol (C-20 unit). This is the first report on the occurrence of such compounds in nature, and they appear to be important because of their structural similarity with the biologically important phytosphingosines (24). Phytosphingosines (C_{18} & C_{20}) are widely distributed in the plant sphingolipids and certain

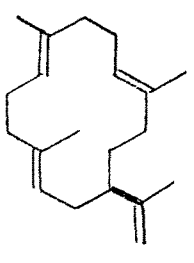


■ Anti-inflammatory activity.

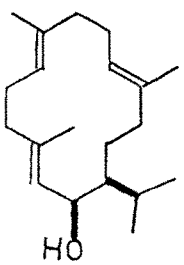
● Hypo-cholesterolemic activity.

▲ Toxic.

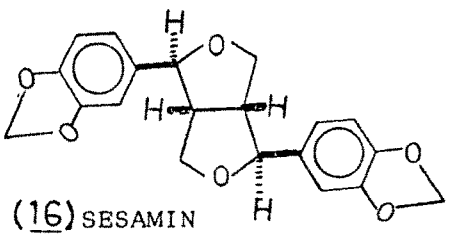
Segregation of Guggulu gum-resin.



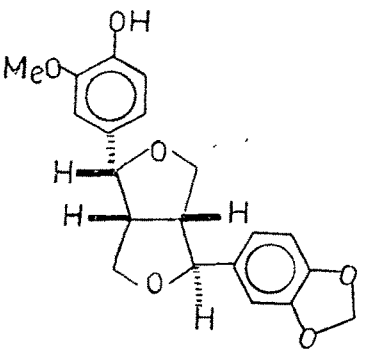
CEMBRENE-A
(14)



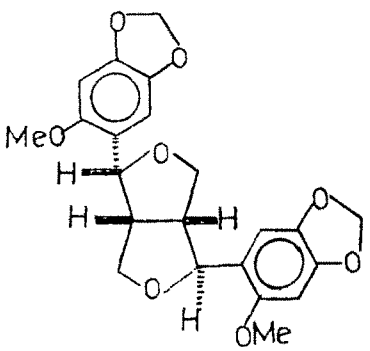
(15) MUKULOL



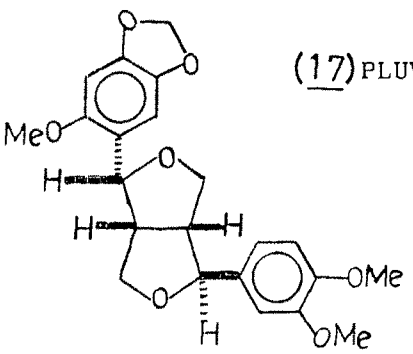
(16) SESAMIN



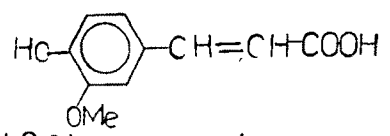
(17) PLUVIATILOL



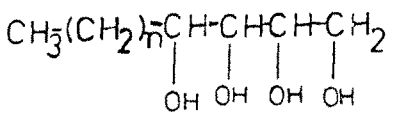
GUGGULLIGNAN-I
(18)



(19) GUGGULLIGNAN-II

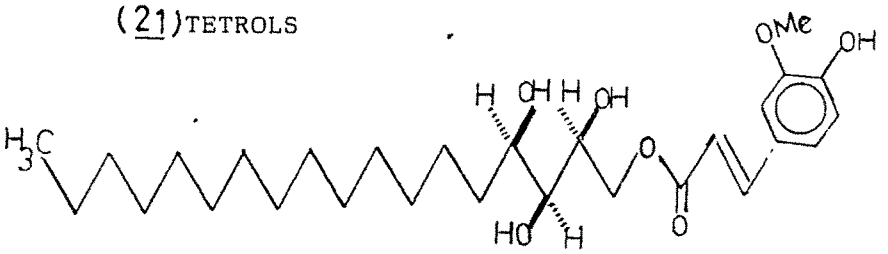


(20) FERULIC ACID

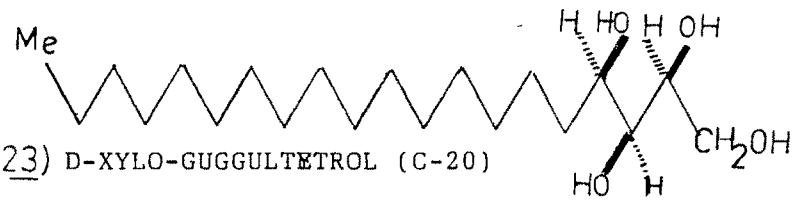


[n=13,15
11,12,14,16,17 (minor)]

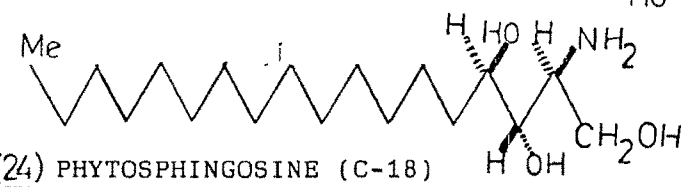
(21) TETROLS



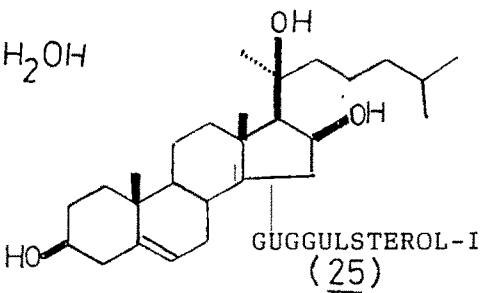
(22) TETROL ESTER (D-XYLO-GUGGULTETROL-18-FERULATE)



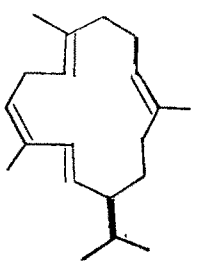
(23) D-XYLO-GUGGULTETROL (C-20)



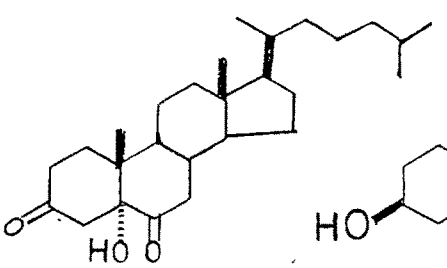
(24) PHYTOSPHINGOSINE (C-18)



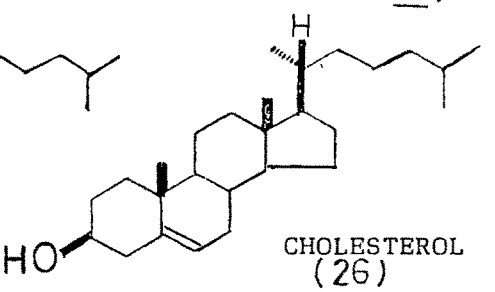
GUGGULSTEROL-II
(25)



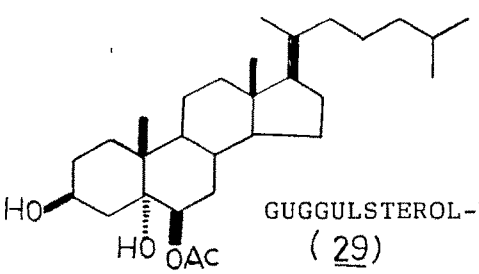
CEMBRENE
(27)



(28) GUGGULSTEROL-IV



CHOLESTEROL
(26)



GUGGULSTEROL-V
(29)

animal tissues and possess well-defined 2S,3S 4R-configuration [e.g. D-(+)-ribo-2-amino-1,3,4-trihydroxy octadecane] (24)[14,15].

When a modified procedure for separation was employed another steroid, designated as guggulsterol-II (25)[5a], sesamine (16)[5a] and cembrene (27)[11] were isolated.

Purushothaman et al.,[16] have reported two sterols, guggulsterol-IV (28) and guggulsterol-V (29) from the neutral $CHCl_3$ extract of gum-resin.

Guggulu in Ayurveda

Guggulu has a wide range of usefulness in indigenous medicine. Fresh guggulu is moist, viscid, fragrant and of golden colour. Old guggulu is dry and without falvour and is never used in medicinal preparations. It is astringent and antiseptic. Like all oleo-resins, it causes an increase of leucocytes in the blood and stimulate phagocytosis. It acts as diaphoretic, expectorant and diuretic and it is said to be a uterine stimulant and emmenagogue. The resin is used in the form of a lotion for indolent ulcers and as a gargle in caries of the teeth, weak and spongy gums, pyorrhoea, alveolaris, chronic tonsilitis and pharangytis and ulcerated throat. It is also used as stomachic in chronic dyspepsia with dilatation and atony of the walls of the stomach. Inhalation of the fumes from burnt guggulu is recommended in hay fever, acute and chronic nasal catarrh, chronic laryngitis, chronic bronchitis and phthisis. In rheumatism it is used in a great variety of forms.[12,17]. Yogaraja guggulu is a favourite preparation used for rheumatism[18]. It is also recommended for the treatment of obesity and lipid disorder. Thirtythree compound preparations containing guggulu as a component are described in Bhava Prakasha[19]. It is a non-toxic drug and the only side

effects reported are rashes and mild kidney irritation which disappear on withdrawal of the drug.[17]

Pharmacological and clinical studies

The oleoresin portion of the plant was found to be highly potent anti-inflammatory agent as compared to hydrocortisone and butazolidin against Brownlee's formaldehyde-induced arthritis in albino rats.[21]

The anti-arthritic and anti-inflammatory activities of acidic and non-acidic fractions of guggulu were studied, using a number of methods, in albino rats. Only the acidic fraction showed significant activity. The activity of the acid fraction was found to be present even in the adrenalectomised animals.[22] The minimum effective dose being 12.5 mg/100 g body weight.

Oleoresin was found to cause a reduction in the weight of rate uterus, ovaries and cervix with a concommitant increase in their glycogen and sialic acid levels, thereby showing that it might possibly possess a promising antifertility effect as well.[23]

S. Nityanand et al.,[27] have found significant hypocholesterolemic activity for Z-guggulsterone. Their results showed that Z-guggulsterone (25-50 mg/kg body weight) reduced cholesterol level, 25 % in seven days and 36% in 14 days, in normal albino rats, whereas the decrease in cholesterol level was as much as 55 %/18-20 hrs in the case of triton treated albino rats.

The crude aqueous extract of the oleo-gum resin was found to

suppress acute rat-paw oedema induced by carrageenium. It also had suppressive action against the granuloma pouch test. In adjuvant arthritis, the extract suppressed the secondary lesions very effectively without having any significant action on the primary phase. Side effects such as gastric ulceration, loss of weight and mortality were negligible in animals treated with the extract compared to those treated with betamethasone.[24]

The oleo-gum resin was found not only to lower the serum cholesterol in hypercholesteralemic rabbits but also to protect the animals against hypercholesterolemia induced by hydrogenated vegetable oil.[28]

Clinical efficacy of gum guggulu as a hypolipideamic agent was evaluated in comparison with ethyl-p-chlorophenoxy isobutyrate and Cibe-13437-Su. Stastistical analysis revealed that guggulu significantly lowered the serum levels of all the lipid fractions (serum total lipids, triglyceride, cholesterol, phospholipids and beta-lipoprotein)[26].

For developing a hypocholesterolemic/hypolipemic drug, a standard ethyl acetate extract of guggulu containing 4 gm of Z and E-guggulsterones per 100 gm of the extract (named gugulipid) was prepared and its detailed pharmacological studies have been conducted on rat, rabbits and monkeys.[10] In normal rats oral administration of gugulipid at 100 mg/kg body weight daily for 30 days led to serum cholesterol lowering by 34% and of serum triglycerides by 26% respectively. The corresponding values with 100 mg of clofibrate were 39% and 30% respectively. The treated monkeys showed 50 and 30 per cent decrease in low density and very low-density lipoproteins respectively. In a similar study with hyperlipidaemic rabbits (high-fat diet), the oral ingestion of gugulipid at 50 mg/kg body weight (bw) daily for eight

weeks caused a fall in serum cholesterol by 40 % and triglycerides by 30 per cent.

Gugulipid displays mild anti-inflammatory activity and no C.N.S. or diuretic activity. In mice the LD_{50} value was 1600 mg/kg bw both for oral and intraperitonially administered drug. Subacute and chronic toxicity studies were carried out in rats, dogs and monkeys; no adverse effects were noticed. Gugulipid was shown to be devoid of any teratogenic or mutagenic effects.

Gugulipid was given to human volunteers in doses of 1200 to 1500 mg per day in three divided doses for 4 weeks. There was a mean reduction of 15 per cent and 21 per cent in cholesterol and triglyceride levels respectively. In a similar study with clofibrate (1500 mg/day) the mean reduction was 16 per cent and 28 per cent respectively for cholesterol and triglycerides.

RESULTS AND DISCUSSION

A series of long chain polyol esters was isolated from Commiphora mukul gum resin. These esters (22) are derived from homologous polyols and ferulic acid.[12] For isolation of these esters, ethylacetate extract of gum-resin was partitioned between hexane and 90% aq. MeOH. The MeOH extract after work-up was again partitioned between 50 % aq. MeOH and benzene. Benzene extract was chromatographed to get the ester-rich fraction, which on crystallization gave a mixture of esters. On saponification the mixture gave a mixture of tetrols (21) and ferulic acid (20). The mother liquor from the crystallization of tetrol esters was found to contain unsaturated tetrol esters (NMR).

Our main objective, at the start of our work on guggulu was to isolate these unsaturated tetrol ester either as tetrol esters or as tetrols.

The tetrols being highly polar compounds are difficult to separate without derivatization, using ordinary techniques. We devised our scheme in such a way as not to damage the other biologically active compounds during the isolation. The convenient way was to convert the tetrols into bis-acetonides, which can be handled more easily.

PART - I Methods for isolation of tetrols from guggulu.

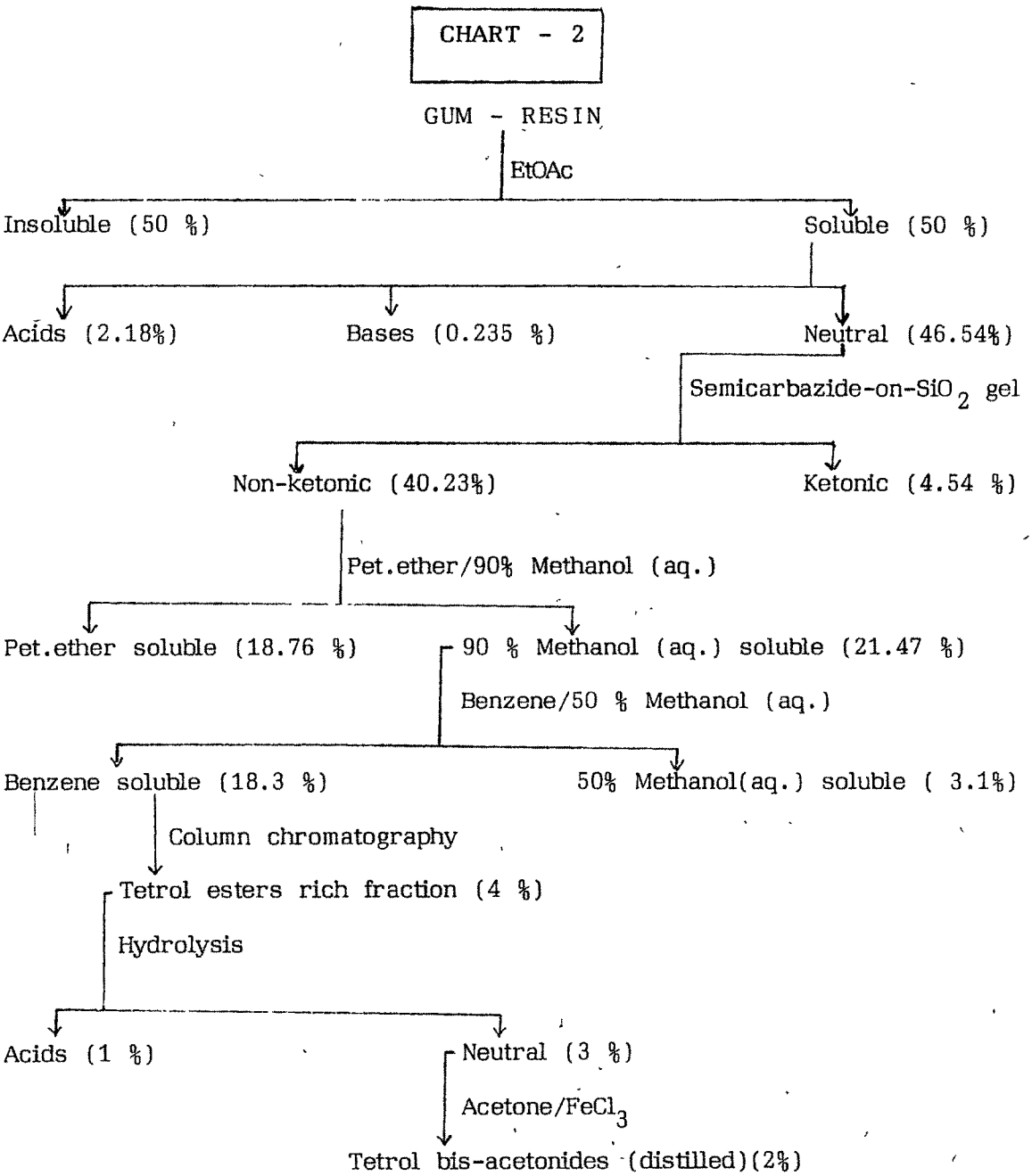
The gum-resin used for the study was obtained from Himatnagar (Gujarat) three years back and preserved carefully. It was in the form of light to dark brown conglomerates of tears, slightly sticky to touch and having faint balsamic odour.

Method - I

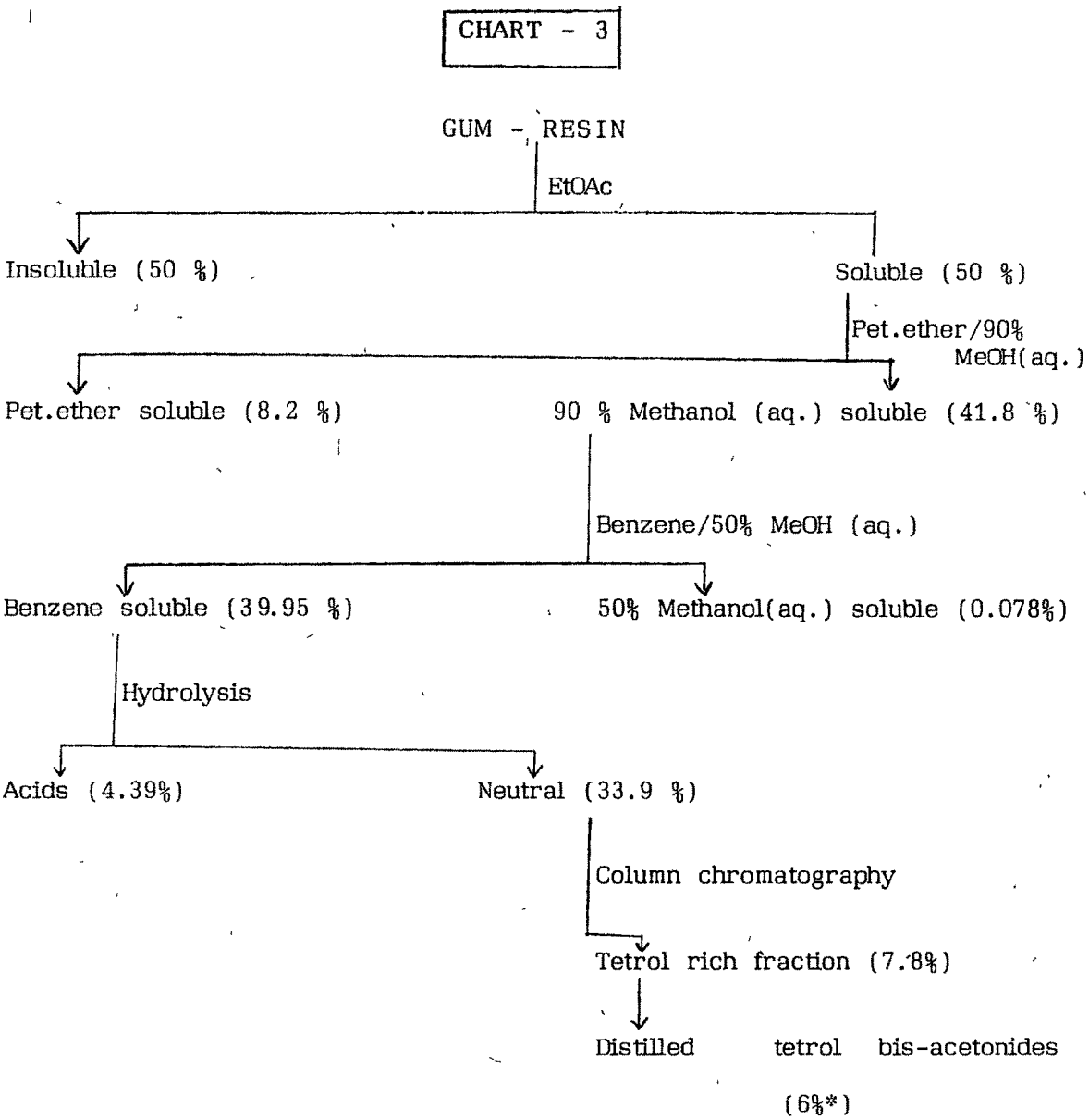
The method was followed as per Scheme-1 shown in Chart-2. The gum-resin was resolved into ethyl acetate soluble (50%) and insoluble (50%) portions. The ethyl acetate soluble part was further separated into its acidic (2.18%), basic (0.23%) and neutral (46.54%) components. The neutral portion was further separated into ketonic (4.54%) and non-ketonic fraction (40.23%) using semicarbazide on SiO_2 gel.[30] The non-ketonic fraction was segregated into pet.ether soluble (18.76%) and 90% methanol (aq.) soluble (21.47%). The methanol soluble was further divided into benzene soluble (18.3%) and 50% (aq.) methanol soluble (3.1%). The benzene soluble fraction was subjected to column chromatography on SiO_2 gel/IIb. The major waxy solid containing the tetrol esters eluted with ethyl acetate, was saponified and the neutral (3%) after removal of the acids (1%) was treated with acetone/$FeCl_3$ to convert the tetrols into their bis-acetonides.[31] The product after usual work-up and distillation afforded TLC pure ($\sim$ 90%) tetrol bis-acetonides (2 %) (solvent system 5% ethyl acetate in pet.ether, Rf. 0.46).

Method - II

The method used above was modified and the tetrols were isolated following the Scheme-2 given in the Chart-3. In the modified procedure, the EtOAc soluble fraction was divided into pet.ether-soluble(8.2 %), benzene-soluble (39.9%) and 50% aq. MeOH-soluble (0.078%) parts. The benzene soluble fraction was subjected to hydrolysis with dilute NaOH and separated into the acid (4.39%) and neutral (33.9%) fractions. Tetrols enriched fraction was collected from the neutral fraction by column chromatography. The crude tetrols were purified by converting into bis-acetonides, which on distillation yielded TLC pure ($\sim$ 90%) bis-acetonides (6%).



Scheme - 1 for separation of tetrols (as bis-acetonides) from gum-resin of Commiphora mukul.



* Expected yield ~6 %.

Scheme - 2 for separation of tetrols (as bis-acetonides) from gum-resin of Commiphora mukul.

Method - III

The method is depicted in Chart-4. As the tetrol esters present in gum-resin are phenolic in nature, the benzene soluble portion obtained as above was dissolved in benzene and extracted with dil. NaOH at 3-5°C to remove acidic and phenolic compounds. The acidic part (6.5%) thus obtained after work-up was again separated into acidic (2.5%) and phenolic (4%) compounds by extraction with dilute $NaHCO_3$. On TLC, the phenolic part showed a faint spot corresponding to the tetrol esters, but the neutral part showed appreciable quantity of the tetrols. The two parts were separately saponified, unsaponifiables in both the cases showed tetrols. Presence of tetrols in the neutral fraction indicated possible hydrolysis of the tetrol esters during extraction with dil. NaOH.

Method - IV

In the final separation scheme for isolation of tetrols from gum-resin, was sought which is shown in Chart-5. The ethyl acetate soluble portion of gum-resin was dissolved in ethyl acetate* and directly separated into acids (15.6%) and neutral (34.4%) by extracting with dil. NaOH at 3-5°C. The neutral portion on TLC showed absence of tetrols or tetrol esters. The acid portion after work-up was again separated into acids (1.3%) and phenols (14.25%) by extraction with dil. $NaHCO_3$. Phenolic part thus obtained was treated with NaOH to hydrolyse the esters. The acid (saponifiable matter) part (0.75%) after work up was esterified with methanol/H_2SO_4 to get crude ester, which on distillation furnished a colourless oil (GC-90.7% pure, 10% OV-4, 190°) and was identified as methyl ferulate (IR, NMR). The neutral

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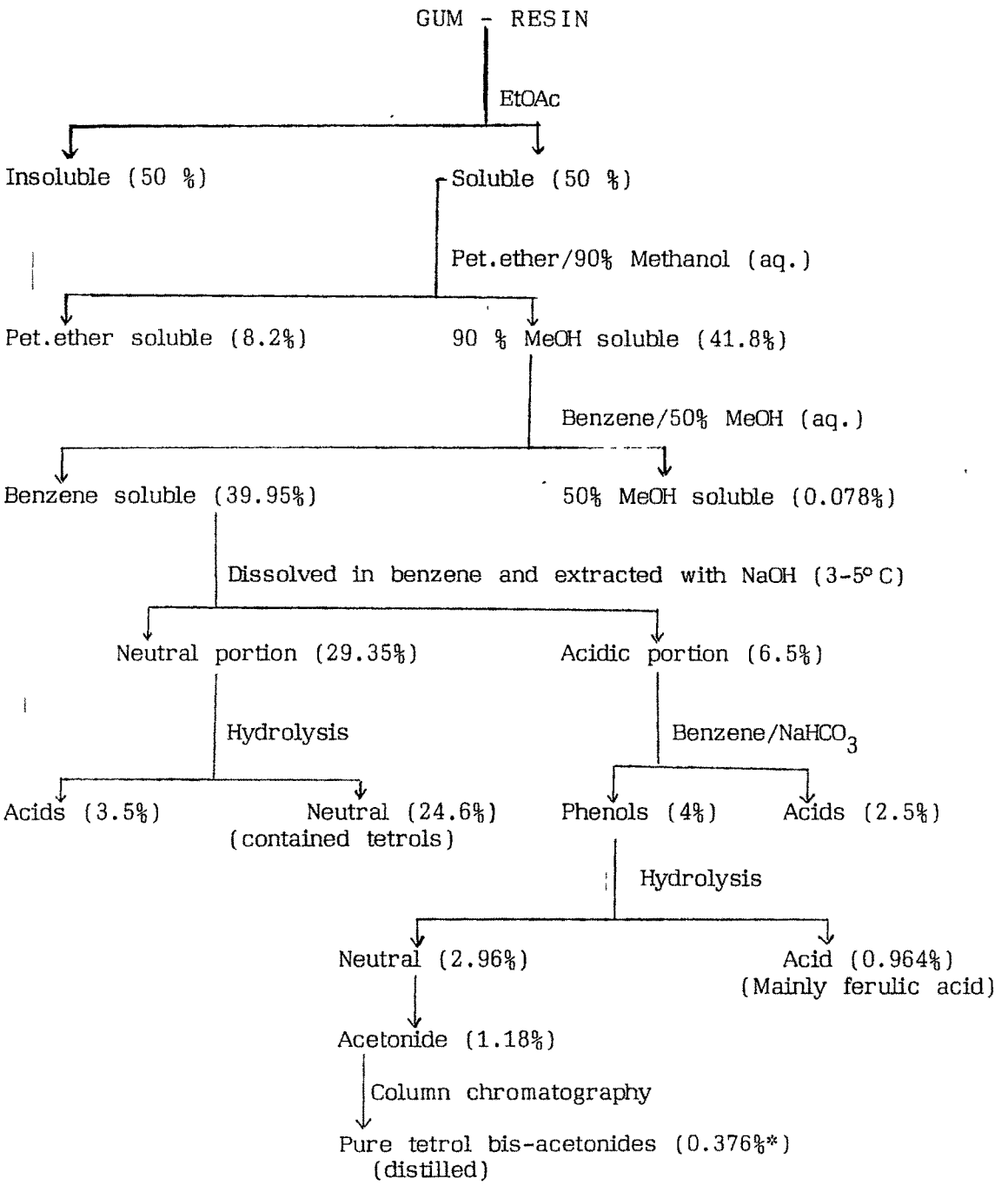
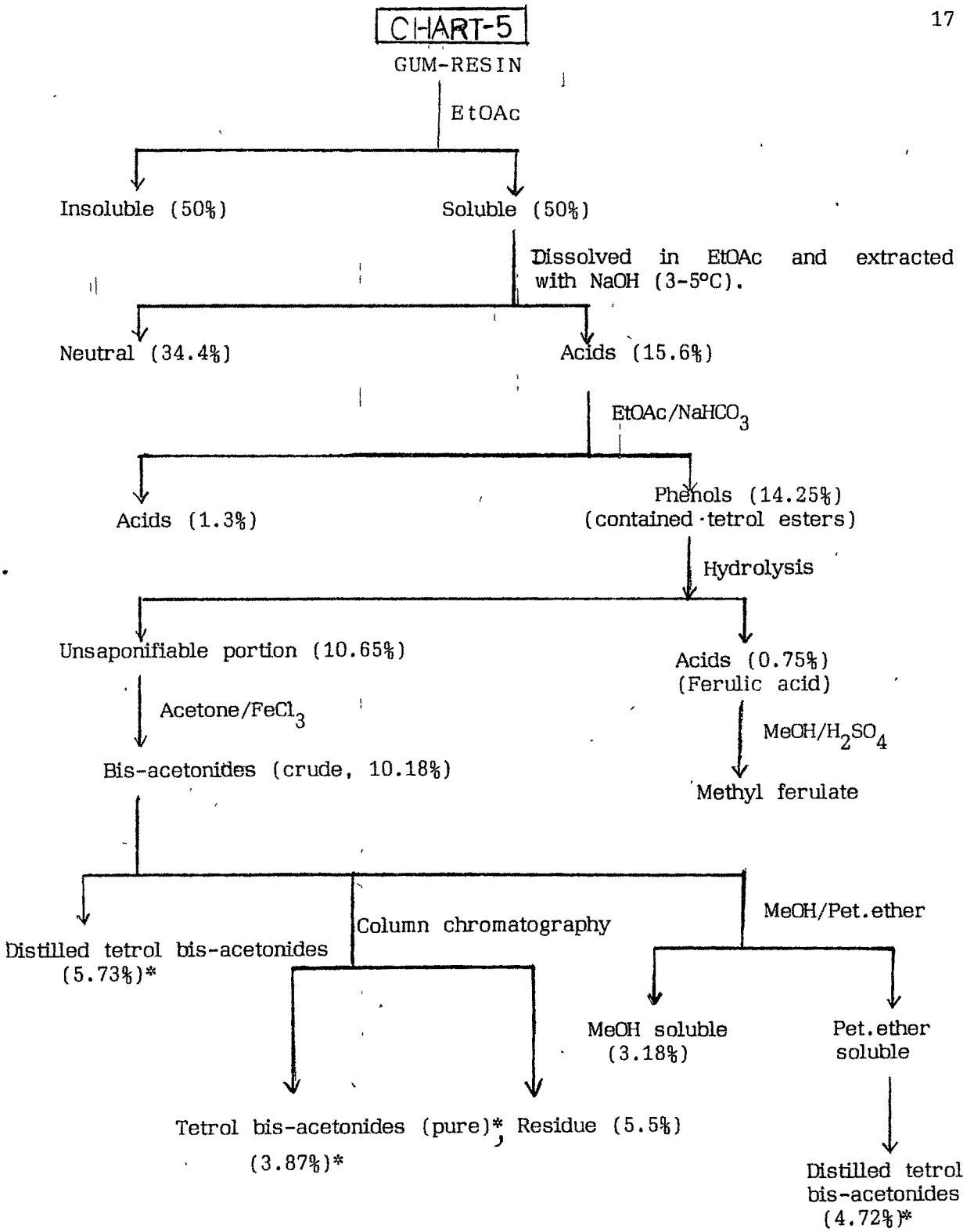
* Selection of ethyl acetate as a solvent instead of benzene (as in method-III) was with the intention to avoid hydrolysis of tetrol esters during extraction with dil. NaOH.

CHART - 4



(* Expected ~ 6%)

Scheme - 3 for separation of tetrols (as bis-acetonides) from gum-resin of Commiphora mukul.



* Expected 6%

Chart - 5 : Scheme 4 for separation of tetrols (as bis-acetonides) from gum-resin of Commiphora mukul.

portion was exposed to acetone/$FeCl_3$ to get dark red gummy mass (10.18%) as tetrol bis-acetonides, which on distillation gave light yellow oil (5.73%) with 90% purity (Fig. 2A). Fig. 1 shows the TLC of various fractions obtained from segregation of gum-resin.

Methods for purification of crude tetrol bis-acetonides.

Distillation of crude tetrol bis-acetonides yielded only 56.7% distillate (i.e. 5.73% of gum-resin, 90% TLC pure). Two other methods were tried to confirm yield and improve quality of tetrol bis-acetonides. (Chart-5)

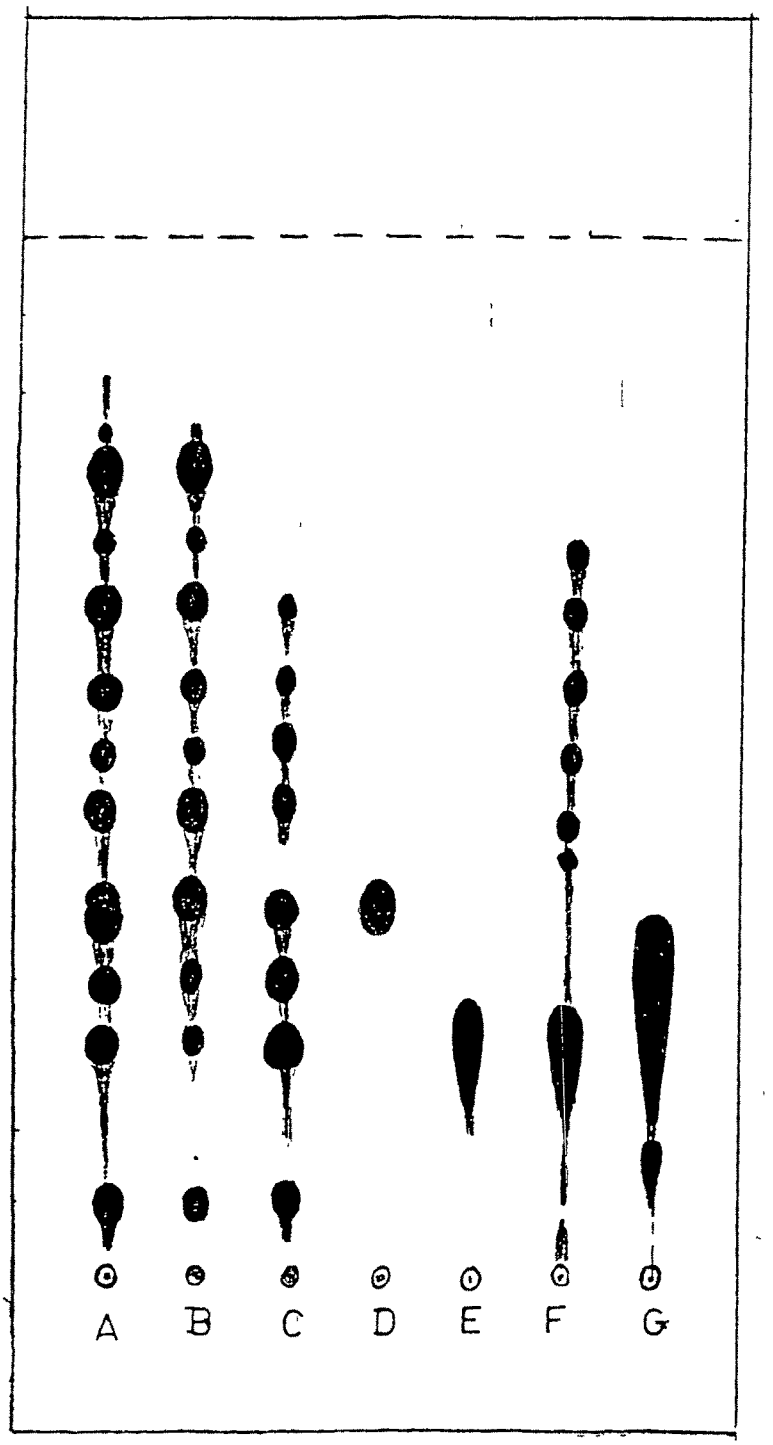
(A) Chromatography

The crude tetrol bis-acetonides mixture was subjected to chromatography on SiO_2 gel/IIb and eluted with pet.ether-ethyl acetate with increasing polarity. Fractions containing the bis-acetonides were combined, freed of solvent and distilled to get light yellow oil (~98% TLC pure), yield 3.87 %.

(B) Partition between pet.ether and methanol

The crude product was dissolved in methanol, filtered and repeatedly extracted with pet.ether till methanol phase was devoid of the bis-acetonides (monitored by TLC). Usual work-up of both the phases yielded 5.6% pet.ether soluble and 3.18% methanol soluble portions. The pet.ether portion on distillation gave TLC pure ($\sim$ 95%) tetrol bis-acetonides.

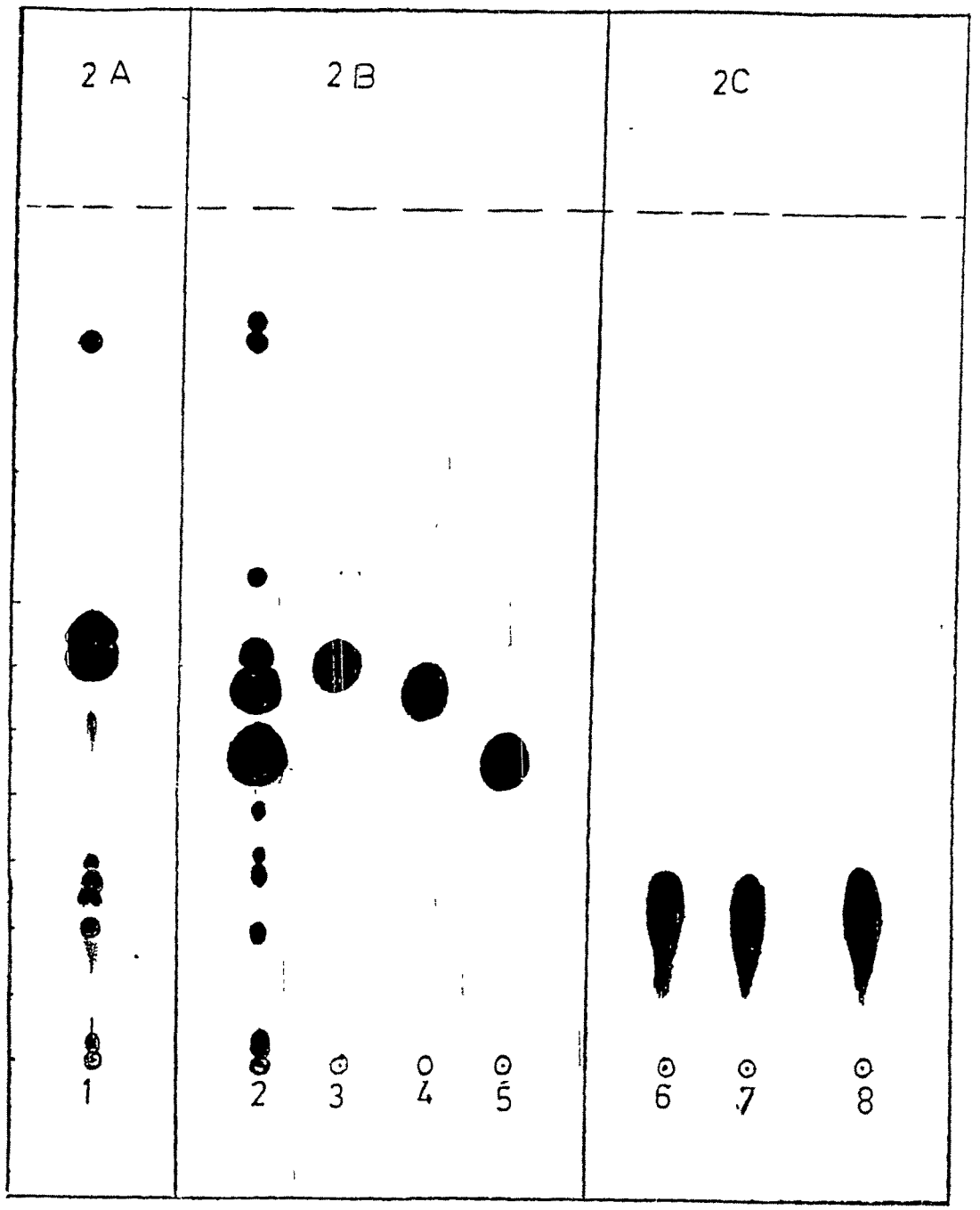
Above process (B) is more favourable because the methanol soluble portion remained intact and can be used further for the isolation of compounds as the process is totally non-destructive.



(A) EtOAc soluble portion (B) Neutral portion and
(C) Phenolic portion.of gum-resin. (D) Authentic tetrol esters
(E) Authentic tetrols (F) Unsaponifiable portion and
(G) Acids obtained from phenolic portion of gum-resin.

Silica gel - G plate Spray reagent : H_2SO_4
Solvent system : 80% EtOAc in pet.ether

Fig. 1 TLC of fractions obtained from segregation of C. Mukul gum-resin.



2A and 2C-Silica gel - G plate, 2B - 15% $AgNO_3$ impregnated silica gel-G plate.
Spray reagent : H_2SO_4
Solvent system : (1) 5% EtOAc in pet.ether (for plate 2A & 2B) (2) 80% EtOAc in pet.ether.(for plate 2C).
(1 and 2) : Total tetrol bis-acetonides (distilled) (3) Ribo-tetrol bis-acetonides (4) Xylo-tetrol bis-acetonides (5) Unsaturated xylo-tetrol bis-acetonides (6) C_{20}-Ribo-tetrol , (7 and 8) C_{18} & C_{20} unsaturated xylo-tetrols respectively.
Fig. : 2 -TLC of tetrols and tetrol bis-acetonides isolated from C. mukul gum-resin.

PART - II Separation of saturated and unsaturated tetrol bis-acetonides:

The tetrol bis-acetonides, thus obtained, showed two overlapping spots on TLC (Fig. 2A) on SiO_2 gel and major three spots on SiO_2gel impregnated with $AgNO_3$ (15%, Fig. 2B), indicating two new types of tetrols over and above the already known xylo-tetrols of saturated type.[5c] In GLC (Fig. 3A) four major peaks were shown. From the spectral analysis, the mixture was found to be consisting of the saturated as well as unsaturated components.

The distilled mixture of tetrol bis-acetonide was then subjected to chromatography on SiO_2 gel impregnated with 13% $AgNO_3$ (Chromatogram-2) and separated into tetrol bis-acetonides of Type-I (Rf 0.43), Type-II (Rf 0.37) and Type-III (Rf 0.34) (Fig. 2B). They were identified as follows.

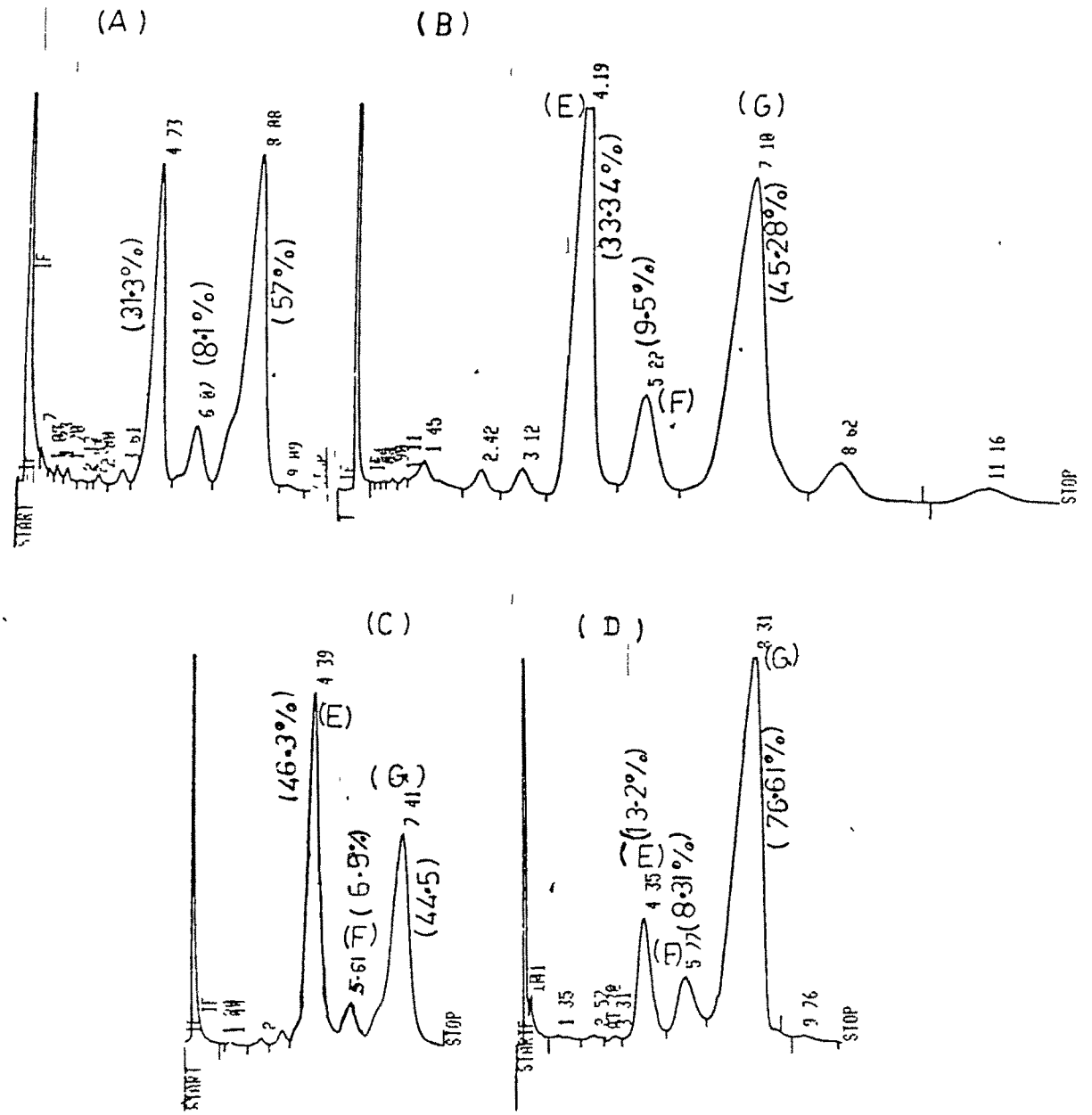
Type-I : This type was obtained by elution with 2% ethyl acetate in pet.ether followed by subsequent rechromatography. It was found to be saturated tetrol bis-acetonides (NMR, IR and GC, Fig. 3B).

Type-II : This type was eluted with 2-3% ethyl acetate in pet.ether and was also found to be saturated tetrol bis-acetonide different from Type-I (NMR, IR and GC, Fig. 3C).

Type-III : This was eluted with 4-6% ethylacetate in pet.ether and was found to be unsaturated tetrol bis-acetonides [NMR, IR and GC, Fig. 3D).

PART - III Structure elucidation of saturated and unsaturated tetrols.

Type-I GLC analysis (column 10% OV-4, 230°, Fig. 3B) of this type showed presence of atleast seven compounds with RRT (% present) of 2.42 (1.01%), 3.12 (1.31%), 4.19 (33.34%), 5.22 (9.5%), 7.1 (45.28%), 8.62 (4.93%), 11.16 (2.59%) and 11.16 (2.59%). The two major compounds



Bis-acetonides of (A) Total tetrols (B) Ribo-tetrols (C) D-xylo tetrols (D) Unsaturated D-xylo tetrols (E) C_{18} (F) C_{19} (G) C_{20} tetrol.

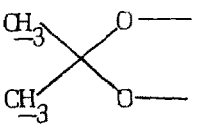
Column : 10% OV-4, Temp. 230°C.

Fig. 3 : GC analysis of tetrol bis-acetonides isolated from Commiphora mukul gum-resin.

termed as comp. A (RRT 4.19) and comp. B (RRT 7.1) were separated by preparative GLC (column 20% SE-30, 12 feet, 270°C) and identified by mass-spectrometry as the bis-acetonides of C_{18}-tetrol (RRT 4.19, M^+, m/e 398) and C_{20}-tetrol (RRT 7.1, M^+, m/e 426) respectively. The remaining five minor constituents were considered to be the other homologous members (i.e. C_{16}, C_{17}, C_{19}, C_{21}, C_{22}) of same configuration. This is supported by the plot of log of GLC retention time *vs* the number of carbon atoms of the aliphatic chains (of derived acetonides), when all the points fall nicely on a straight line[5c, 32] (Fig. 4). Comparison of NMR and IR spectra of bis-acetonides derived from both C-18 and C-20 tetrol shows that both these tetrols have the same configuration at chiral centres.

Compound A was purified by distillation [b.p. 192-198°C(bath temp.)/ 1.5 mm], GC purity 97.2%.

IR (neat)(Fig. 5) : 1465, 1380, 1370, 1250, 1220, 1160, 1070, 853, 800 cm^{-1}.

PMR (CCl_4)(Fig. 6)δ : CH_3-CH_2 (3H, bt, 0.9 ppm), $(CH_2)_{13}$ & two 
(38 H, 2S, 1.27 and 1.32 ppm), OCH, OCH_2 (5H, bm, 3.6-41. ppm).

It was identified as 1,2:3,4-*O*-bis-isopropylidene-ribo-octadecane-1,2,3,4-tetrol (30) by comparison (IR, NMR, GC, TLC) with an authentic sample (prepared from the parent tetrol*), corresponding to the tetrol ribo-octadecane-1,2,3,4-tetrol (32).

Compound-B was purified by distillation, b.p. 200-250°C (bath temp.)/ 1.5 mm, GC purity 96.36%.

IR (neat) (Fig. 7) : 1470, 1373, 1265, 1215, 1065, 1050, 853 and 720 cm^{-1}

* L-ribo-Octadecane-1,2,3,4-tetrol was obtained from Prof. Sukh Dev.

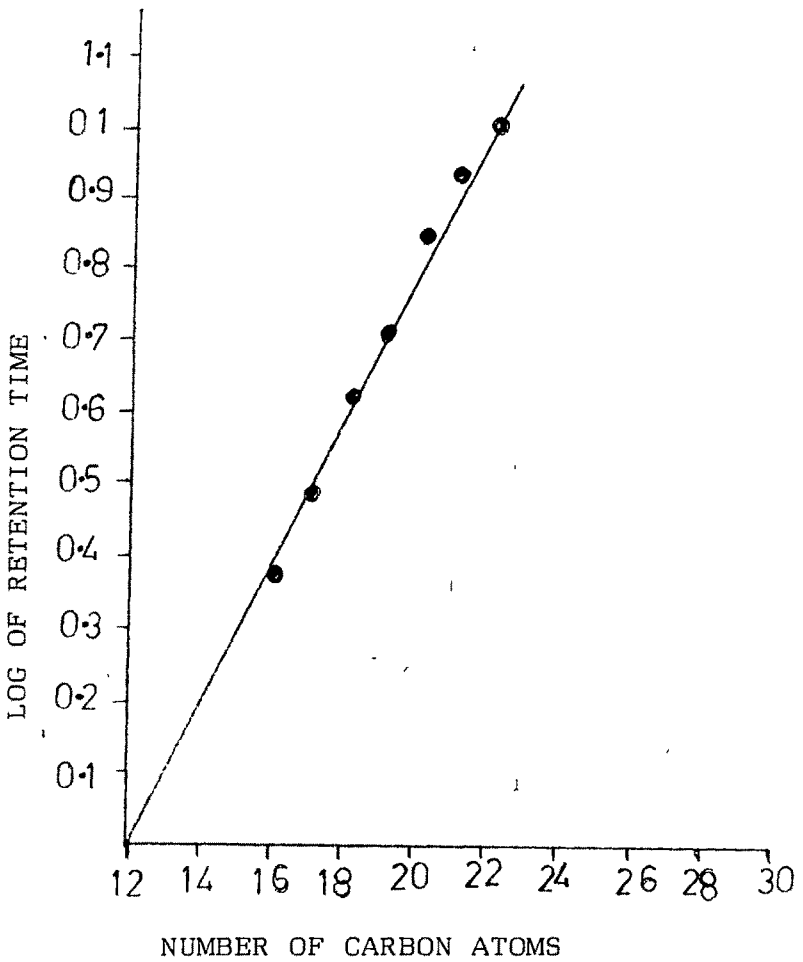
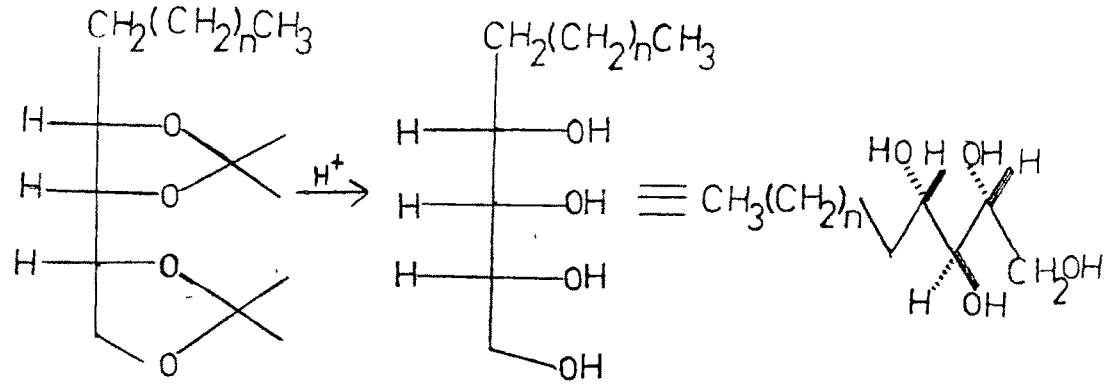
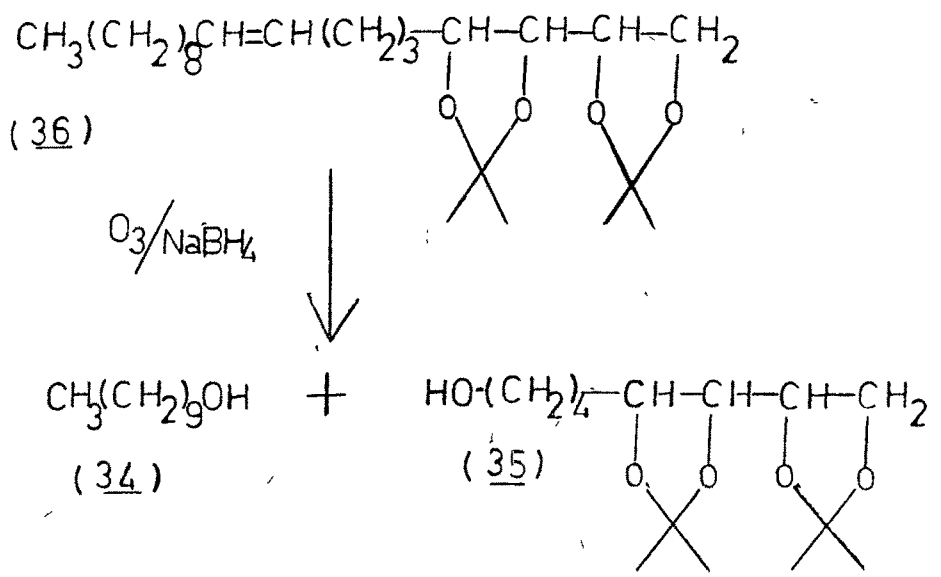


Fig. 4 : Graph of log of the retention time vs. the number of carbon atoms of the aliphatic chain of the ribo-tetrol bis-acetonides.



(30) n =12
(31) n =14

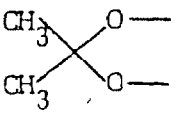
(32) n =12
(33) n =14



(36)

(34)

(35)

PMR (CCl_4)(Fig.8) δ : $\underline{CH_3}$-$\underline{CH_2}$ (3H, bt, 0.9 ppm), $(\underline{CH_2})_{15}$ and two  (42H, 2S, 1.27 and 1.32 ppm), O$\underline{CH}$, O$\underline{CH_2}$ (5H, bm, 3.6-4.1 ppm).

It was identified as 1,2:3,4-$\underline{O}$-bis-isopropylidene-ribo-eicosane-1,2,3,4-tetrol (31) by direct comparison (IR, GC, TLC) with an authentic sample (prepared from parent tetrol+). On mild hydrolysis[5c] (10% $HClO_4$, aq. dioxane), it regenerated the parent tetrol, which was purified by crystallisation (ethanol), to furnish white crystalline solid (m.p. 103-105°C).

IR (neat)(Fig. 9) : 3400, 3260, 1468, 1400, 1295, 1215, 1120, 1100, 1075, 1052, 1025, 1005, 955, 905, 880, 718 cm^{-1}.

It was identified as ribo-eicosane-1,2,3,4-tetrol (33) by comparison (IR*, TLC, mixed m.p., reported[33] m.p. is 106°C) with an authentic sample.

Thus Commiphora mukul gum-resin found to contain C-18 and C-20 ribo-tetrols (32 and 33). These compounds, though isolated from nature for the first time, had been known synthetically much earlier.[13,33] Due to paucity of samples rotations could not be recorded.

Type-II GLC analysis (Fig. 3C) of these saturated tetrol bis-acetonides showed it to be a mixture of at least seven compounds. It was found to be a mixture of C_{16}-C_{21} tetrols (as bis-acetonides) reported earlier, with C_{18} and C_{20} compounds predominating (21 and 23), having the D-xylo configuration.

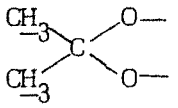
+ D-ribo-eicosane-1,2,3,4-tetrol was obtained from Prof. A. Kjaer (Denmark).

* Tetrols with different configurations (eg. L-xylo, L-Ribo, D-Lxylo) display distinct patterns in their IR spectra in the 900-1300 cm^{-1} region and this is of clear diagnostic value. The ^{1}H-NMR spectra (90 MHz) of the tetrols or their derived acetonides are not distinct enough in the C$\underline{H}$-O region for identification purposes.[13]

They were identified by comparison with the authentic sample (NMR, IR, TLC, GC).

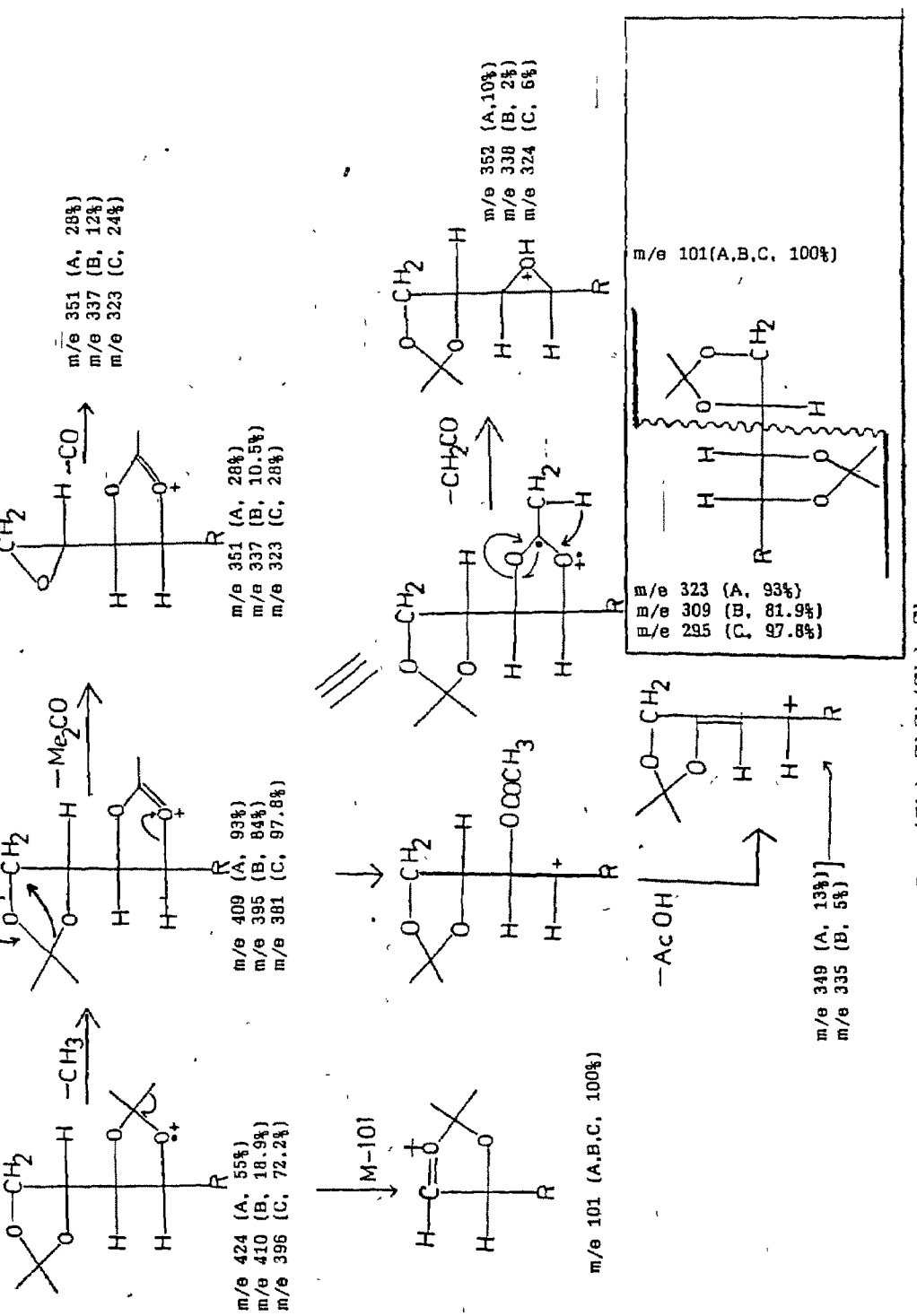
Type - III GLC analysis (Fig. 3D) of these unsaturated tetrol bis-acetonides showed it to be consisting of at least three compounds with RRT (% present) of 4.35 (13.2%), 5.77 (8.31%) and 8.31 (76.6%). All the three compounds were separated by preparative GLC (column 20% SE-30, 12 feet, 270°C) and identified by mass spectrometry as the bis-acetonides of C_{18}-tetrol (RRT, 4.35, M^+, m/e 396, Fig. 10), C_{19}-tetrol (RRT, 5.77, M^+, m/e 410, Fig. 11) and C_{20}-tetrol (RRT 8.31, M^+, m/e 424, Fig. 12) respectively. The important ions in the mass spectrum of bis-acetonides of C_{18},C_{19} and C_{20} tetrols are summarised in Chart-6.

The PMR and IR spectrum of C_{18}-tetrol bis-acetonide showed the following structural features.

PMR (CCl_4)(Fig.13)δ : $\underline{CH_3}CH_2$ (3H, bt, 0.9 ppm), $(\underline{CH_2})_{18}$ and two  (30 H, bs, 1.32 ppm), $\underline{CH_2}$-CH=CH-$\underline{CH_2}$ (4H, m, 2 ppm), $\underline{CH}$=$\underline{CH}$ (2H, m, 5.3 ppm), $O\underline{CH_2}$(1H, dd, 3.5 ppm, J_1=10 Hz, J_2=2 Hz; 1H, m, 3.9 ppm), $O\underline{CH}$ (3H, bm, 3.7-4.2 ppm).

IR(neat)(Fig. 14) : 1450, 1360, 1240, 1205, 1150, 1055, 870, 840 cm^{-1}

The PMR (CCl_4) and IR (neat) spectrum of C_{19} and C_{20} tetrol bis-acetonide (Fig. 15, 16, 17 and 18) display similar features and are virtually superimposable with that of the C_{18}-tetrol bis-acetonides (except for CH_2 count)



A, R = $-(CH_2)_9-CH=CH-(CH_2)_4-CH_3$

B, R = $-(CH_2)_m-CH=CH-(CH_2)_n-CH_3$

C, R = $-(CH_2)_3-CH=CH-(CH_2)_8-CH_3$

Chart - 6 : Mass spectral analysis of C_{18}(C), C_{19}(B) and C_{20} (A) unsaturated tetrol bis-acetonides.

^{13}C-NMR spectrum of bis-acetonides of C_{18}, C_{19} and C_{20} tetrol shows the following structural features.

C_{18}-tetrol bisacetonide ($CDCl_3$) δ C(ppm)(Fig.18A) : 65.95 ($\underline{C}H_2O$); 75.73, 81.01, 77.5 (3 x $\underline{C}H$-O); 32.02, 27.3, 32.7, 32.89, 27.52, 29.72, 29.64, 29.45, 29.3, 32.56, 22.76 (11 x $\underline{C}H_2$); 129.92, 131.54 (2 x $\underline{C}H$=); 14.15 ($\underline{C}H_3$); 27.51, 26.01, 26.33, 27.02 (4 x $\underline{C}H_3$-CO_2); 109.3, 109.96 (2 x >$\underline{C}$-O_2).

C_{19}-tetrol bisacetonide ($CDCl_3$) δ C(ppm)(Fig.18B) : 65.33 ($\underline{C}H_2O$); 76.19, 77.03, 80.32 (3 x $\underline{C}H$-O); 25.18, 25.64, 25.81, 26.51 (4 x $\underline{C}H_3$-CO_2); 33.06, 26.78, 31.11, 29.33, 29.25, 29.05, 28.86, 27.02, 21.91 (12 x $\underline{C}H_2$); 129.51, 129.43 (2 x $\underline{C}H$=); 13.62 ($\underline{C}H_3$); 108.48, 109.16 (2 x >$\underline{C}$-O_2).

C_{20}-tetrol bisacetonide ($CDCl_3$) δ C(ppm)(Fig.18C) : 65.28 ($\underline{C}H_2O$); 74.92, 76.8 80.22 (3 x $\underline{C}H$-O); 25.14, 25.6, 25.7, 26.44 (4 x $\underline{C}H_3$-CO_2); 33, 31.07, 29.3, 29.22, 29.06, 28.82, 26.97, 26.7, 22.1 (13 x $\underline{C}H_2$); 129.35 (2 x $\underline{C}H$=), 13.57 ($\underline{C}H_3$); 108.38, 109.07 (2 x >$\underline{C}$-O_2)

Bis-acetonides derived from C-18 and C-20 tetrols on mild hydrolysis[34] (Amberlyst-15, aq. dioxane) generated the parent tetrols, which failed to crystallize from different solvents. Tetrols were purified separately by passing through a small column of silica gel. The PMR and IR spectrum of C_{18}-tetrol shows the following structural features.

PMR ($CDCl_3$)(Fig. 19) δ : $CH_3\underline{C}H_2$ (3H, bt, 0.9 ppm), $(\underline{C}H_2)_9$ (18H, bs, 1.3 ppm), $\underline{C}H_2$-CH=CH-$\underline{C}H_2$ (4H, bm, 2 ppm), O$\underline{C}$H and O$\underline{C}H_2$ (5H, bm, 3.42, 3.7, 4.3 ppm), $\underline{C}H$=$\underline{C}H$ (2H, m, 5.3 ppm).

IR (neat)(Fig. 20) : 3400, 1710, 1470, 1075 cm^{-1}.

The PMR and IR spectrum of C_{20} tetrol (Fig. 21 & 22) are also virtually superimposable with that of C_{18} tetrol, except for CH_2 count.

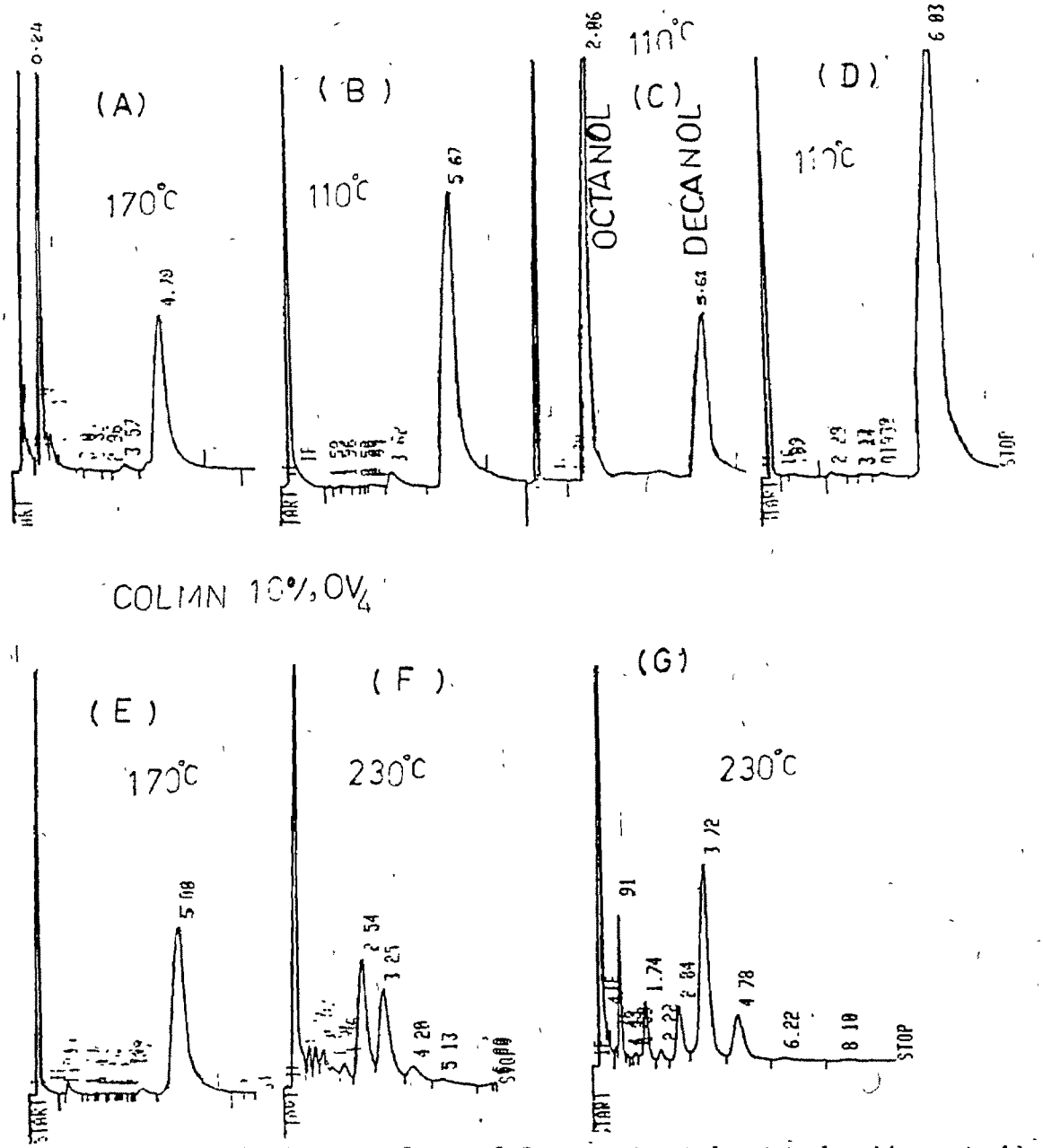
From IR spectrum of C_{18} & C_{20} tetrol bis-acetonides (absence of strong band at ~970 cm^{-1} and presence of band at 730 cm^{-1}), it was concluded that the olefinic linkage is cis-configurated* and from PMR it is clear that tetrols contain single double bond.[35]

Position of double bond in tetrols.

Our next objective was to find out the position of the double bond in the tetrols. For that, the process attempted was ozonolysis.

C_{18}-tetrol bis-acetonide on reductive ozonolysis ($O_3/NaBH_4$) furnished a mixture of alcohols (NMR, IR) with at least two major compounds (GC, Fig. 23A). When subjected to chromatography, the mixture yielded two compounds in pure form. One of them with RRT 0.84 in GC, was identified as decanol (34) by direct comparison with the authentic sample (mixed GC, TLC, IR and NMR). The second compound from its spectral data was found to be the other part of the molecule i.e. alcohol consisting of the bis-acetonide portion (35). Identification of n-decanol made it easy to assign the structure (36) to the C_{18}-tetrol bis-acetonide and thus the parent tetrol. Position of double bond is at C_8-C_9.

* Cis-and trans-isomers of symmetrically disubstituted ethylene are easily distinguishable. In the trans-forms the absorption is strong and occur at ~970 cm^{-1} and in the cis-form, the band is very weak or absent. Cis-isomers have the band at 675-725 (variable). Methyl ester of oleic acid (cis) and elaidic acid (trans) are easily distinguished by IR spectrum by absorption band at 970 cm^{-1} (see reference 29)



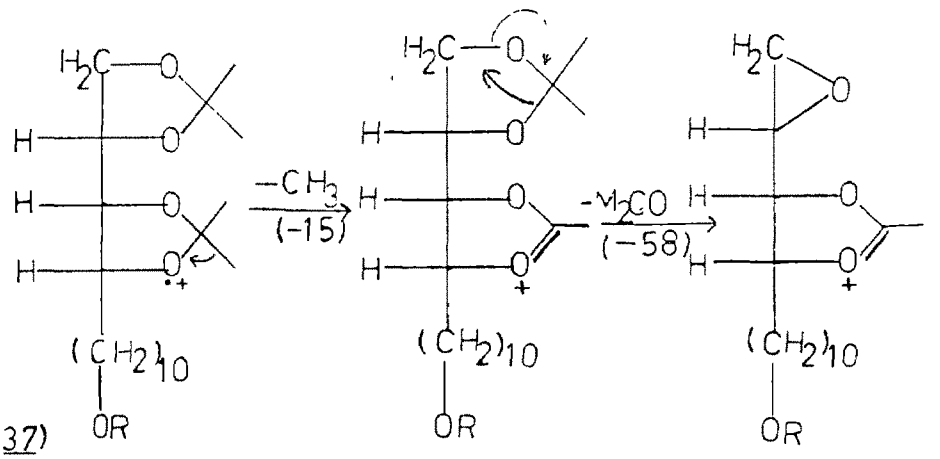
(A) Product of reductive ozonolysis of C_{18} unsaturated tetrol bis-acetonide (B) Alcohol of aliphatic portion and (E) alcohol of bis-acetonide part from C_{18}-unsaturated tetrol bis-acetonide (C) Mixture of authentic octanol and decanol (D) Mixed GC of B with authentic decanol (F) Alcohol of bis-acetonide part from C_{19} and (G) C_{20}-unsaturated tetrol bis-acetonide.

Fig. - 23 : GLC analysis of product obtained from reductive ozonolysis of pure C_{18}, C_{19} and C_{20} unsaturated tetrol bis-acetonides.

In case of C-19 tetrol bis-acetonide also, reductive ozonolysis gave a mixture of alcohol as evident from GC, IR and NMR. Column chromatography of the mixture afforded a TLC single spot compound, which was a mixture of two major compounds as observed in GC (Fig. 23F) and NMR, and both the components had the bis-acetonide part. This led us to suspect about presence of positional isomers having double bond at different position in the compound. The other part of the ozonolysis products, consisting of aliphatic alcohol was lost during aq. work up, which prevented us from the assignment of the position of the double bond.

C_{20}-tetrol bis-acetonide, on reductive ozonolysis (Chart-8, Scheme-1) furnished a mixture of alcohols (GC and NMR). Chromatographic purification afforded a compound exhibiting a single spot on TLC, but a mixture of at least four compounds, as evident from GC (Fig. 23G) and having the acetonide portion [with RRT (% present) 1.74 (7.2), 2.84(10.6), 3.72(53.8), 4.78 (14.91)](The aliphatic alcohol part was again lost during aqueous work up). This observation led us to suspect about presence of positional isomers of double bond in case C-20 tetrol. The mixture of alcohols obtained from chromatography, in mass spectrum (Chart-7) revealed a major series which starts with the compound having m/e 358 (in case of acetate at m/e 400), which is major and corresponds to the bis-acetonide of the formula $C_{20}H_{38}O_5$ (in case of acetate $C_{22}H_{40}O_6$). Calculated from this, the major isomer in the C_{20}-tetrol bis-acetonide has a double bond at C_{14}-C_{15} having structure (38).

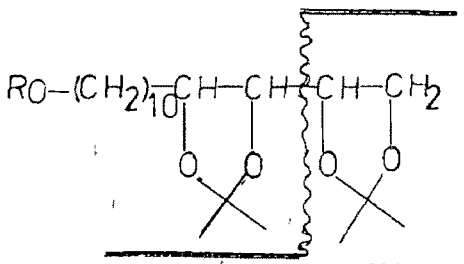
To confirm our hypothesis of the positional isomers, the compound was cleaved at the double bond by two different methods (Chart-8).



(37)

(1) M^+, m/e 358 (40%) (1) m/e 343 (92%) (1) m/e 285 (8%)

(2) M^+, m/e 400 (71%) (2) m/e 385 (100%) (2) m/e 372 (22.5%)



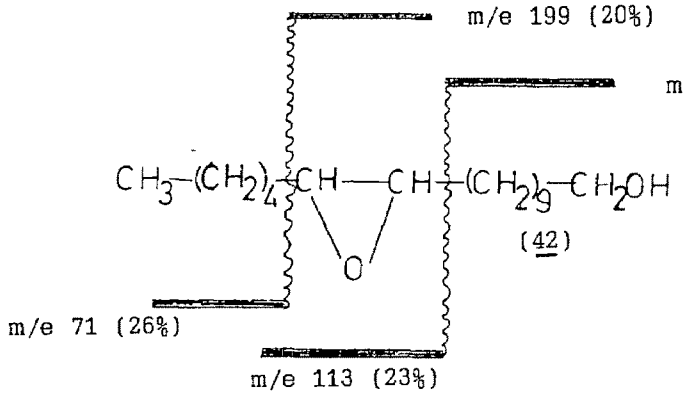
(1) m/e 101 (100%)

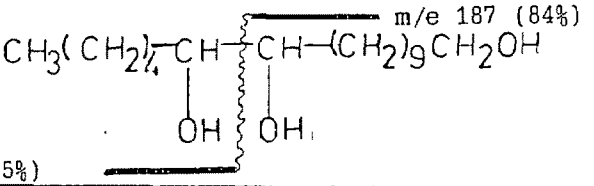
(2) m/e 101 (58%)

(1) R = H

(2) R=$COCH_3$

(1) m/e 257 (26%) (2) m/e 299 (51.6%)



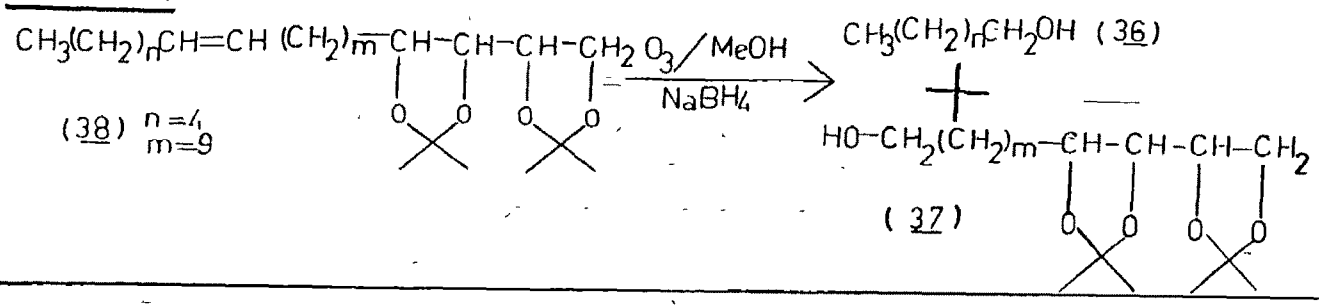


(43)

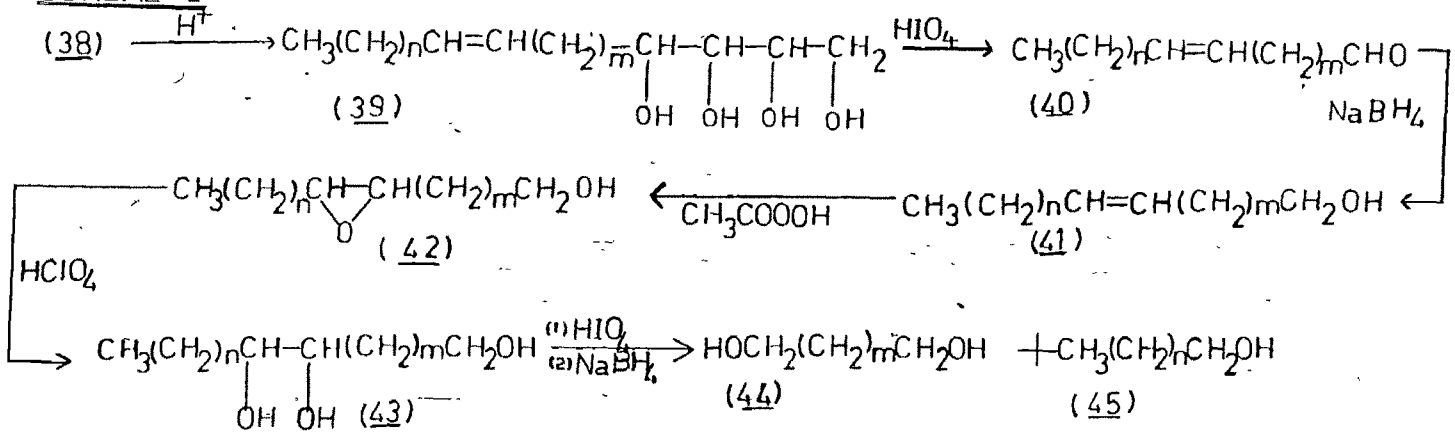
m/e 101 (7.5%)

CHART - 7

SCHEME-1



SCHEME-2



SCHEME-3

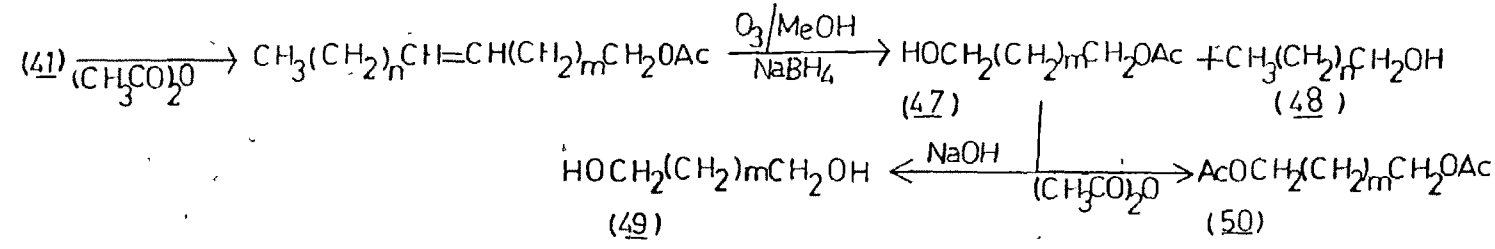
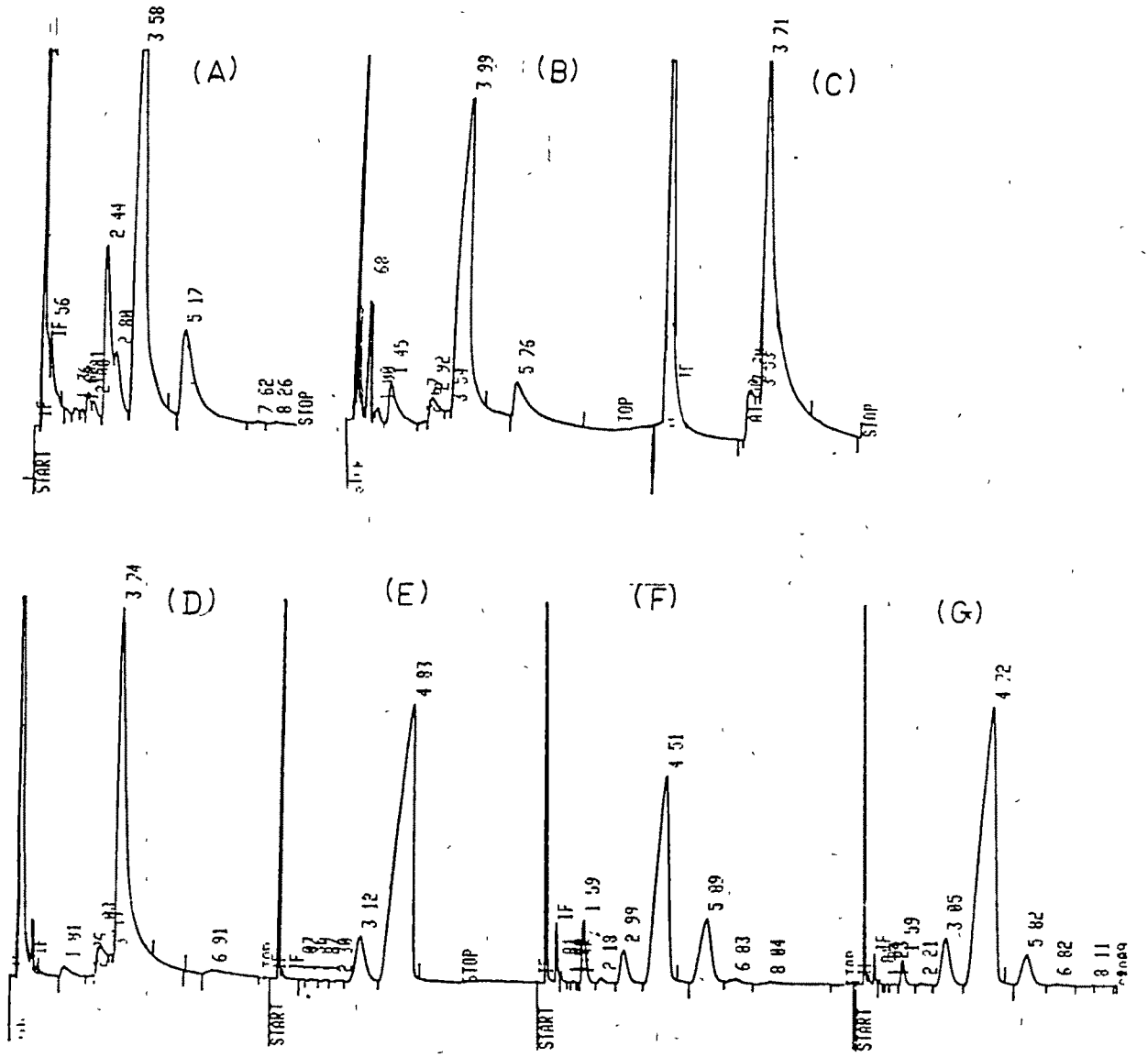


CHART - 8

In the first method (Scheme-2, Chart-8), the parent tetrol (39) was regenerated by mild hydrolysis[34] (Amberlyst-15, dioxane) of the tetrol bis-acetonides (38) (85% yield). It was then oxidised with periodic acid[5c] to afford the aldehyde (40, 94.8% yield), which was treated with $NaBH_4$ to get the unsaturated alcohol (41) which after purification by chromatography (70% yield, M^+, m/e 254), was subjected to epoxidation[36] at the olefinic linkage using peracetic acid to give the epoxy alcohol (42, 91.5% yield, M^+, m/e 270). When treated with perchloric acid[37], it gave the triol (43, 26.78% yield), which was treated with HIO_4 followed by reduction with $NaBH_4$ to get a mixture of alcohols. On chromatographic purification a mixture of diols (44) was obtained as evident from NMR, IR and GC (Fig. 24A). The alcohol part (45) was probably lost during aqueous work up. Ending up with the mixture of diols was an evidence for the presence of the mixture of positionally isomeric unsaturated tetrols.

As a further support for our assumption, another method of cleavage was applied (Scheme 3, Chart-8). The unsaturated alcohol (41) was exposed to acetylation with acetic anhydried/pyridine to get the acetate (46, 88.6% yield). The acetate (46) on reductive ozonolysis ($O_3/NaBH_4$) gave the product (TLC single spot) which was identified as a mixture monoacetylated diols (47)(from GC, IR, NMR). The alcohol part (48) was lost during aqueous work up. Hydrolysis of (47) gave mixture of corresponding diols (49) which was same as obtained earlier (NMR, IR, GC Fig. 23B). It was converted into diacetate (50) by acetic anhydried and pyridine (GC, Fig. 23F, NMR, IR).

Mass spectral studies (Chart-7) of epoxide (42), triol (43) and alcohol of bis-acetonide part (37) and its acetate also support the position



(A and B) Diols obtained by Scheme-2 and 3, (C) Authentic 1,11-undecandiol, (D) Mixed GC of B and C (E) Authentic 1,11-undecan diacetate (F) Diacetates obtained by Scheme-3 (G) Mixed GC of E and F.

Column : 10% OV-4 Temp. 170°C (for A - D), 190°C (for E - G).

Fig. 24 : GC analysis of diols and diacetates obtained from cleavage of double bond of C_{20}-tetrol bis-acetonide (Chart-7).

of double bond in major isomer at C_{14}-C_{15}. In order to confirm the identity of the major isomer present in a mixture diols (44 and 49), 1,11-undecandiol was synthesized for comparison.

1,11-Undecandiol (57) was synthesized from 10-undecenoic acid (51) following the scheme given in Chart-9. Esterification[38] of 10-undecenoic acid with methanol p-toluene sulfonic acid yielded methyl ester (52, 92.97% yield). Reduction[38] of (52) with LAH gave 10-undecenol (53, 84% yield), which was acetylated with acetic anhydride/pyridine to furnish acetate (54, 82.8% yield). Addition of HBr to acetate (54) in presence of benzoyl peroxide yielded 11-bromo-undecan acetate (55, 80.4% yield) as a major product (NMR, IR). Acetylation[39] of (55) with CH_3COOH/CH_3COONa furnished required 1,11-undecandiacetate (56, 68.7% yield), which on hydrolysis[39] with NaOH gave 1,11-undecandiol (57, 74% yield) as white solid.

Major isomer present in diols (44, 49) and diacetate (50) obtained from cleavage of double bond of C-20 unsaturated tetrol (or its bis-acetonide) by above mentioned two different routes was found to be 1,11-undecandiol (57) and 1,11-undecandiacetate (56) by direct comparison (IR, NMR and co-injection in GC (Fig. 24)] with the authentic sample.

Above studies confirmed presence of positional isomers at the double bond and that the major isomer has a double bond at C_{14}-C_{15}.

NMR and IR spectrum of all the unsaturated tetrols and their derived bis-acetonides are virtually superimposable with each other indicates the same configuration at the chiral centres.

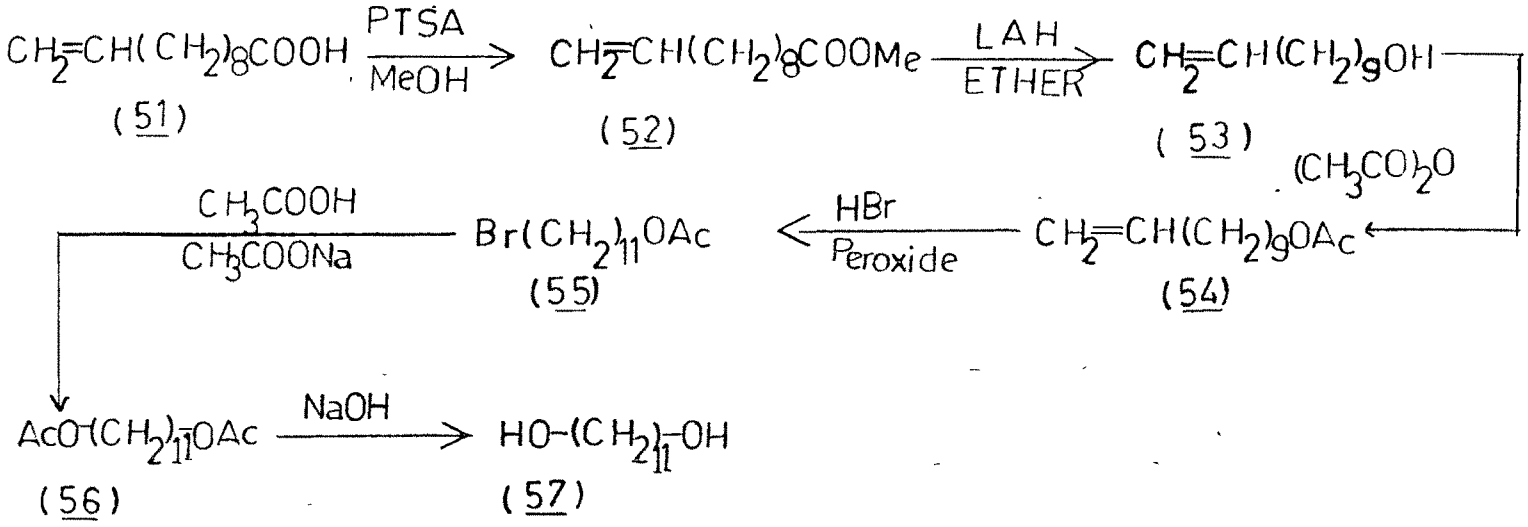
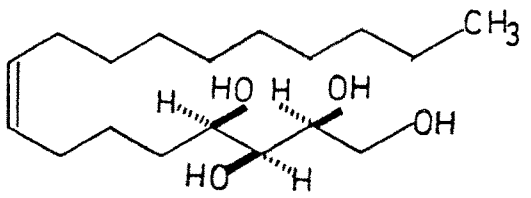


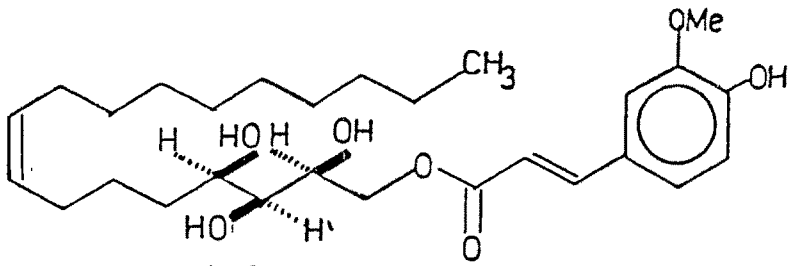
CHART - 9 : SYNTHESIS OF 1,11-UNDECANDIOL (57) FROM 10-UNDECENOIC ACID (51).

Separate hydrogenation of C_{18} and C_{20} unsaturated tetrol bis-acetonides using 5% Rh/Al_2O_3 gave corresponding saturated compounds. Both the saturated products were found to be exactly matching with the authentic C_{18} and C_{20} D-xylo-tetrols bis-acetonides (superimposable NMR and IR) respectively. Mild hydrolysis of both the saturated tetrol bis-acetonides furnished parent tetrols, which were purified by crystallisation to get white crystalline solids (C_{18}-tetrol, m.p. 78-81°C and C_{20}-tetrol m.p. 83-86°C). The tetrols were characterised as xylo-octadecane-1,2,3,4-tetrol (64) and xylo-eicosane-1,2,3,4-tetrol (65) by direct comparison with the authentic sample (NMR, IR and m.p.).

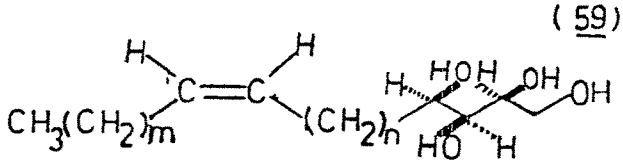
Thus, from above studies unsaturated tetrols isolated from C. mukul gum-resin are D-xylo-octadec-8(Z)-ene-1,2,3,4-tetrol (58), D-xylo-nonadecene-1,2,3,4-tetrol (60) and D-xylo-eicos-14(Z)-ene-1,2,3,4-tetrol (62). As mentioned earlier tetrols are present in the form of ester of ferulic acid, and are assigned the structures (59), (61) and (63) for C_{18}, C_{19} and C_{20} tetrol respectively. These compounds isolated and reported for the first time.



(58)

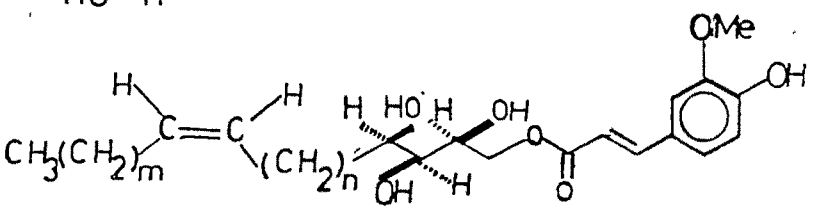


(59)

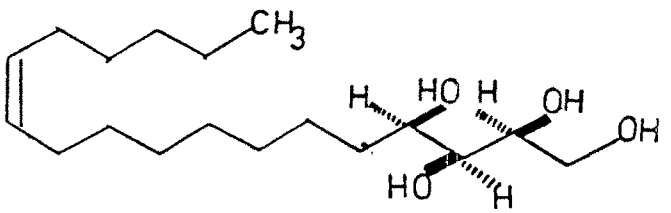


(60)

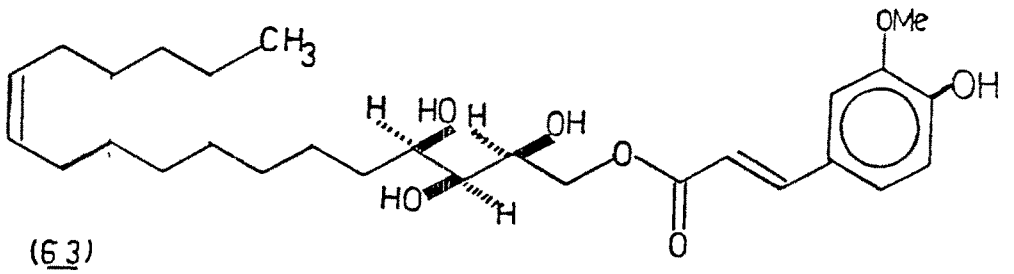
(m + n = 12)



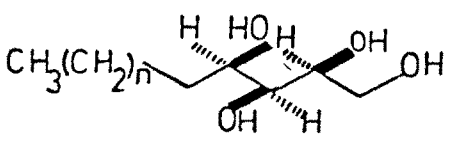
(61)



(62)



(63)



(64) n = 12

(65) n = 14

EXPERIMENTAL

All melting points and boiling points are uncorrected. All the melting points were recorded in melting point apparatus. Petroleum ether (pet.ether or P.E.) refers to the fraction boiling at 60-80°C.

The IR spectra were recorded on a Perkin-Elmer spectrometer model 267 and 781. The UV spectra were recorded on a Perkin-Elmer spectrometer model 402. The PMR spectra were recorded on a Perkin-Elmer model R-32 (90 MHz) spectrometer (unless stated to the contrary) and the Mass spectra were recorded on a Varian Mat. mass spectrometer model CH-7 (mass, 70 ev, direct inlet). C,H analyses (by modified Liebig's method) were carried out in the Chemistry department, M. S. University, Baroda. ^{13}C-NMR spectra were recorded on a Varian 200 MHz (Purdue university, U.S.A.) and 300 MHz (NCL, Poona) Spectrometer. Optical rotations were measured on a Rudolph polarimeter Autopol-III.

Gas chromatography analyses were carried out on Hewlett-Packard, model 5712A; stainless steel column, 180 cm x 0.3 cm; support 60-80 mesh chromosorb-w; stationary phase 10% SE-30; carrier gas H_2, flow rate 60 ml/min; mode TCD. Hewlett-Packard, model 5712A; stainless steel column, 360 cm x 0.3 cm; support 60-80 mesh chromosorb-w; stationary phase 10% CW (carbowax), 20 M; carrier gas H_2, flow rate 60 ml/min; mode TCD. Hewlett-Packard, model 7624A; glass column, 100 cm x 0.15 cm; support 80-100 mesh chromosorb-w; stationary phase 10% $DCQF_1$; carrier gas H_2, flow rate 60 ml/min, mode TCD. Hewlett-Packard, model 7624A; stainless steel column, 120 cm x 0.3 cm; support 80-100 mesh chromosorb-w; stationary phase 10% OV_4; carrier gas N_2, flow rate 40 ml/min; mode FID. And 7624A

(for preparative GC); Al column, 360 cm x 0.9 cm preparative column; support 45-60 mesh chromosorb-w; stationary phase 20% SE-30; carrier gas H_2; flow rate 100 ml/min; TCD 270°, inj 270°, column 150°; 30 ml (each injection) gas chromatograph.

IR spectra were recorded as smears or in nujol or in KBr pellets and values are reported in wavenumbers (cm^{-1}). All PMR spectra were recorded with 15-20% solution in $CCl_4/CDCl_3$ or else as stated, with TMS as internal standard, signals are recorded in ppm (δ). While citing PMR data, the following abbreviations have been used : s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet) and b(broad). J values in PMR are mentioned in Hz. While summarising mass spectral data, besides the molecular ion, about ten most abundant ions (m/e) are reported with their relative intensities. All UV spectra were recorded in 95% ethanol or methanol.

Silica gel for column chromatography (100-200 mesh, Bhavana Chemical, V.V.Nagar, Gujarat) was used as such after gradation[40](IIb), unless stated contrary. TLC were carried out on Silica gel-G (13% gypsum, 75 microns; (Bhavana Chemical, V.V.Nagar, Gujarat) layer 0.25 mm and activated at 110-115° for 2 hrs. Alumina used for chromatography was the commercial basic alumina, which was seived (100-200 mesh), washed with 10% HNO_3 at 90° followed by washing with H_2O till neutral. It was activated at 450°C and required grade was prepared and standardized according to Brockmann procedure[41]. Visualization of the spot on TLC was done by spraying with 10% HNO_3 in H_2SO_4, H_2SO_4, vanillin-phospharic acid, I_2 or suitable reagent as described in references.[42,43]

All solvents were purified and distilled prior to use. Anhydrous peroxide free ether was prepared by treating pre-dried ether over fused $CaCl_2$, with sodium-benzophenone ketyl. Alcohols were dried over their respective magnesium alkoxides or by anhydrous K_2CO_3 followed by distillation over sodium and then stored over molecular sieves (4A). All solvent extracts were washed with brine and dried over Na_2SO_4. Moisture sensitive reactions were carried out in an atmosphere of oxygen free nitrogen.

For generating ozone, Welsbach ozonator model T-408, supplied by Welsbach corporation, USA was used. Chromatotron model 7924 T used for chromatography, was supplied by Harrison research, California. Silica gel used for making both 1 mm and 2 mm plates (rotors) for chromatotron was same as used for TLC (but with 17% gypsum). Plates of required thickness were prepared as per the procedure given in manual.

PART - 1 Methods for isolation of tetrols as bis-acetonides.

Broad separation of Commiphora mukul gum-resin (Chart-5).

The gum-resin (1000 g) was precolated with ethyl acetate (2000 mlx 1, 1000 ml x 6) at room temperature ($\sim$ 30°) to furnish EtOAc soluble material (500 g) as dark brown gum and insoluble material (500 g), essentially a mixture of white powder and solid residue.

The ethyl acetate soluble material (500 g) was dissolved in 1500 ml of EtOAc and extracted with 10% NaOH (10 g NaOH in 95 ml H_2O + 5 ml methanol)(100 ml x 5) at 3-5°C. The organic layer was washed with water (100 ml x 3), brine (100 ml x 2) and dried (Na_2SO_4). Solvent removal furnished neutral material as dark brown gum (344 g).

The aqueous portion was first treated with 50% H_3PO_4 (aq.) till slightly acidic to pH (to liberate acids and phenols) and then treated with saturated solution of $NaHCO_3$ (to dissolve acids) till basic to pH. Insoluble phenolic material from aqueous portion was then extracted with ethylacetate (100 ml x 5), which was washed with brine (30 ml x 2) and dried (Na_2SO_4). Solvent removal furnished phenolic material (142.5 g) as a red gum. The aqueous portion (containing acids) was acidified with 50% H_3PO_4 (aq.) and after saturation with salt, it was extracted with EtOAc (1000 ml x 3), which after usual work-up furnished Acidic material (13 g) as a yellow gummy solid.

Saponification of phenolic material

The phenolic extract (142.5 g) was refluxed with 10% (aq.) methanolic KOH (500 ml) for 3 hrs. Water (200 ml) was added and methanol ($\sim$ 300 ml) removed. Residue was extracted with $CHCl_3$ (100 ml x 3), which after usual work up and solvent removal yielded unsaponifiable material (106.5 g) as a gummy solid.

The aqueous portion was acidified with 50% H_3PO_4 (till neutral to pH) and then extracted with EtOAc (100 ml x 4), which after usual work up and solvent removal furnished acidic material as yellow solid (7.5 g).

Acidic material (1 g) was esterified with absolute methanol (20 ml) and concentrated H_2SO_4 (0.5 ml) at room temp. ($\sim$ 30°) for 15 hrs. Anhydrous CH_3COONa was then added to the esterified product and methanol ($\sim$ 15 ml) distilled off. Residue was diluted with H_2O (5 ml) and extracted with EtOAc (15 ml x 3), which after usual work-up and solvent removal

gave methyl ester as a yellow oil (0.92 g). Crude ester was distilled under reduced pressure [b.p. 180-200° (bath)/2mm] to furnish colourless liquid (0.81 g), TLC single spot (40% EtOAc in pet.ether, Rf 0.5), GC(10% OV-4, 190°) 90.7% pure.

IR(neat) : OH 3450 cm^{-1}, >C=C< 1630 cm^{-1}, COOMe 1710 cm^{-1}, aromatic 1600, 1510, 1450, 846 cm^{-1}.

PMR(CCl_4)δ: $ArOCH_3$ (3H, s, 3.92 ppm), $-COOCH_3$ (3H, s, 3.8 ppm), Ar-CH= CH-C(=O)- (2H, d, 6.3 and 7.65 ppm, J=16 Hz, AB quartet), aromatic protons (3H, m, 6.78-7.2 ppm); identified as methyl ferulate by comparison (IR, PMR) with the authentic sample.

Bis-acetonide of unsaponifiable portion.[31]

Unsaponifiable portion of phenolic material (106.6 g) in dry acetone (250 ml) was treated with anhydrous $FeCl_3$ (15 g) at 5°C and then stirred at room temp. for 1.5 hrs. The reaction mixture was made alkaline with 10% K_2CO_3 and acetone (~200 ml) was removed on rotavapor at 40°/100 mm. The residue after diluted with H_2O (100 ml), filtered through celite and the filtrate was extracted with $CHCl_3$ (100 ml x 5), which after usual work -up and solvent removal gave bis-acetonides as dark red liquid (101.8 g). It was distilled at 170-220°(bath)/1.5 mm to furnish light yellow liquid (57.3 g). GC (10% OV-4, 230°) showed it to be a mixture of at least four compound.

Column chromatography of crude tetrol bis-acetonides.

Crude tetrol bis-acetonides was chromatographed on a SiO_2 gel column.

Table : 1 CHROMATOGRAM-1

Material : 0.9579 g.

Adsorbent : SiO_2 gel/IIb

Column dimension : 26 cm x 1.4 cm.

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
01.	2% EtOAc in pet.ether	100 ml x 3	0.0268	
02.	3% EtOAc in pet.ether	100 ml x 3	0.3653	Colourless liquid
03.	4% EtOAc in pet.ether	100 ml x 3	0.0640	
04.	EtOAc	150 ml x 1		
05.	Methanol	250 ml x 1	0.4214	
		Total :	0.8775	

Fraction-2 (365 mg) was distilled at 180°(bath)/1.5 mm to furnish tetrol bis-acetonides as a colourless liquid. TLC single spot (Rf 0.46, 5% EtOAc in pet.ether). GC showed mixture of at least four compounds.

Partition of crude tetrol bis-acetonide between pet.ether and methanol.

Crude tetrol bis-acetonide (0.6558 g) was dissolved in 15 ml methanol and undissolved brown particles were separated by filtration through filter paper. It was then extracted with pet.ether (10 ml x 4) till methanol layer almost freed from tetrol bis-acetonides (TLC monitoring). Removal of solvent from both the phases furnished a colourless liquid as a pet.ether extract (0.3646 g) and gummy material as a methanol extract (0.2055 g). Pet.ether extract on TLC showed one major spot ($\sim$ 90% pure, Rf 0.46).

PART - 2 Separation of saturated and unsaturated tetrol bis-acetonides.

Distilled tetrol bis-acetonide was chromatographed on $AgNO_3$ impregnated SiO_2 gel.

Table-2 : CHROMATOGRAM-2

Material : 25.3 g.

Adsorbent : 750 g, 13% $AgNO_3$ impregnated SiO_2 gel.

Column dimension : 52 cm x 7.5 cm.

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
01.	Pet.ether	500 ml x 2	0.1841	
02.	1%-1.2% EtOAc in pet.ether	500 ml x14		
03.	1.5% EtOAc in pet.ether	500 ml x 8	0.0731	
04.	2% EtOAc in pet.ether	500 ml x 9	3.3858	Mixture of two compounds.
05.	2% EtOAc in pet.ether	500 ml x 9		TLC single
06.	2.5% EtOAc in pet.ether	500 ml x10	6.0411	spot compound.
07.	3% EtOAc in pet.ether	500 ml x 3		
08.	3.5% EtOAc in pet.ether	500 ml x 3	2.1576	Mixture
09.	4% EtOAc in pet.ether	500 ml x 2	7.8372	TLC single
10.	5% EtOAc in pet.ether	500 ml x10		spot compound.
11.	10% EtOAc in pet.ether	500 ml x 2	0.4081	
12.	20% EtOAc in pet.ether	500 ml x 1	0.9740	
13.	EtOAc	500 ml x 1	2.6550	
14.	Methanol	500 ml x 1	1.3213	
		Total :	25.0373 g	

Fraction-4 on TLC (SiO_2 gel and 15% $AgNO_3$-SiO_2 gel) showed it to be a mixture of two compounds. It was further chromatographed on SiO_2 gel column.

Table-3 : CHROMATOGRAM - 3

Material : 3.31 gm.

Adsorbent : 250 g, SiO_2 gel/IIb.

Column dimension : 65 cm x 3.4 cm

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
4(1)	Pet.ether	500 ml x 0	0.0950	
4(2)	0.5% pet.ether in EtOAc	500 ml x 6	0.0210	
4(3)	1% pet.ether in EtOAc	500 ml x 3	0.0028	
4(4)	1% pet.ether in EtOAc	500 ml x 4	0.2301	TLC pure compound
4(5)	1.5% pet.ether in EtOAc	500 ml x 7	2.1990	TLC pure compound
4(6)	EtOAc	500 ml x 1	0.3182	
		Total :	2.8661 g	

Ribo-tetrol bis-acetonides

Fraction 4(4) on TLC showed a single spot (Rf 0.43, 5% EtOAc in pet.ether). It was found to be a mixture of Ribo-tetrol bis-acetonides (type-I) by comparison with the authentic sample (GC, NMR, IR).

Saturated xylo-tetrol bis-acetonides

Fraction 5-7 and 4(5) on TLC showed a single spot (Rf 0.37). It was found to be a mixture of saturated xylo-tetrol bis-acetonides (type-II) by comparison with the authentic sample.

Unsaturated xylo-tetrol bis-acetonides

Fraction 9-10 also on TLC ($AgNO_3$) showed a single spot (Rf 0.34, 5% EtOAc in pet.ether). It was found to be a mixture of unsaturated xylo-tetrol bis-acetonides (type-III) from its spectral data (NMR & IR) and GC (10% OV-4 230°) analysis.

PART - 3 Structure elucidation of saturated and unsaturated tetrol.

Saturated tetrol bis-acetonides (Type-I)

GC analysis of this type showed it be a mixture of seven compounds (Fig. 3B). Major two compound with RRT (% present) of 4.19 (33.34%) and 7.1 (45.28%) were separated by preparative GLC. The tetrol bis-acetonide mixture (230 mg) was separated on 20% SE-30 (12 feet) column (temp. 270°, carrier gas hydrogen, flow rate 120 ml/min, detector TCD, injection size 30 Ml, to afford two pure compounds.

(1) Tetrol bis-acetonide RRT 4.19 (47 mg), b.p. 192-198°C (bath)/ 1.5 mm, 97.24% pure (GC). Mass spectrum important ions at m/e 398 (M^+, 5.67%), 297(100%), 101(100%), 383(98.99%), 57(98.9%), 59(98.28%), 298 (91.7%), 65(90.09%), 83(77.49%), 95(72.45%), 384((63%), 109(42.84%), 325(27.09), 265(20.16%), 157(15.12%). It was identified as 1,2:3,4-O-bis-isopropylidene-ribo-octadecane-1,2,3,4-tetrol (30) by comparison (NMR, IR, GC) with the authentic sample.

(2) Tetrol bis-acetonide RRT 7.1(53 mg), b.p. 200-205°(bath temp.)/ 1.5 mm, 96.36% pure (GC). Mass spectrum m/e 426 (M^+, 5%), 411(100%), 325(100%), 101(100%), 325(69.3%), 57(52.92%), 60(52.29%), 139(37.17%), 95(35.91%), 143(23.94%), 108(22.05%), 297(12.6%), 311(11.34%), 157(10.08%), It was identified as 1,2:3,4-O-bis-isopropylidene-ribo-eicosane 1,2,3,4-tetrol (31), by comparison with the authentic sample (NMR, IR, GC).

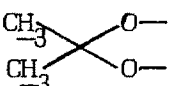
Regeneration of tetrol from tetrol bis-acetonide (RRT 7.1)

The tetrol bis-acetonide RRT 7.1 (42 mg) in dioxane (5 ml) was treated[5c] with 10% $HClO_4$ (1 ml) at 25°c for 1 hr with stirring (TLC monitoring, 80% EtOAc in pet.ether). The acid was neutralised with 10% $NaHCO_3$(aq.)

and dioxane (4 ml) was removed on rotavapor (80°/100 mm). The residue after diluting with water (2 ml) extracted with ethyl acetate (7mlx3), which after usual work-up and solvent removal furnished tetrol as sticky solid (30 mg). Crude tetrol was purified on chromatotron (SiO_2 gel, 1mm plate) by eluting with 30% EtOAc in pet.ether (100ml) and then 70% EtOAc in pet.ether. Pure tetrol (10mg) eluted in second fraction was crystallized from ethanol to furnish a white crystalline solid (5 mg, m.p. 103-105°C, reported[33] m.p. 106°). It was identified as ribo-eicosane-1,2,3,4-tetrol (33) by comparison with the authentic sample (IR, TLC, m.p.).

Saturated tetrols (Type-II)

GLC analysis of this type showed it to be a mixture of at least 7 compounds (Fig. 3B).

PMR($CDCl_3$) : $\underline{CH_3}CH_2$-(3H, t, 0.86 ppm), two  and $-(\underline{CH_2})_n-$(~38H, 2S, 1.25 and 1.31 ppm), $-O\underline{CH}$, $O\underline{CH_2}$ (5H, m, 3.34-4.2 ppm).

IR (neat) : 1460, 1368, 1245, 1210, 1155, 1060, 880, 850 cm^{-1}. It was identified as mixture of C_{16}-C_{21} xylo-tetrol bis-acetonides by direct comparison with the authentic sample (NMR, IR and mixed GC).

Unsaturated tetrols bis-acetonides (Type-III)

GLC analysis of this type showed presence of at least three compounds RRT (% present) of 4.35(13.2 %), 5.77(8.31%) and 8.31(76.6 %). All the three compounds were separated from mixture (~3g) by preparative GLC (column 20% SE-30, 270°) same as above.

(1) Tetrol bis-acetonide RRT 4.35(1.2g), b.p. 147-150°/0.2 mm $[\alpha]_D^{23}$ + 20 (C 0.465%, $CDCl_3$) 97% pure GC).

Mass spectrum : m/e 396(M^+, 72.2%), 101(100%), 295(97.8%), 381(97.8%), 59(95%), 237(80.38%), 55(72.7%), 81(68.5%), 94(65.7%), 95(64.3%), 180(43.48%), 338(48.9%), 157(32.85%)(Found : C 72.34%; H 11.19%, $C_{24}H_{44}O_4$ requires C 72.72%; H 11.11%). It was identified as 1,2:3,4-O-bis-isopropylidene-xylo-octadec-8(Z)-ene-1,2,3,4-tetrol (36) by its spectral data (NMR, IR, Mass).

(2) Tetrol bis-acetonide RRT 5.77 (48 mg), b.p. 180°(bath)/0.2 mm. $[\alpha]_D^{23}$ = + 15° (C 0.305%, MeOH), 90% pure (GC).

Mass spectrum : m/e 410 (M^+, 18.9%), 101(100%), 309(81.9%), 395(84%), 59 (58.9%), 352(39.9%), 69(38.85%), 95(37.8%), 83(35.7%), 81(28.35%), 97(26.25%), 109(18.9%), 337(10.5%),(Found C 69.76 %, H 9.996 %. $C_{25}H_{46}O_4$ requires C 73.17%, H 11.21%). It was identified as 1,2:3,4-O-bis-isopropylidene-xylo-nonadecene-1,2,3,4-tetrol

(3) Tetrol bis-acetonide RRT 8.31 (150 mg), b.p. ~180° (bath)/0.2 mm. $[\alpha]_D^{23}$ = + 20.84° (C 1.18%, MeOH). 98% pure (GC).

Mass spectrum : m/e 424 (M^+, 55%), 101(100%), 366(99.8%), 323 (93%),409 (93%), 55(97%), 59(89%), 69(62%), 324(60%), 95(48%), 97(43%), 351(28%), 308 (26%). (Found : C 73.16%; H 11.24%, $C_{26}H_{48}O_4$ require : C 73.58%, H 11.32%). It was identified as 1,2:3,4-O-bis-isopropylidine-xylo-eicos-14(Z)-ene-1,2,3,4-tetrol (38).

Regeneration of tetrol from tetrol bis-acetonide (RRT 8.31)

The tetrol bis-acetonide (0.139 g, 0.45 m, mole) in aq. dioxane (90%, 3ml) was treated with Amberlyst-15 resins (95 mg) and refluxed (90°C) for 4 hrs. The reaction mixture was then diluted with $CHCl_3$ (10ml) and filtered. Solvent removal furnished tetrol as gummy solid (153 mg), TLC

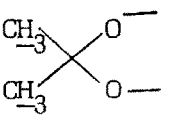
essentially single spot (80% EtOAc in pet.ether, Rf 0.18). The crude tetrol was purified by chromatography on chromatotron (rotor 1mm) and eluted with 40% EtOAc in pet.ether (100 ml) and then 80% EtOAc in pet.ether (200ml) Second fraction furnished TLC pure tetrol (132.24 mg, 84.45%).

Regeneration of tetrol from tetrol bis-acetonide (RRT 4.35)

Regeneration of tetrol from tetrol bis-acetonide RRT 4.35 (30 mg) was also carried out under similar condition as above. The crude tetrol (25 mg) after purification on chromatotron furnished pure product (11 mg, 46%), TLC single spot (Rf 0.18).

Hydrogenation of tetrol bis-acetonide (RRT 4.35)

Tetrol bis-acetonide (14 mg) in 2 ml ethanol was treated with 5% rhodium on alumina (5 mg) and stirred for 1 hr in hydrogen atmosphere. It was then filtered through celite, which after solvent removal furnished light yellow liquid (14 mg). Distillation of crude product [b.p. 190°(bath temp.)/0.4 mm] furnished colourless liquid (12 mg, 84.5%), GC 96.6% pure (column 10% OV-4, 230°)

PMR(CCl_4)δ: CH_3CH_2 (3H, t, 0.89 ppm), two  and $(CH_2)_{15}$ (42H, 2S, 1.26 and 1.31 ppm), OCH_2(1H, dd, 3.5 ppm, J=10 Hz, J_2 = 2 Hz; 1H, m, 3.9 ppm), OCH (3H, bm, 3.7-4.2 ppm).

IR(neat) : 1460, 1365, 1240, 1150, 1090, 1060, 990, 960, 870, 850, 800, 790 cm^{-1}.

It was identified as 1,2:3,4-O-bis-isopropylidene-xylo-octadecan-1,2,3,4-tetrol by direct comparison with the authentic sample (NMR, IR, GC).

Hydrogenation of tetrol bis-acetonide (RRT 8.31)

Hydrogenation of tetrol bis-acetonide (28 mg) was carried out under similar condition as above. Distillation of crude product (27 mg) at ~190°C (bath)/0.4 mm, furnished colourless liquid (25 mg, 87%), GC 97.6% pure. Its NMR and IR spectrum are virtually superimposable with that of hydrogenated product obtained from tetrol bis-acetonide RRT 4.35 except for CH_2 count. It was identified as 1,2:3,4-O-bis-isopropylidene-xylo-eicosane-1,2,3,4-tetrol by comparison with the authentic sample (NMR, IR, GC).

Regeneration of tetrol from hydrogenated tetrol bis-acetonide RRT 4.35 and RRT 8.31.

Regeneration of tetrols from hydrogenated tetrol bis-acetonide RRT 4.35 (11 mg) and RRT 8.31 (13 mg) were separately carried out with aq. dioxane (90%, 1 ml) and Amberlyst-15 resins (5 mg) under similar conditions as mentioned earlier. The crude tetrols, a waxy light yellow solid (~8mg) were recrystallized from ethanol to afford white crystalline solids (~5 mg) TLC single spot (Rf 0.18, 80% EtOAc in pet.ether). IR spectrum of both the tetrols were superimposable with each other.

IR(KBr) : 3460, 3330, 1480, 1315, 1150, 1085, 935, 870, 805, 725, 700 cm^{-1}.

Tetrol (RRT 4.35) was identified as xylo-octadecan-1,2,3,4-tetrol (m.p. 78-81°C, reported[5c] m.p. 80-82°C) and tetrol (RRT 8.31) was identified as xylo-eicosane-1,2,3,4-tetrol (m.p. 83-86°C, reported[5c] m.p. 85-87°C) by comparison with the authentic samples (NMR, IR).

Position of double bond in tetrols.

Reductive ozonolysis of C-18 unsaturated tetrol bis-acetonide (RRT 4.35)(36)

Unsaturated tetrol bis-acetonide (36 mg, 0.09 m. mole) RRT 4.35 was taken in 25 ml methanol and chilled the contents in assembly for ozonation to -18°C. Initially oxygen was passed (pressure 6 psi) through the reaction mixture at the rate of 0.5 lit/min. for 30 mins and then ozone was passed under similar condition (voltage 7 eV) for calculated time (~ 4 mins.). The reaction was monitored by TLC (disappearance of starting material). The content was then transferred to a three necked round bottom flask equipped with thermowell, dropping funnel and condenser. The ozonide was cooled to -5°C and aq. ethanolic solution of $NaBH_4$ [40 mg in 0.6 ml aq. ethanol (50%)] was added. Allowed the temperature to rise to room temp. The reaction mixture was stirred for 2 hrs. and then chilled it to -10°C. Slowly added 10% solution of acetic acid (frothing occurs) to pH 6-7. Methanol was removed from the mixture and residue was extracted with chloroform, which after usual work up furnished gummy liquid (30 mg). Which on TLC showed major two spots (Rf 0.57 and 0.07, 15% EtOAc in pet.ether). It was chromatographed on a chromatotron as follows :

TABLE - 4 CHROMATOGRAM - 4

Material 27 mg.

Adsorbent SiO_2 gel.

Thickness of plate (rotor) : 1mm

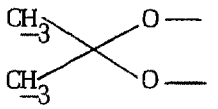
Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
01.	20% EtOAc in pet.ether	10 ml x 3	2	
02.	..do..	..do..	8	TLC single spot.
03.	..do..	..do..	1	
04.	..do..	..do.. -	-	
05.	40% EtOAc in pet.ether	10 ml x 4	3	

06.	40% EtOAc in pet.ether	10 ml x 2	11	TLC pure compound.
07.	40% EtOAc in pet.ether	10 ml x 2	2	
		Total :	27	

Decanol : Fraction -2 furnished colourless liquid (8 mg), GC 94.4% pure (10% OV-4, 110°), identified as decanol by comparison (IR mixed GC) with the authentic compound.

Alcohol of bis-acetonide part :

Fraction-6 furnished colourless liquid, GC 94.36% pure (10% OV-4, 170°).

PMR (CCl_4)δ: CH_2OH, CH_2O(3 H, m, 3.58 ppm; 1H, m, 3.9 ppm); CH-O (3H, m, 3.8-4.15 ppm); $(CH_2)_n$, two  (18H, 2s, 1.32 and 1.55 ppm).

IR(neat) : 3425, 1735, 1455, 1365, 1245, 1210, 1155, 1066, 870, 840 cm^{-1}.

It was identified as Alcohol of bis-acetonide (35) part from the spectral data (NMR, IR).

Reductive ozonolysis of C_{19}-unsaturated tetrol bis-acetonide (RRT 5.77)

Reductive ozonolysis of unsaturated tetrol bis-acetonide RRT 5.77 (11 mg) furnished light yellow liquid (5 mg) after purification, TLC single spot (Rf 0.4, 15% EtOAc in pet.ether). Its GC analysis (10% OV-4, 230°) showed it to be a mixture of major two compounds. It was identified as mixture of alcohols derived from tetrol bis-acetonide part (IR).

Reductive ozonolysis of C_{20}-unsaturated tetrol bis-acetonide (RRT 8.31) (38).

Reductive ozonolysis of tetrol bis-acetonide RRT 8.31 (308 mg, 0.72 m.mole) furnished gummy liquid (308 mg). Which on TLC showed major

one compound (~90%) (Rf 0.36, 15% EtOAc in pet.ether). The crude product was chromatographed on chromatotron as follows.

TABLE - 5 CHROMATOGRAM - 5

Material 0.308 g.

Adsorbent Silica gel.

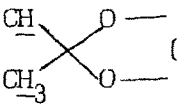
Thickness of rotor : 2 mm.

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
01.	5 % EtOAc in pet.ether	30 ml x 3	0.0184	
02.	5 % EtOAc in pet.ether	30 ml x 1	0.0118	
03.	7 % EtOAc in pet.ether	100 ml x 1	0.0090	
04.	8 % EtOAc in pet.ether	15 ml x 8	0.0090	
05.	12% EtOAc in pet.ether	25 ml x 4	0.0111	
06.	12% EtOAc in pet.ether100	100 ml x 1	0.0073	
07.	20% EtOAc in pet.ether	50 ml x 2	0.2072	TLC pure compound
08.	Methanol	100 ml x 1	0.0184	
		Total :	0.2832 g	

Alcohols of tetrol bis-acetonide

Fraction-7 (207 mg) was distilled [b.p. ~ 170-180°C(bath)/2 mm] to get colourless liquid (200 mg, 65%), TLC single spot (Rf 0.36, 15% EtOAc in pet.ether). Its GC analysis (10% OV-4, 230°) showed it to be a mixture of major four compounds with RRT (% present) 1.74(7.2%), 2.84(10.6), 3.72(53.8 %) and 4.78(14.91%) respectively.

Mass spectrum : m/e 358 (M^+, 40%), 101(100%), 59(94%), 343(92%), 95(50%), 257(26%), 157(20%), 163(16%), 239(14%), 285(8%).

PMR (CCl_4)δ : $(CH_2)_n$, two  (~30H, bs, 1.3 ppm), CH_2OH, CH_2-O

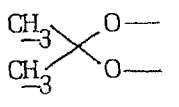
(3H, m, 3.55 ppm; 1H,m, 3.9 ppm), CH-O(3H,m, 3.7-4.15 ppm).

IR(neat) : 3450, 1455, 1370, 1245, 1210, 1150, 1060, 875 cm^{-1}.

From spectral data and GC it was identified as a mixture of alcohols (major 37) derived from tetrol bis-acetonide part. Alcohol RRT 3.72 (53.3 %) probably derived from cleavage of double bond at C_{14}-C_{15} (from mass spectrum) of C_{20} tetrol bis-acetonide (38).

Acetate of alcohols derive from cleavage of C_{20} unsaturated tetrol bis-acetonide (RRT 8.31)

The alcohols of bis-acetonide portion (major 37, 45 mg) in pyridine (1 ml) was acetylated with AC_2O (1 ml) at 25° for 20 hrs, to furnish crude acetate as yellow liquid (47 mg). Distillation of crude product [145°(bath)/ 100 mm] furnished colourless liqui (40 mg), TLC single spot (10% EtOAc in pet.ether). Its GC analysis showed to be a mixture of major four compounds.

PMR (CCl_4) : $(CH_2)_n$, two  (~30 H, bs, 1.3 ppm), CH_3CO

(3H, s, 1.95 ppm), CH_2OAC, CHO (5 H, m, 3.7-4.1 ppm), CH_2-OC(1 H, dd, 3.5 ppm, J_1=9 Hz, J_2 = 2 Hz; 1H, m, 3.9 ppm).

IR(neat) : 1740, 1465, 1370, 1240, 1165, 1070, 885, 855 cm^{-1}.

It was identified as mixture of acetate of alcohols derived from bis-acetonide part.

Chart - 8 : Scheme - 2

H_5IO_6 - Oxidation of tetrol (39)

The tetrol (144 mg, 0.41 m.mole) in dioxane (5 ml) was treated with 6 ml H_5IO_6 solution (stock solution 1 g H_5IO_6 + 2 ml H_2O + 15 ml dioxane) and left in a dark room at 25°/15 hrs. Unreacted periodic acid was neutralized by adding saturated solutions of $NaHCO_3$. Dioxane was removed on rotavapor (80°/100 mm) and residue after diluting with water (10 ml), extracted with $CHCl_3$ (20 ml x 4). Which after work-up furnished faint yellow oil (100 mg, 94.8%).

Reduction of aldehyde (40) with $NaBH_4$

Aldehyde (100 mg, 0.039 m.mole) in methanol (3 ml) was chilled to -5°C and to that was added aq. solution of $NaBH_4$ (100 mg in 2 ml 50% ethanol (aq.)]. The mixture was stirred at room temp. (~30°C) for 2 hrs (TLC monitoring) and then chilled the mixture to -15°C. Excess of $NaBH_4$ was destroyed by adding 10% aq. solution of CH_3COOH to pH 6-7. Methanol was removed from the mixture and residue after diluting with water (3 ml) extracted with $CHCl_3$ (10 ml x 5), which after work-up and solvent removal furnished colourless liquid (93 mg). It was purified on chromatotron as follows.

TABLE - 6 CHROMATOGRAM - 6

Material 90 mg.

Adsorbent SiO_2 gel

Thickness of plate (rotor) : 1 mm.

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(mg)	Remarks
01.	6% EtOAc in pet.ether	10 ml x 5	03	
02.	6% EtOAc in pet.ether	10 ml x 4	75	TLC PURE compound
03.	10% EtOAc in pet.ether	10 ml x 5	05	
04.	EtOAc	50 ml x 1	05	
		TOTAL :	88	

Fraction-2 (75 mg) was distilled at 130-140°C (bath temp.)/1 mm to furnish colourless oil (72 mg, 70% yield), TLC single spot (Rf 0.54, 10% EtOAc in pet.ether). GC 91.5% pure (10% OV-4, 200°C).

Mass spectrum : m/e 254 (M^+, 2%), 82(100%), 55(88.2%), 96(84%), 68(48.72%) 110(35.28%), 236(20.16%), 138(12.6%), 152(7.56%), 208(6%), 180(5.88%), 194 (3.5%), 222(2.5%).

PMR(CCl_4)δ: $\underline{CH_3}CH_2$ (3 H, t, 0.9 ppm , J= 7Hz), $(\underline{CH_2})_{11}$ (~22H, bs, 1.3 ppm), $\underline{CH_2}$-CH=CH-$\underline{CH_2}$(4 H, m, 2.2 ppm), $\underline{CH}$=$\underline{CH}$ (2H, m, 5.28 ppm), $\underline{CH_2}$-OH (2H, t, 3.56 ppm, J=6 Hz).

IR(neat) : 3380, 1480 and 1070 cm^{-1}.

It was identified as C_{17}- unsaturated alcohol (41).

Epoxidation of C_{17}- unsaturated alcohol (41)

C_{17}-unsaturated alcohol (70 mg, 0.27 m.mole) in 3.5 ml methylene chloride was chilled to 0°C. To that was added peroxyacetic acid (50%, 3 ml) and mixture was stirred at 8-12° for 1 hr and 15-20° for 2 hrs (TLC monitoring, 20% EtOAc in pet.ether). It was then diluted with $CHCl_3$(10 ml) and washed with water (3 ml x 3), 10% Na_2CO_3 (2 ml x 3), Water (3 ml x 3) brine (3 ml x 1) and dried (Na_2SO_4). Solvent removal furnished colourless liquid (70 mg, 91.5%), TLC single spot (Rf 0.43, 20% EtOAc in pet.ether). GC 90% pure (10% OV-4, 200°).

Mass spectrum : m/e 270 (M^+, 2.1%), 55(100%), 82(86%), 69(70%), 95(55%), 68((45%), 96(40%), 71(22%), 199(20%), 71(26%), 213(7%).

PMR (CCl_4) : $\underline{CH_3}$-CH_2 (3H, bt, 0.92 ppm), $(\underline{CH_2})_{13}$(~ 26H, 2S, 1.31 and 1.4 ppm), $\underline{CH}$-O(2H, m, 2.72 ppm), $\underline{CH_2}$-OH(2H, t, 3.54 ppm, J=6 Hz).

IR (neat) : 3400, 1480, 1275, 1090, 905, 855, 745 cm^{-1}.

It was identified as C_{17}-epoxy alcohol (42).

Acid cleavage of C_{17}- epoxy alcohol (42)

A solution of C_{17}-epoxy alcohol (70 mg, 0.25 m.mole) in 2 ml of tetrahydrofuran (THF) was treated with 0.3 ml of 25% (aq.) perchloric acid and stirred at 20-25° for 5 hrs (TLC monitoring). Excess of acid was neutralized by adding saturated solution of $NaHCO_3$. THF was removed and residue after diluted with water (1 ml) extracted with $CHCl_3$ (5 ml x 3), which after usual work up gave viscous oil (50 mg). Crude product was purified by chromatography on chromatotron (1 mm plate) by eluting with 25% EtOAc in pet.ether and then 50% EtOAc in pet.ether. Later fraction furnished colourless liquid (20 mg, 26.78%), TLC single spot (Rf 0.68, 60% EtOAc in pet.ether).

Mass spectrum : m/e 95(100%), 187(84%), 83(77.2%), 55(73.92%), 81(51.84%), 109(45.3%), 151(28.56%), 174(25.7%), 201(18.46%).

PMR($CDCl_3$)δ: CH_3CH_2 (3H, bt, 0.92 ppm), $(CH_2)_{13}$(~26H, bm, 1.2-1.9 ppm), CH_2-OH (2H, t, 3.65, J=6 Hz), CH-OH (2H, m, 3.41 ppm).

IR (neat) : 3400, 1460, 1320, 1135, 1065, 855, 715 cm^{-1}.

It was identified as C_{17}-triol (43).

H_5IO_6 - Oxidation of triol (43)

Oxidation of the triol (20 mg, 0.07 m.mole) with periodic acid was carried out under similar condition as mentioned earlier. The crude aldehyde (14 mg) was subjected for reduction.

Reduction of aldehyde

Reduction of aldehyde (14 mg) with $NaBH_4$ was carried out as mentioned earlier. The crude product (11 mg) was purified on chromatotron by eluting with 20% EtOAc in pet.ether (30 ml) and then 40% EtOAc in pet.ether (30 ml). Fraction-2 furnished gummy solid (8 mg), TLC single spot (Rf 0.3, 40% EtOAc in pet.ether). Its GC analysis (10% OV-4, 170°) showed it to be a mixture of three compounds.

Mass specturm : m/e 69(100%), 96(72.6%), 55(66%), 82(62.7%), 110(35.2%), 109(34.1%), 68(35.2%), 124(13.2%), 138(7.7%), 152(3%).

PMR (CCl_4)δ: $(CH_2)_n$ (~18H, bs, 1.3 ppm), CH_2OH(4H, t, 3.65 ppm, J=6 Hz).

IR(neat) : 3450, 1480, 1070 cm^{-1}.

It was identified as a mixture of diols (44), and a major diol (61%) present in the mixture was identified as 1,11-undecandiol (57) by comparison with the authentic sample (NMR, IR, GC).

Chart - 8 : Scheme - 3

Acetylation of C_{17}- unsaturated alcohol (41)

The C_{17}-unsaturated alcohol (122 mg, 0.48 m.mole) in dry pyridine (1 ml) was acetylated with Ac_2O(1 ml) at 25° for 20 hrs as mentioned earlier, to furnish crude acetate as yellow liquid (130 mg). Distillation of crude product at 100°(bath)/0.3 mm gave colourless liquid (126 mg, 88.6%), TLC single spot (Rf 0.77, 20% EtOAc in pet.ether). GC 96.8% pure (10% OV-4, 200°).

PMR (CCl_4) : CH_3CH_2 (3H, bt, 0.9 ppm), $(CH_2)_{11}$ (~ 22H, bs, 1.3 ppm), CH_2-CH=CH-CH_2, CH_3CO(7H, bs, 1.95 ppm), CH=CH (2H, m, 5.29 ppm), CH_2-OAc (2H, t, 3.99 ppm, J=7 Hz).

IR (neat) : 1745, 1470, 1270, 1235, 1040 cm^{-1}.

It was identified as acetate of C_{17}-unsaturated alcohol (46).

Reductive ozonolysis of acetate of C_{17} unsaturated alcohol (46)

Reductive ozonolysis of acetate of C_{17}-unsaturated alcohol (46) (125 mg, 0.42 m.mole) was carried as mentioned earlier, to get cleaved product as colourless liquid (120 mg). TLC showed major one spot (Rf 0.5, 20% EtOAc in pet.ether. GC showed it to be a mixture of more than four compounds.

PMR (CCl_4) : $(CH_2)_n$ (~18H, bs, 1.3 ppm), CH_2OAc (2H, t, 3.51 ppm, J=6 Hz, CH_2OH (2H, t, 3.51 ppm, J=6 Hz), CH_3-CO (3H, s, 1.98 ppm).

IR (neat) : 3400, 1750, 1475, 1380, 1250, 1060 cm^{-1}.

It was identified as mixture of mono acetylated C_{17}-diols (47).

Acetylation of mono-acetylated diols (47)

Acetylation of mono-acetylated diols (95 mg) was carried out as mentioned earlier to get crude diacetate (50) as liquid (103 mg), which on distillation at 100°(bath)/0.3 mm gave colourless liquid (90 mg). TLC single spot (Rf 0.41, 10% EtOAc in pet.ether). GC analysis showed it to be a mixture of at least four compounds (10% OV-4, 190°).

PMR (CCl_4) : $(CH_2)_n$(~18H, bs, 1.3 ppm), CH_2OAc (4H, t, 3.64 ppm, J=6 Hz), CH_3CO (6H, s, 1.96 ppm).

IR (neat) : 1745, 1475, 1370, 1240, 1040 cm^{-1}.

It was identified as mixture of diacetate (Fig. 24) and the major compound (63.17%) present in the mixture was identified as 1,11-undecan diacetate

by co-injection (GC) with the authentic sample and spectral data.

Hydrolysis of mono-acetylated diols (47)

Mono-acetylated diols (25 mg) in 2 ml methanol was treated with 1 ml 15% aq. NaOH and refluxed it for 10 mins (90°C). Methanol was removed and residue after diluting with water (5 ml), extracted with solvent ether (10 ml x 3), which after solvent removal furnished crude diols as viscous liquid (19 mg). Distillation of crude product at 140-150° (bath)/0.3 mm gave white solid (17 mg) m.p. 48-50°C. TLC single spot (Rf 0.3, 40% EtOAc in pet.ether). GC showed it to be a mixture of at least four compounds (10% OV-4, 170°).

PMR($CDCl_3$) : $(CH_2)_n$(~18H, bs, 1.3 ppm), $\underline{CH_2}OH$(4H, t, 3.64 ppm, J=6 Hz).

IR(Nujol) : 3400, 1125, 1020, 940, 720 cm^{-1}.

It was identified as a mixture of diols and a major compound present (67%) in the mixture was identified as 1,11-undecandiol by co-injection (GC) with the authentic sample.

Chart-9

Esterification of 10-undecenoic acid (51)

10-Undecenoic acid (17 g, 92 m.mole) in 125 ml dry methanol (20 ml) was treated with 0.5 g p-toluenesulphonic acid and refluxed it for 8 hrs (90°C). Methanol (~100 ml) was removed and residue after diluting with water (100 ml), extracted with solvent ether (25 ml x 5), which after usual work-up furnished light yellow liquid (18 g). It was distilled (117°/12mm) to get colourless liquid (17.2 g, 92.7%), TLC single spot (Rf 0.8, 10% EtOAc in pet.ether). GC 99.7% pure (10% OV-4, 170°).

PMR (CCl_4)δ: $(CH_2)_6$ (12H, bs, 1.3 ppm), OCH_3 (3H, s, 3.6 ppm), CH_2=CH (2H, m, 4.8-5.05 ppm), CH_2=CH (1H, m, 5.5-6 ppm), CH_2-CH= (2H, m, 2.05 ppm), CH_2CO (2H, t, 2.2 ppm, J= 8 Hz).

IR (neat) : 1730, 1635, 1460, 1430, 1366, 1190, 1165, 1066, 980, 900 cm^{-1}

It was identified as methyl 10-undecenoate (52).

Reduction of methyl 10-undecenoate (52)

Methyl 10-undecenoate (7 g, 35 m.mole) in dry ether (70 ml) was treated with lithium aluminium hydride (2 g) at 5°C and then stirred for 2 hrs at 25°C. (TLC monitoring, 10% EtOAc in pet.ether). Excess of LAH was destroyed after diluting the reaction mixture with ether (30 ml) by dropwise addition of H_2O at -5°C. It was then filtered through celite, and ether layer after separation from aq. portion washed with brine (20 ml x 2) and dried (Na_2SO_4). Solvent removal furnished light yellow liquid (5.3 g), which on distillation at 105-108°/0.9 mm furnished colourless liquid (5 gm, 84.03%), TLC single spot (Rf 0.36). GC 99.5% pure.

PMR (CCl_4)δ: $(CH_2)_7$ (14H, bs, 1.31 ppm), CH_2=CH (2H, m, 4.8-5.1 ppm), CH_2=CH (1H, m, 5.5-5.95 ppm), CH_2-CH= (2H, m, 2.05 ppm), CH_2OH (2H, t, 3.65 ppm) J=5.5 Hz).

IR (neat) : 3420, 1640, 1465, 1050, 900 cm^{-1}.

It was identified as 10-undecenol (53).

Acetylation of 10-undecenol (53)

Acetate of 10-undecenol (1.8 g, 10.9 m.mole) was prepared with AC_2O and pyridine as mentioned earlier, which after distillation of crude product (2 g) at 100°/0.3 mm furnished colourless liquid (1.9 g, 82.88%)

TLC single spot (Rf 0.85, 10% EtOAc in pet.ether), GC 99.6% pure (10% OV-4, 130°).

PMR (CCl_4) : $(CH_2)_7$ (14H, bs, 1.3 ppm), CH_3CO, $CH_2CH=$ (5H, bs, 1.95 ppm) $CH_2=CH$ (2H, m, 4.75-5.1 ppm), $CH_2=CH$ (1H, m, 4.75-5.1 ppm), CH_2-OAc (2H, t, 3.95 ppm, J=6 Hz).

IR (neat) : 1735, 1640, 1465, 1360, 1230, 1030, 900 cm^{-1}.

It was identified as 10-undecenyl acetate (54)

HBr addition to 10-undecenyl acetate (54)

10-Undecenyl acetate (403 mg., 1.9 m.mole) in dry pet.ether (10 ml) was treated with freshly crystallised benzoyl peroxide (25 mg) and cooled to 10°. A rapid steam of dry HBr (generated[38] from reaction of Br_2, and tetralin) was passed through the reaction mixture for 30 mins and then reaction mixture was kept in a refrigerator for 10 hrs. (GC monitoring, 10% OV-4, 170°) It was diluted with solvent ether (~ 20 ml) and washed with saturated solution of $NaHCO_3$ (20 ml x 5), H_2O (20 ml x 3), brine (20 ml x 2) and dried (Na_2SO_4), solvent removal furnished light yellow liquid (462 mg). It was distilled at 112-114°C/0.1 mm to get colourless liquid, TLC single spot (Rf 0.41). GC showed it to be a mixture of two compounds (80.4% and 11.12%).

PMR (CCl_4) : $(CH_2)_9$ (~18H, bs, 1.3 ppm), CH_2Br (2H, t, 3.34 ppm, J=7 Hz) CH_2OAc (2H, t, 3.99 ppm, J=7 Hz), OCH_3 (3H, s, 1.97 ppm).

IR (neat) : 1735, 1465, 1165, 1235, 1035, 710 cm^{-1}.

Major compound was identified as 11-bromoundecanyl acetate (55) from spectral data.

Acetylation of 11-bromo-undecanyl acetate (55)

A mixture of 1-bromo undecanyl acetate (400 mg, 1.36 m.mole) in CH_3COOH (1 ml) and anhydrous (freshly fused) NaOAc (0.3 g) was refluxed at 150-160° for 4 hrs in an oil bath (TLC monitoring, 10% EtOAc in pet.ether). It was then diluted with water (10 ml) and excess of CH_3COOH was neutralized with saturated solution of $NaHCO_3$. The mixture was extracted with pet.ether (10 ml x 3), which after work-up furnished colourless liquid (390 mg). It was purified by chromatography on chromatotron as follows.

Table - 7 CHROMATOGRAM - 7

Material : 390 mg

Adsorbent : SiO_2 gel

Thickness of plate (rotor) : 2 mm

Fr. No.	Eluent	Vol. of Fr.(ml.)	Wt. of Fr.(g)	Remarks
01.	0.25 EtOAc in pet.ether	100 ml x 1	0.040	
02.	10% EtOAc in pet.ether	10 ml x 2	0.008	
03.	10% EtOAc in pet.ether	10 ml x 1	0.052	
04.	10% EtOAc in pet.ether	10 ml x 3	0.260	TLC pure compound
05.	10% EtOAc in pet.ether	10 ml x 3	-	
06.	Methanol	100 ml x 1	0.030	
		Total :	0.390	

1,11-undecandiacetate

Fraction-4 (260 mg) on distillation [120°(bath)/0.3 mm] furnished colourless liquid (255 mg, 68.73 %). TLC single spot (Rf 0.41, 10% EtOAc in pet.ether), GC 90.84% (10% OV-4, 190°).

PMR (CCl_4)δ: $(CH_2)_9$(~18H, bs, 1.3 ppm), CH_2-OAc(4H,t, 3.98 ppm, J=7Hz), OCH_3 (6H, s, 1.95 ppm).

IR (neat) : 1740, 1365, 1235, 1035 cm^{-1}.

It was identified as 1,11-undecandiacetate (56) from spectral data.

Hydrolysis of 1,11-undecandiacetate (56)

Hydrolysis of 1,11-undecandiacetate (137 mg, 0.5 m.mole) with aq. NaOH was carried out under the condition as mentioned earlier to get crude diol as a gummy liquid (80 mg). It was distilled at 140-150° (bath)/ 0.03 mm to get diol (70 mg, 74%) as white solid (m.p. 58-61°C). TLC single spot (Rf 0.3, 40% EtOAc in pet.ether) GC 89.3% pure (10% OV-4, 170°).

PMR ($CDCl_3$) : $(CH_2)_9$ (18H, bs, 1.3 ppm), CH_2OH(4H, t, 3.64 ppm, J=3.64 Hz)

IR (nujol) : 3380, 1125, 1045, 1020, 980, 940, 890 cm^{-1}.

It was identified as 1,11-undecanoliol (57).

* * *

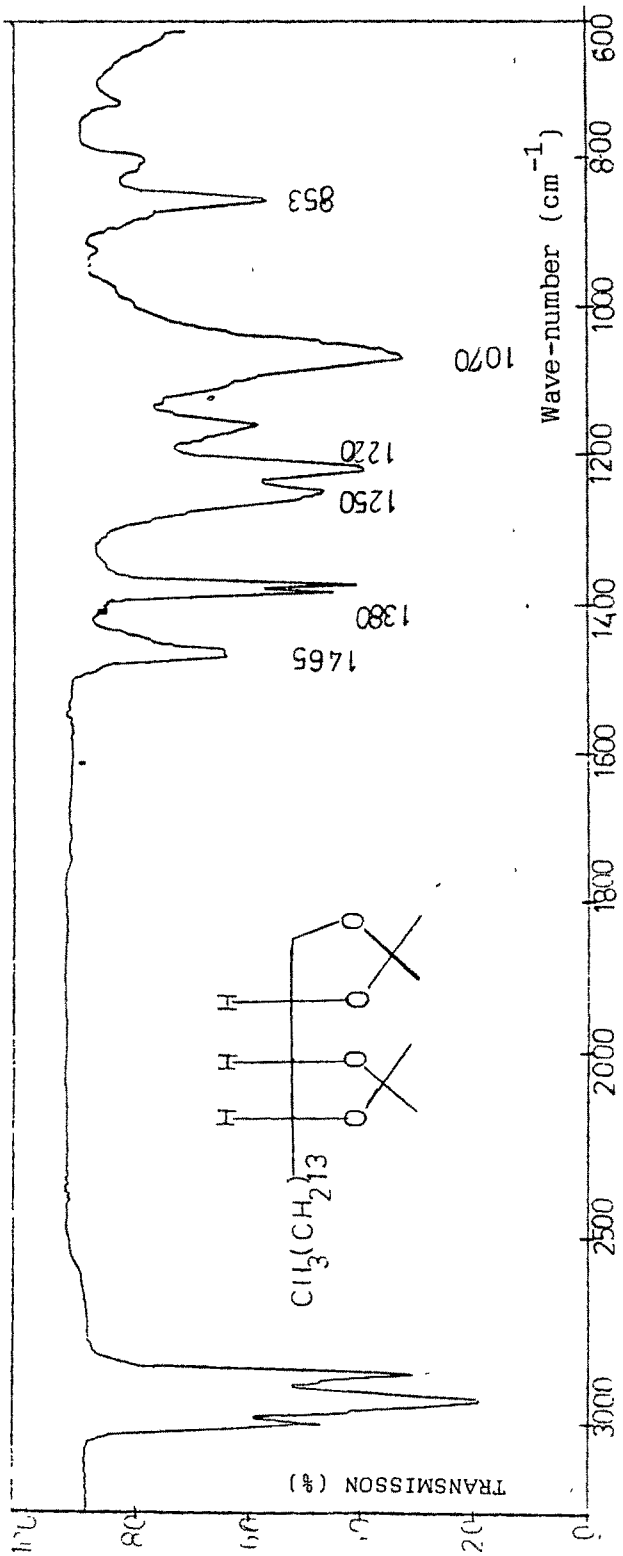


FIG. 5 - IR SPECTRUM OF 1,2:3,4-O-BIS- ISOPROPYLIDENE-RIBO-OCTACECANE-1,2,3,4-TETROL

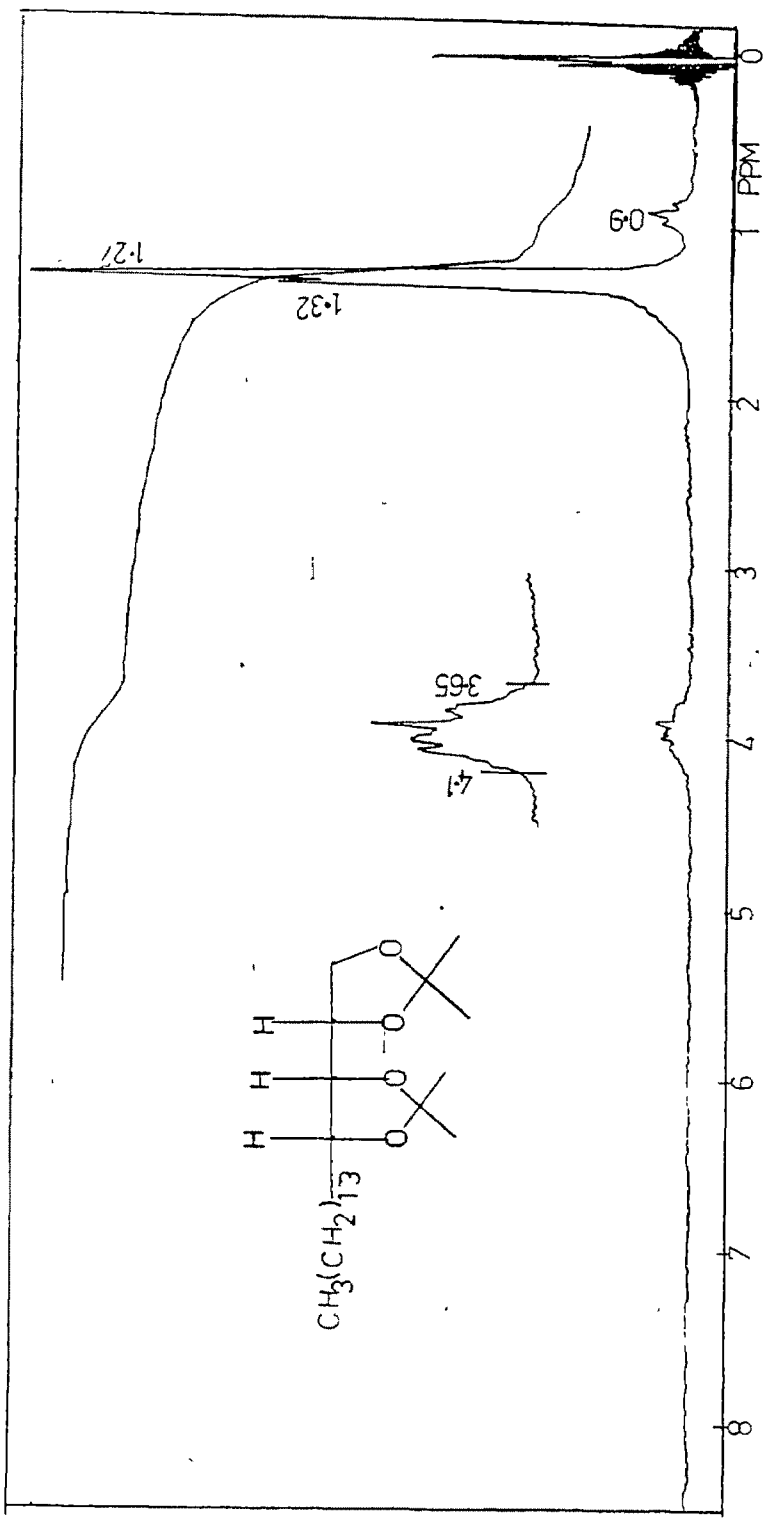


FIG. 6 - PMR SPECTRUM OF 1,2:3,4-O-BIS- ISOPROPYLIDENE-RIBO-OCTADECANE-1,2,3,4-TETROL.

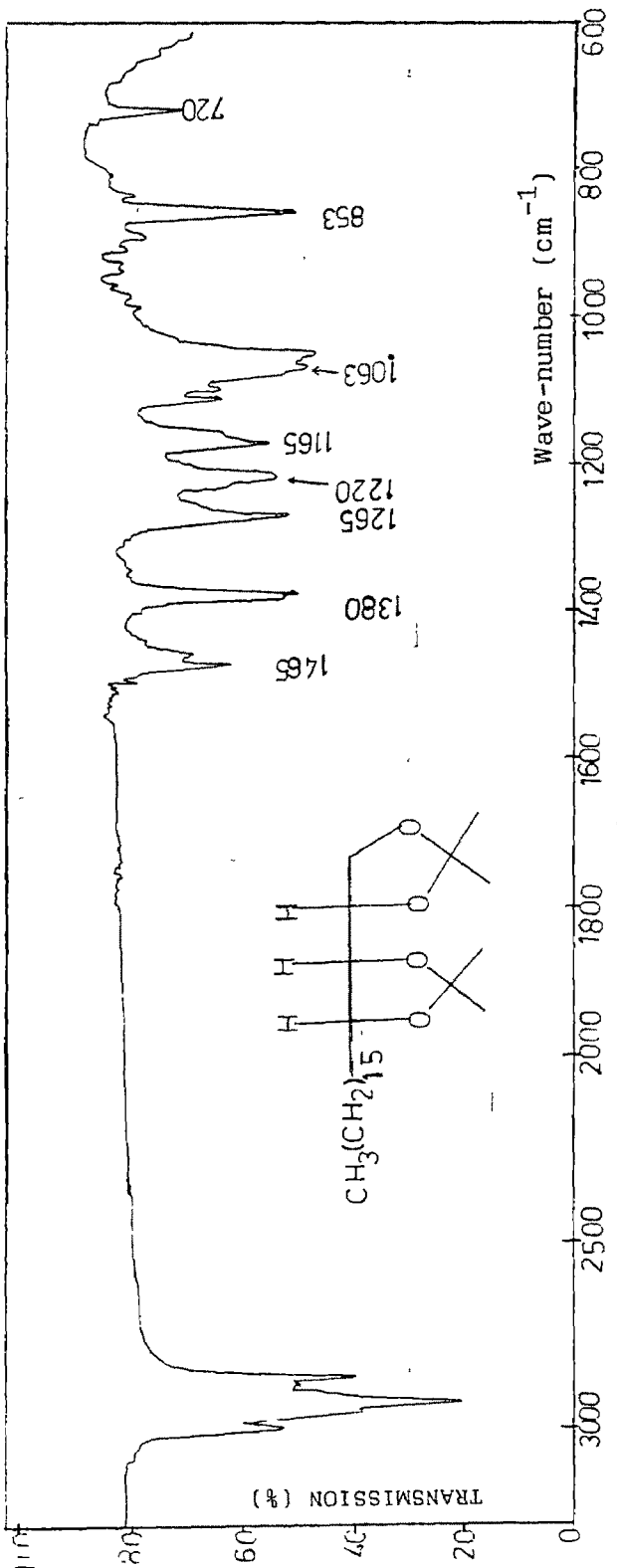


FIG. 7 - IR SPECTRUM OF 1,2:3,4-O-BIS- ISOPROPYLIDENE-RIBO-EICOSANE-1,2,3,4-TETROL.

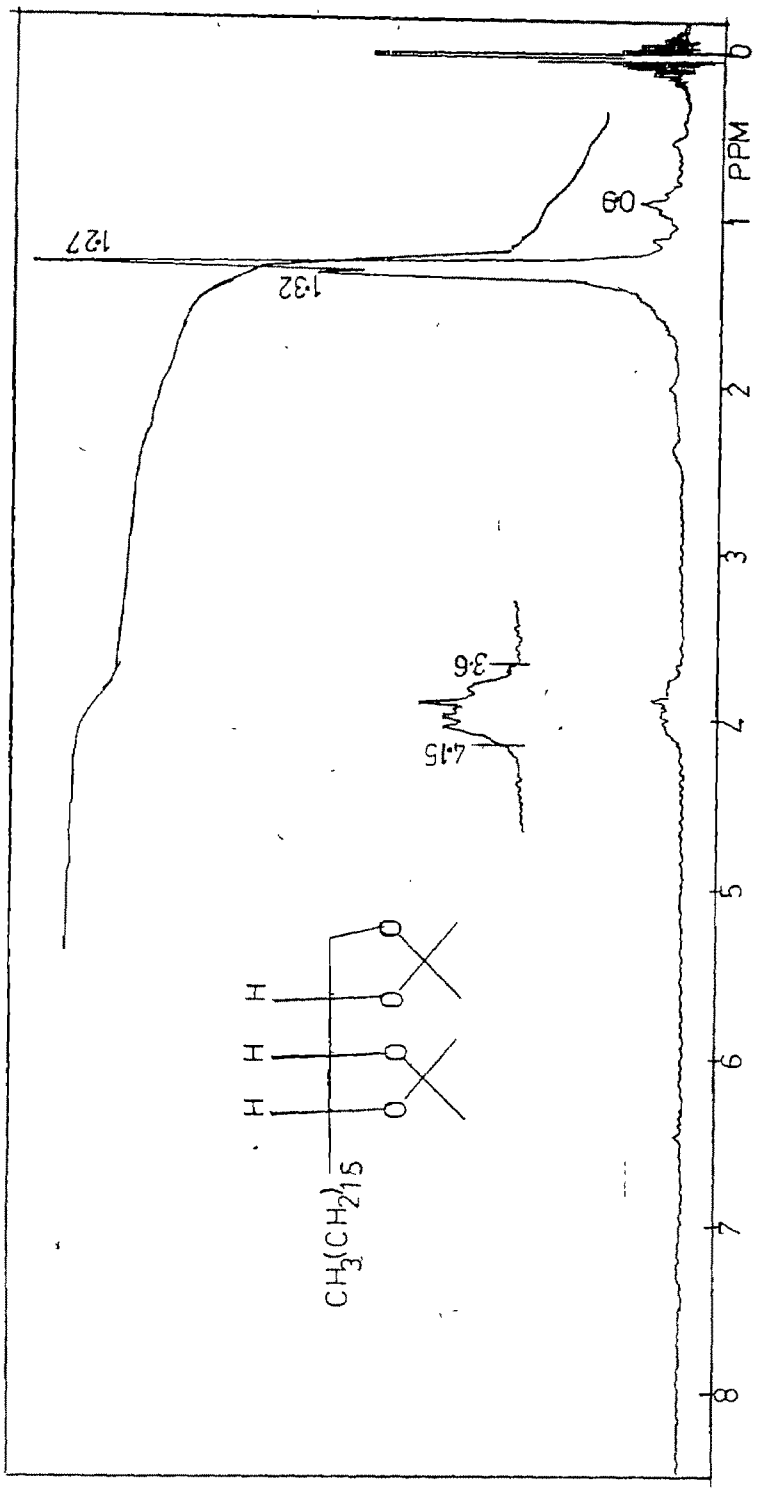


FIG. 8 : PMR SPECTRUM OF 1.2:3.4-O-BIS- ISOPROPYLIDENE-RIBO-EICOSANE-1,2,3,4-TETROL.

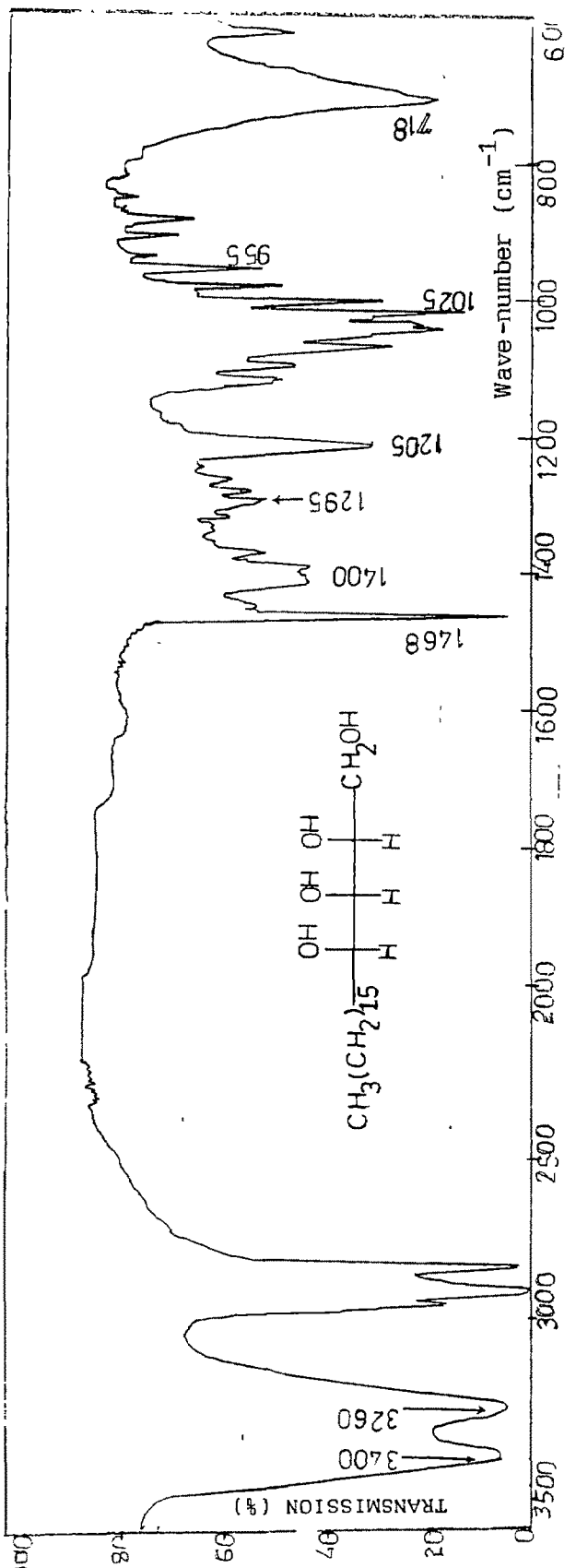


FIG. 9 : IR SPECTRUM OF RIBO-EICOSANE-1,2,3,4-TETROL.

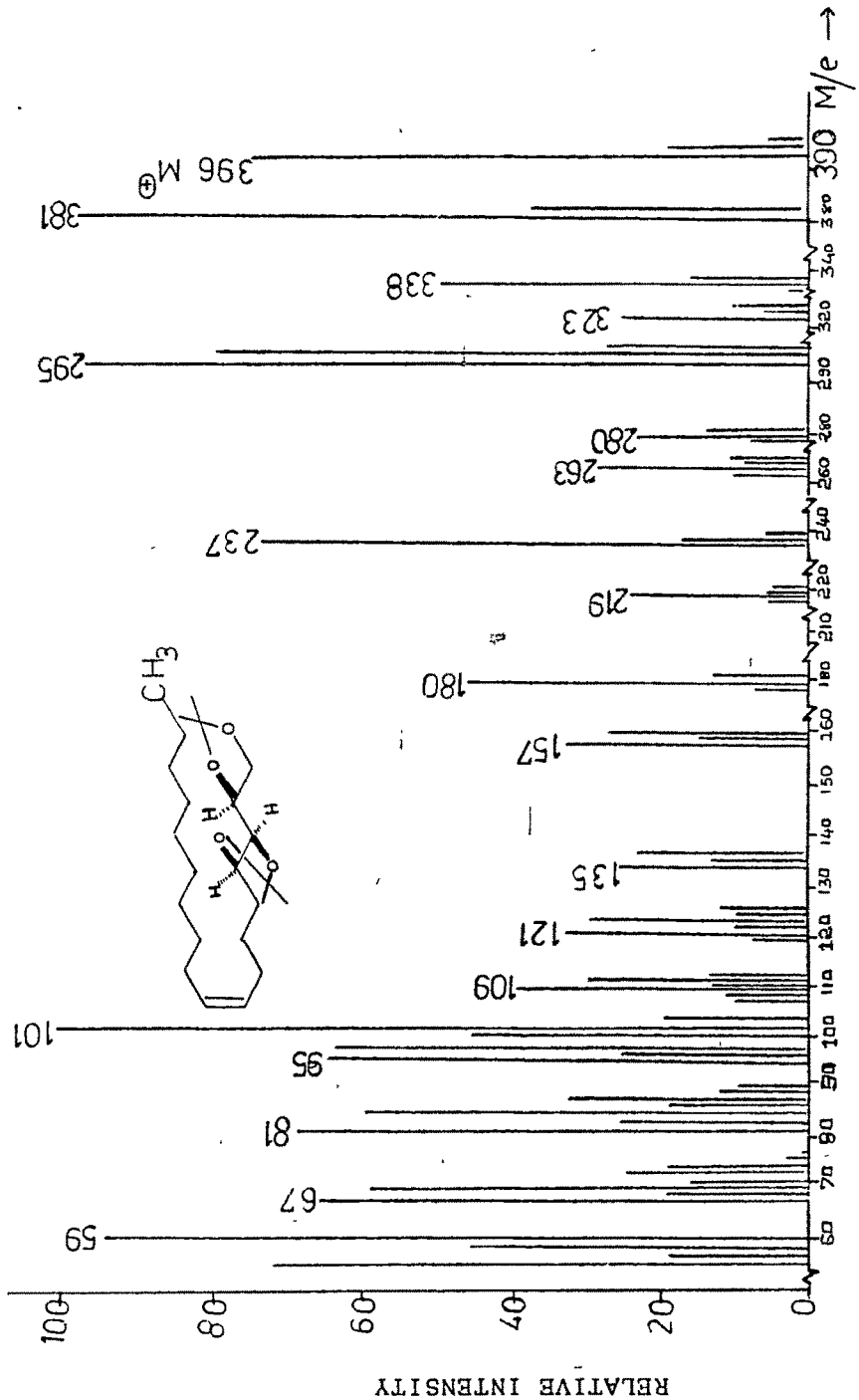


FIG. 10 - MASS SPECTRUM OF 1,2:3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.

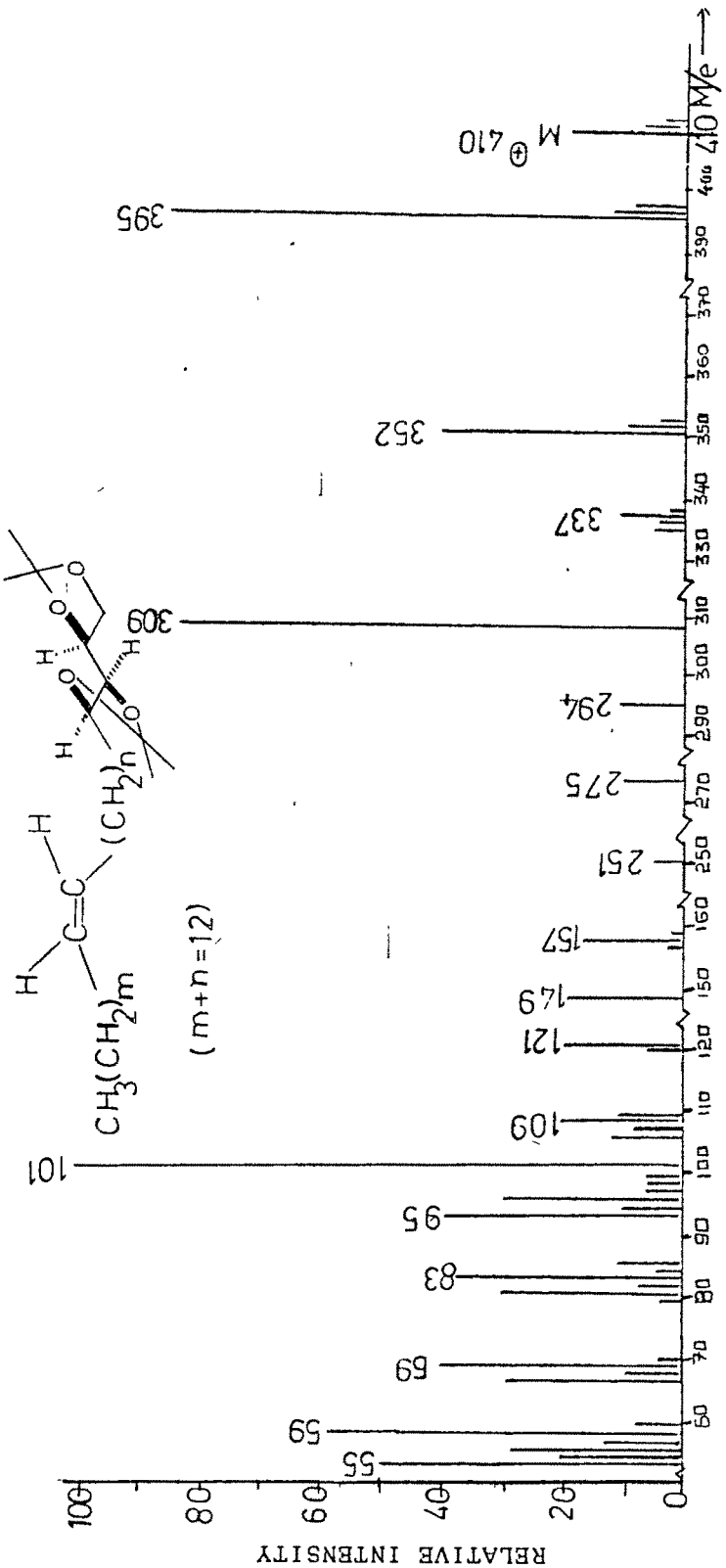


FIG. 11 - MASS SPECTRUM OF 1,2:3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-NONADECENE-1,2,3,4-TEROL.

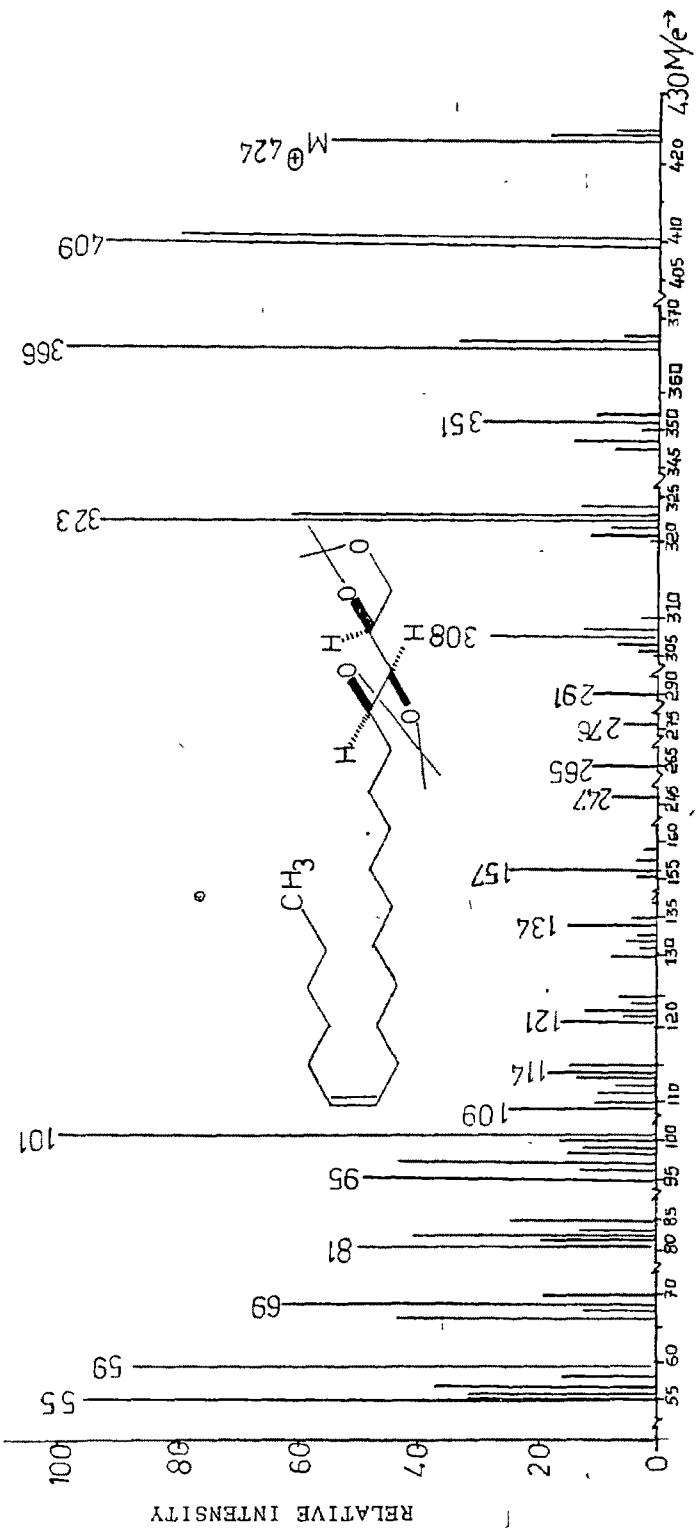


FIG. 12 : MASS SPECTRUM OF 1,2:3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-EICOS-14(Z)-ENE-1,2,3,4,-TETROL
(MAJOR ISOMER)

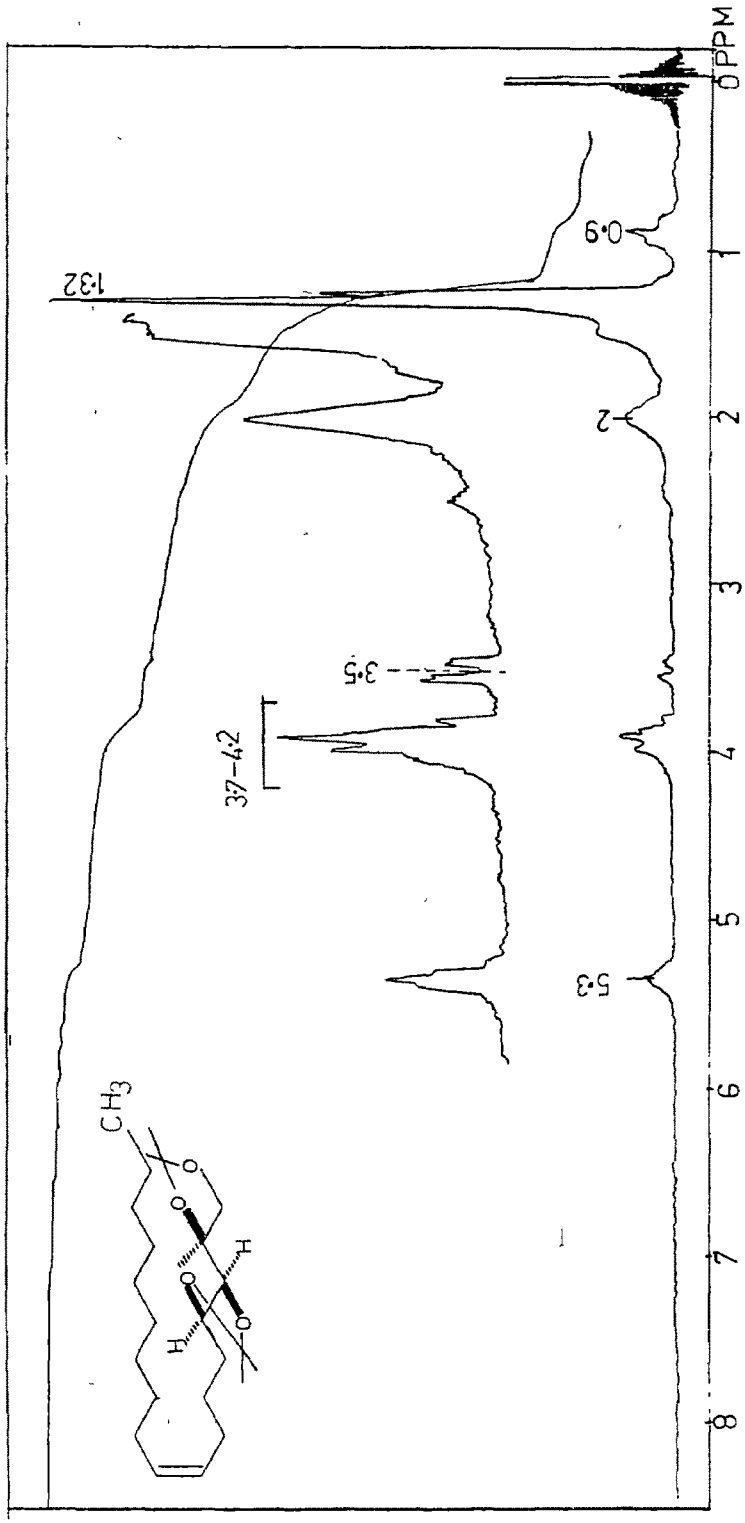


FIG. 13 : PMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.
(SEE FIG. 13A ALSO).

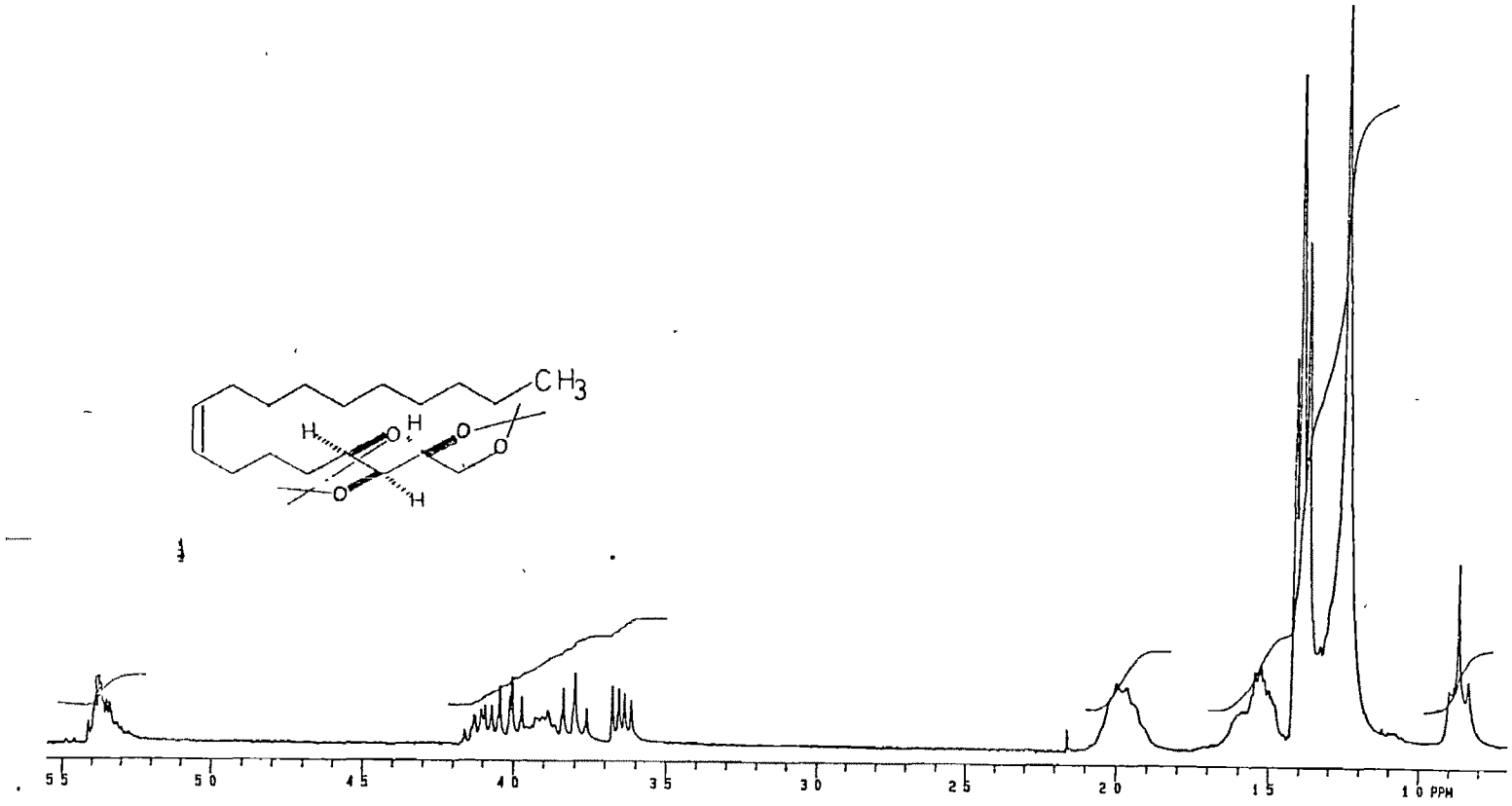


FIG. 13A : PMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.
(VARIAN 200 MHz)

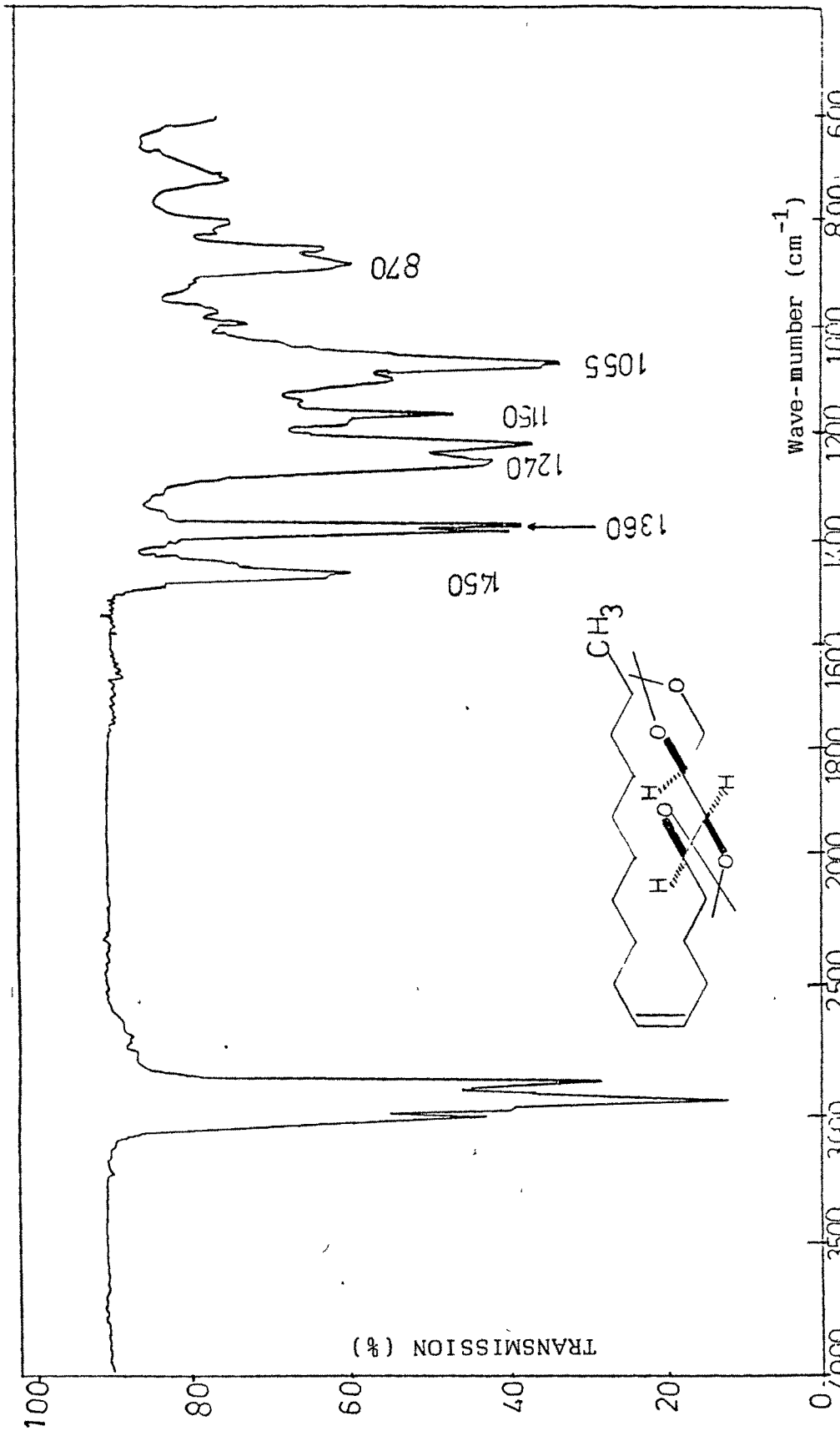


FIG. 14 : IR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.

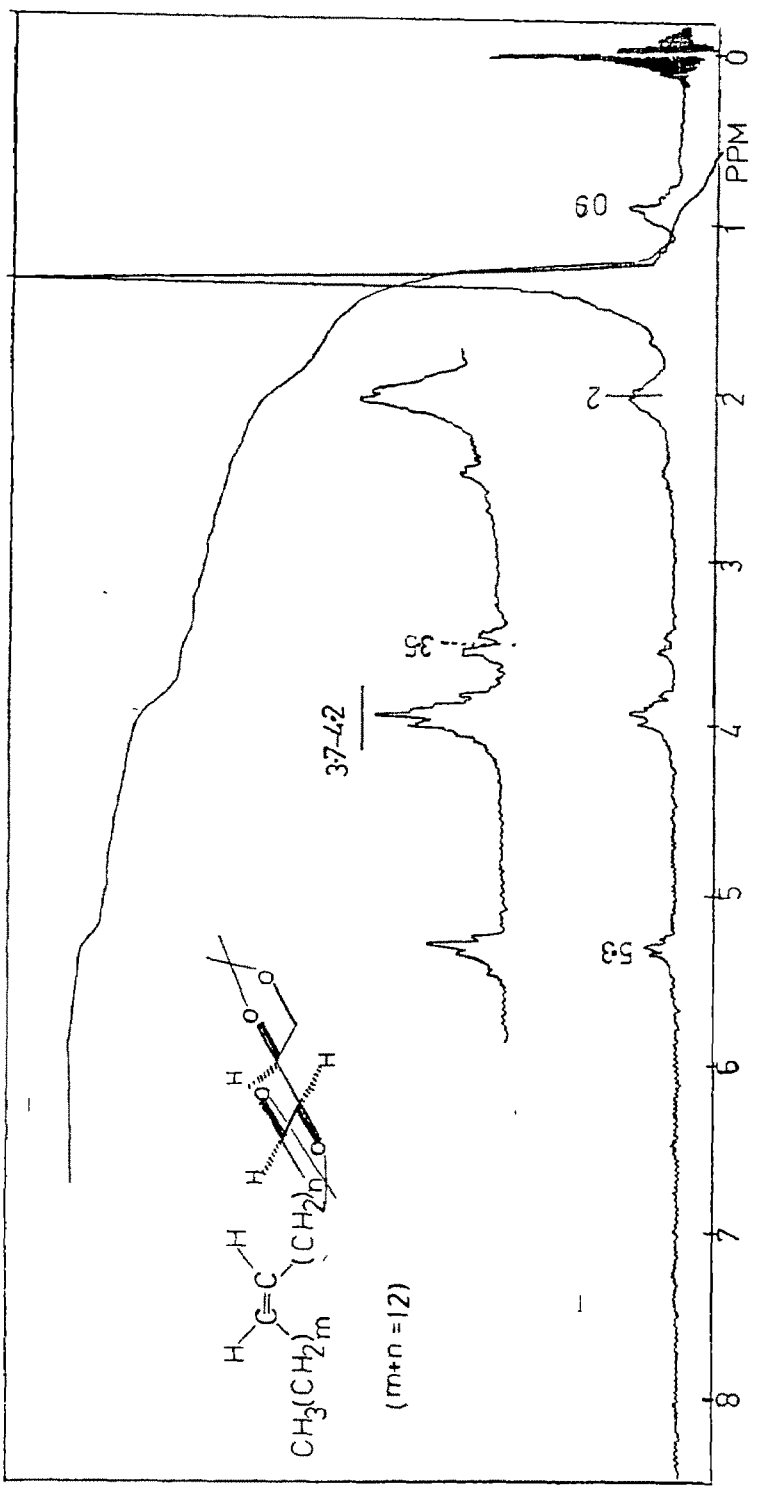


FIG. 15 - PMR SPECTRUM OF 1,2, : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-NONADECENE-1,2,3,4-TETROL.

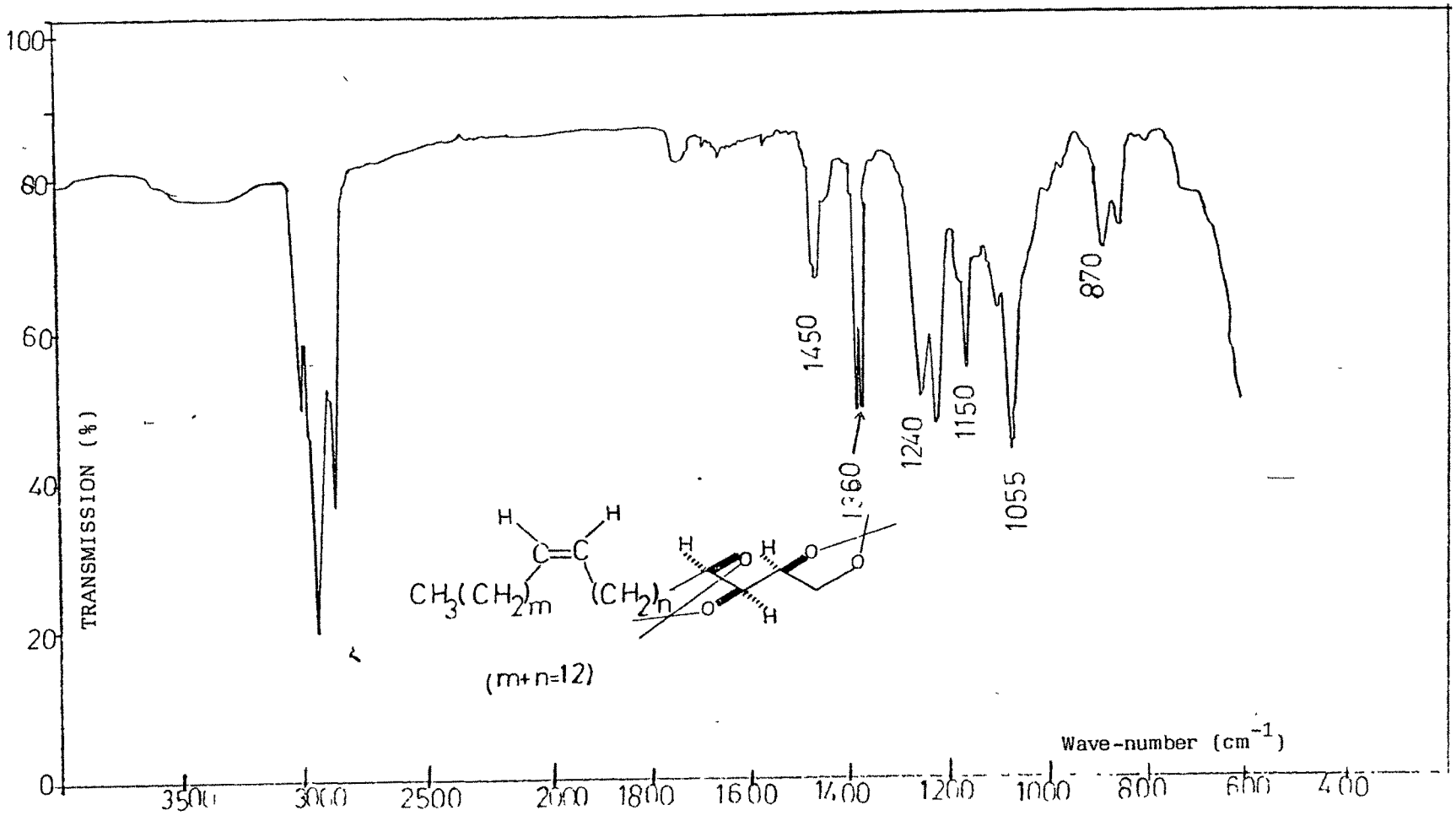


FIG. 16 - IR SPECTRUM OF 1,2:3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-NONADECENE-1,2,3,4-TETROL.

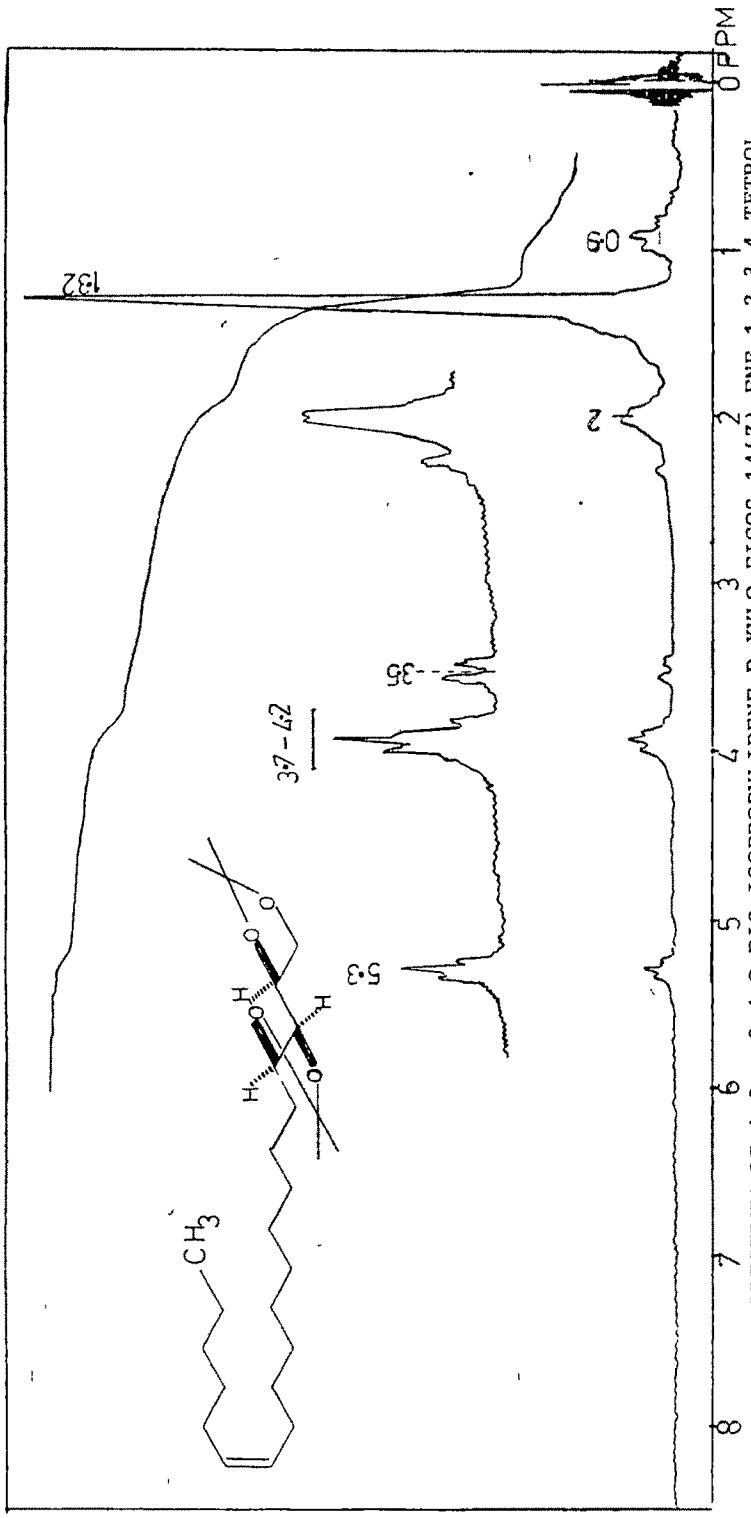


FIG. 17 : PMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL. (MAJOR ISOMER) (SEE FIG. 17A ALSO)

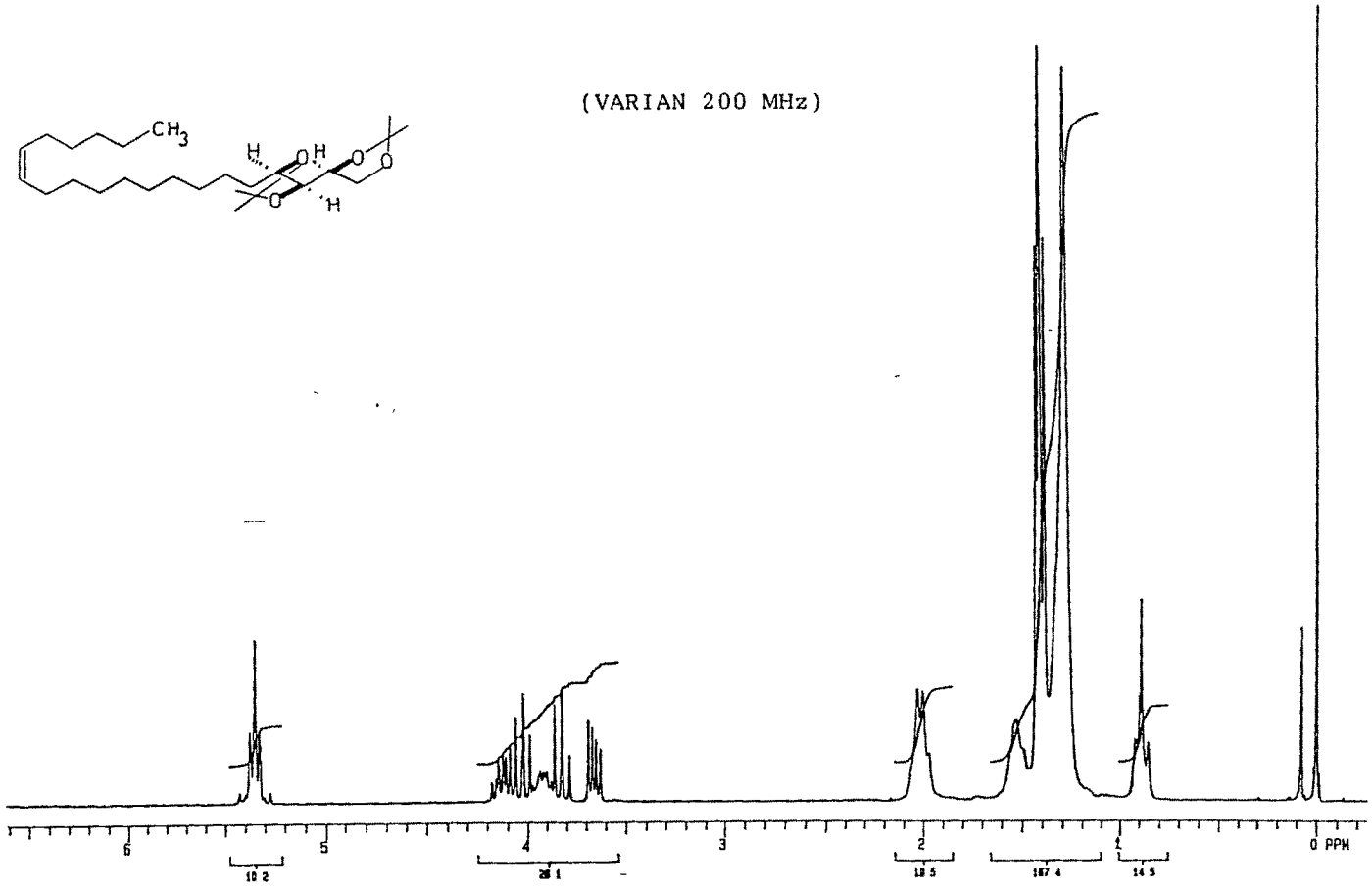


FIG. 17A : PMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL.

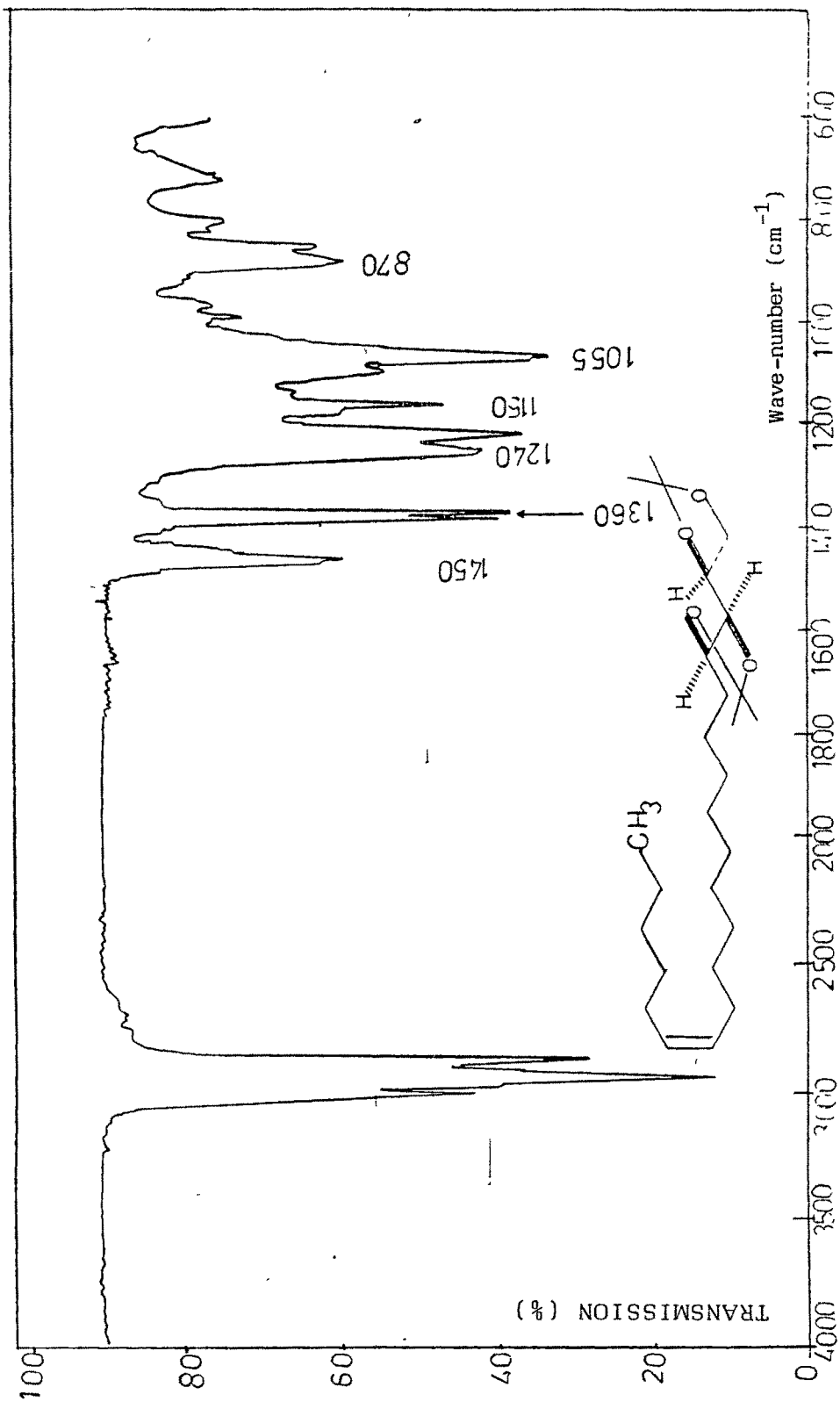


FIG. 18 - IR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL. (MAJOR ISOMER)

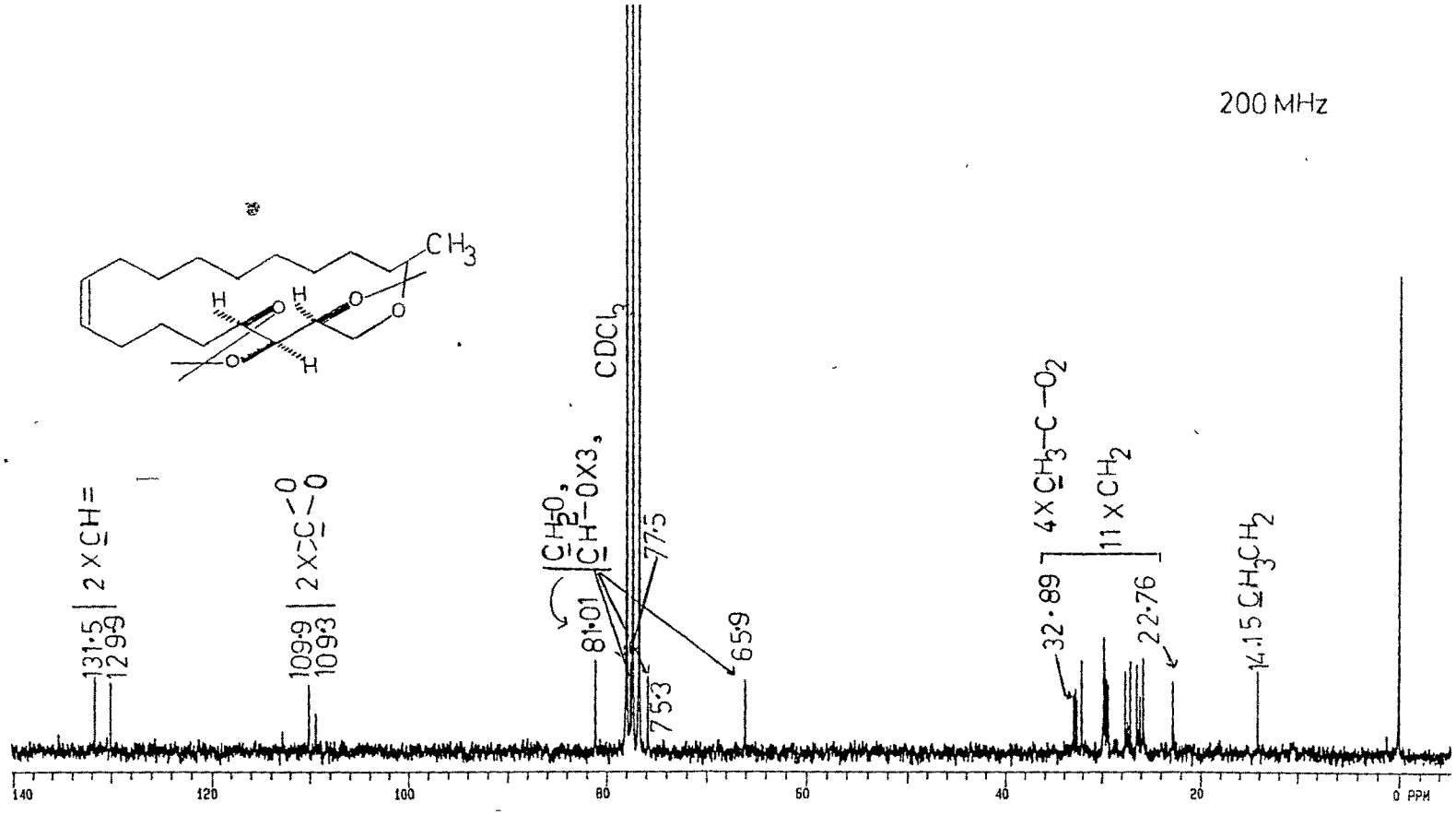


FIG. 18 A : ^{13}C NMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.

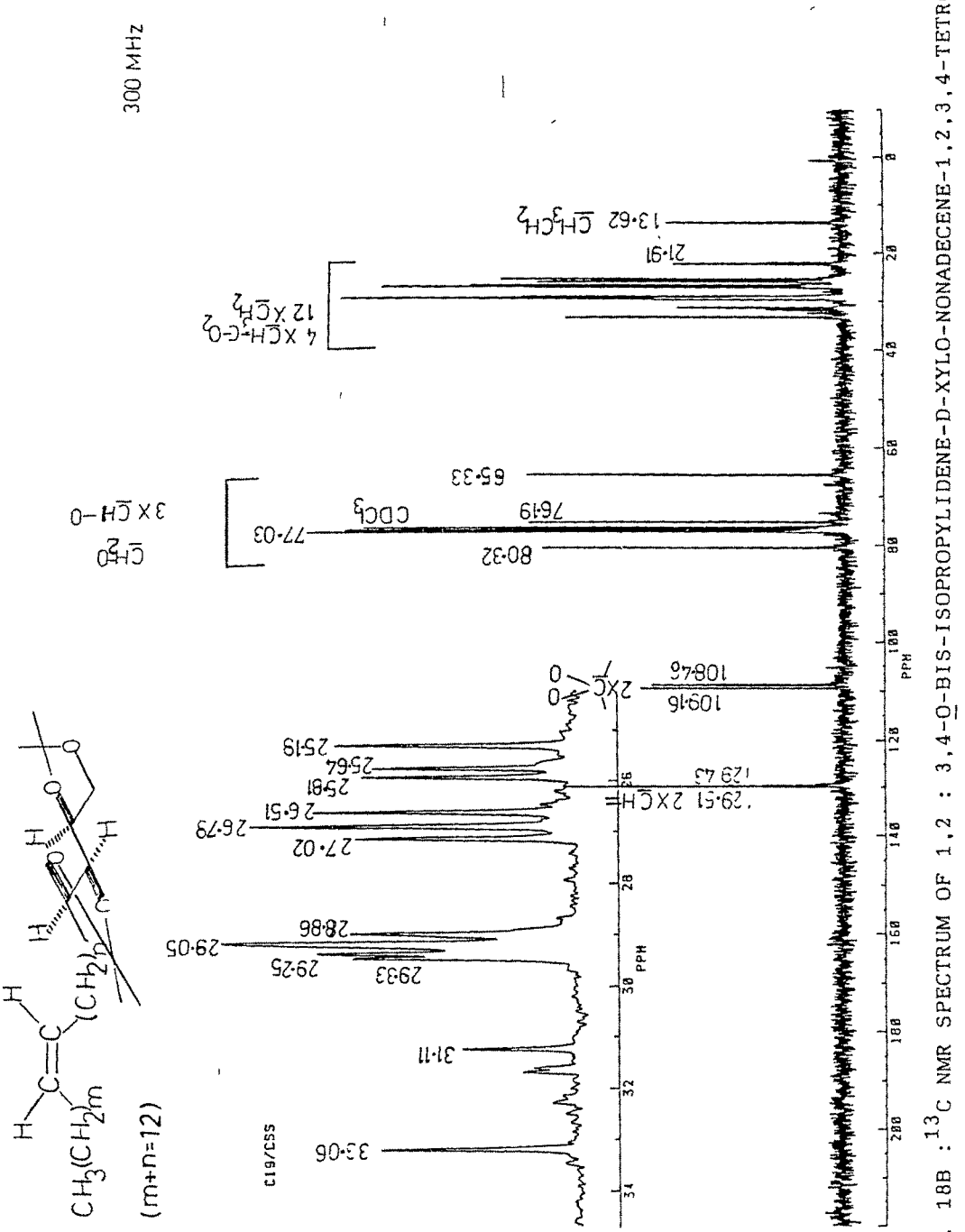


FIG. 18B : ^{13}C NMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-NONADECENE-1,2,3,4-TETROL.

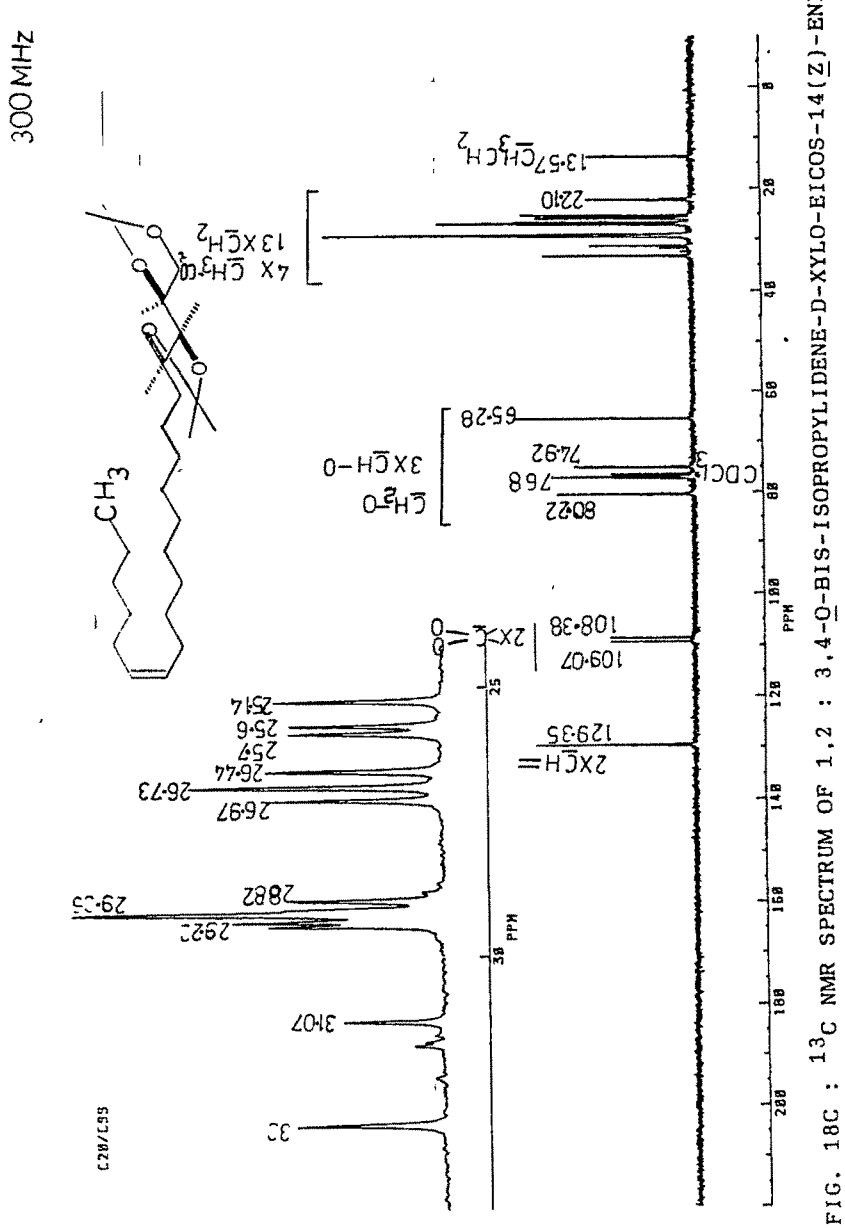


FIG. 18C : ^{13}C NMR SPECTRUM OF 1,2 : 3,4-O-BIS-ISOPROPYLIDENE-D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL.
(MAJOR ISOMER)

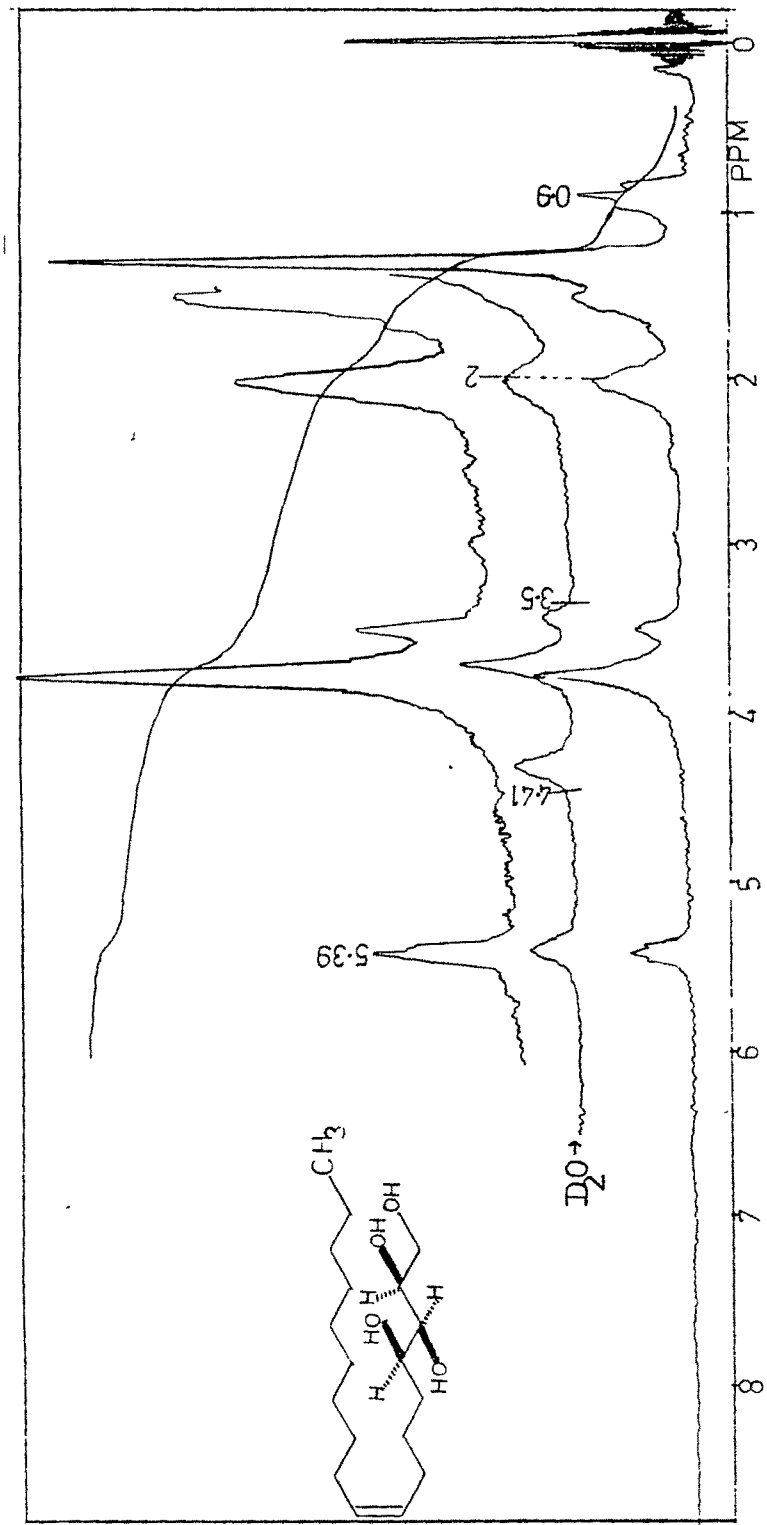


FIG.19 : PMR SPECTRUM OF D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.

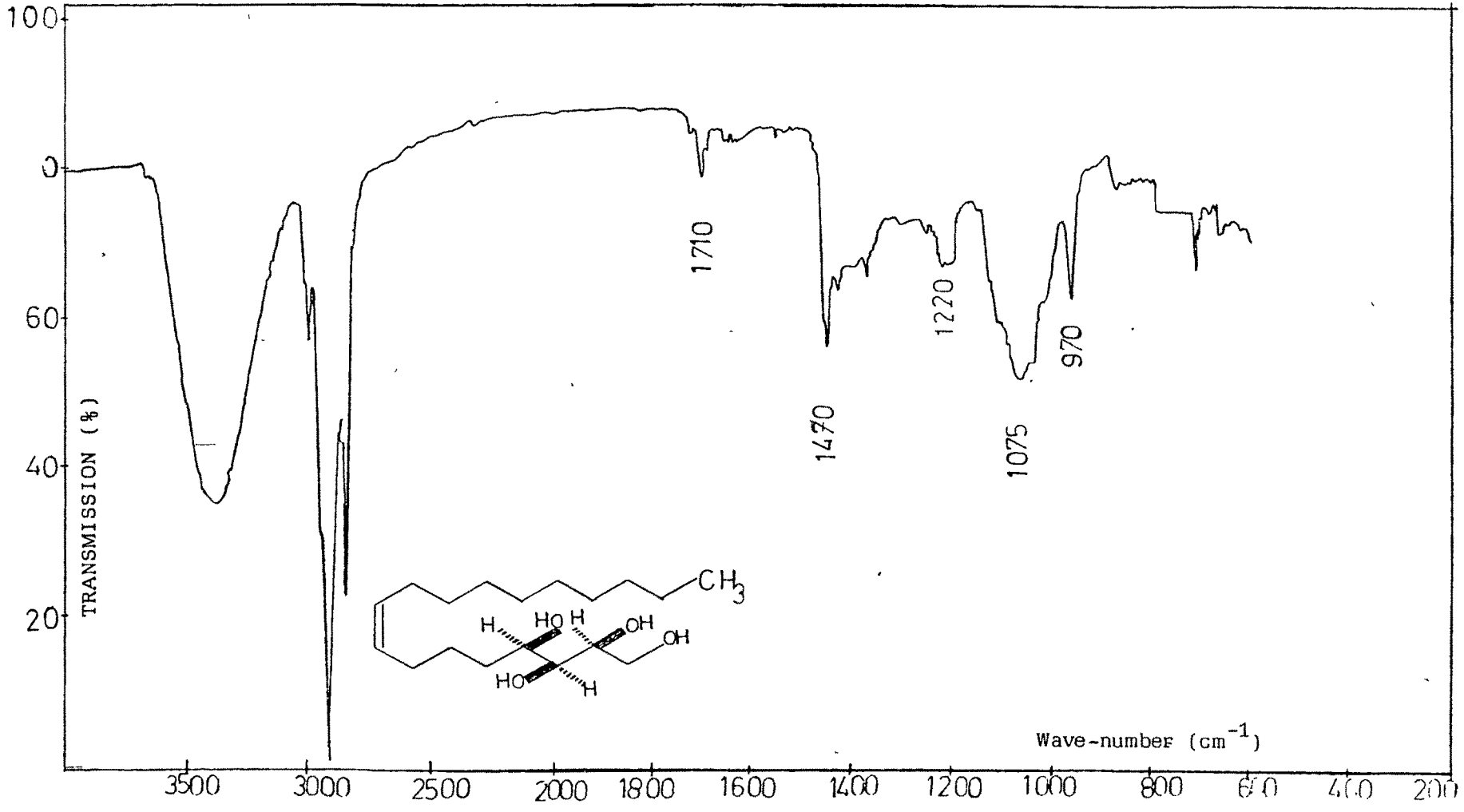


FIG. 20 : IR SPECTRUM OF D-XYLO-OCTADEC-8(Z)-ENE-1,2,3,4-TETROL.

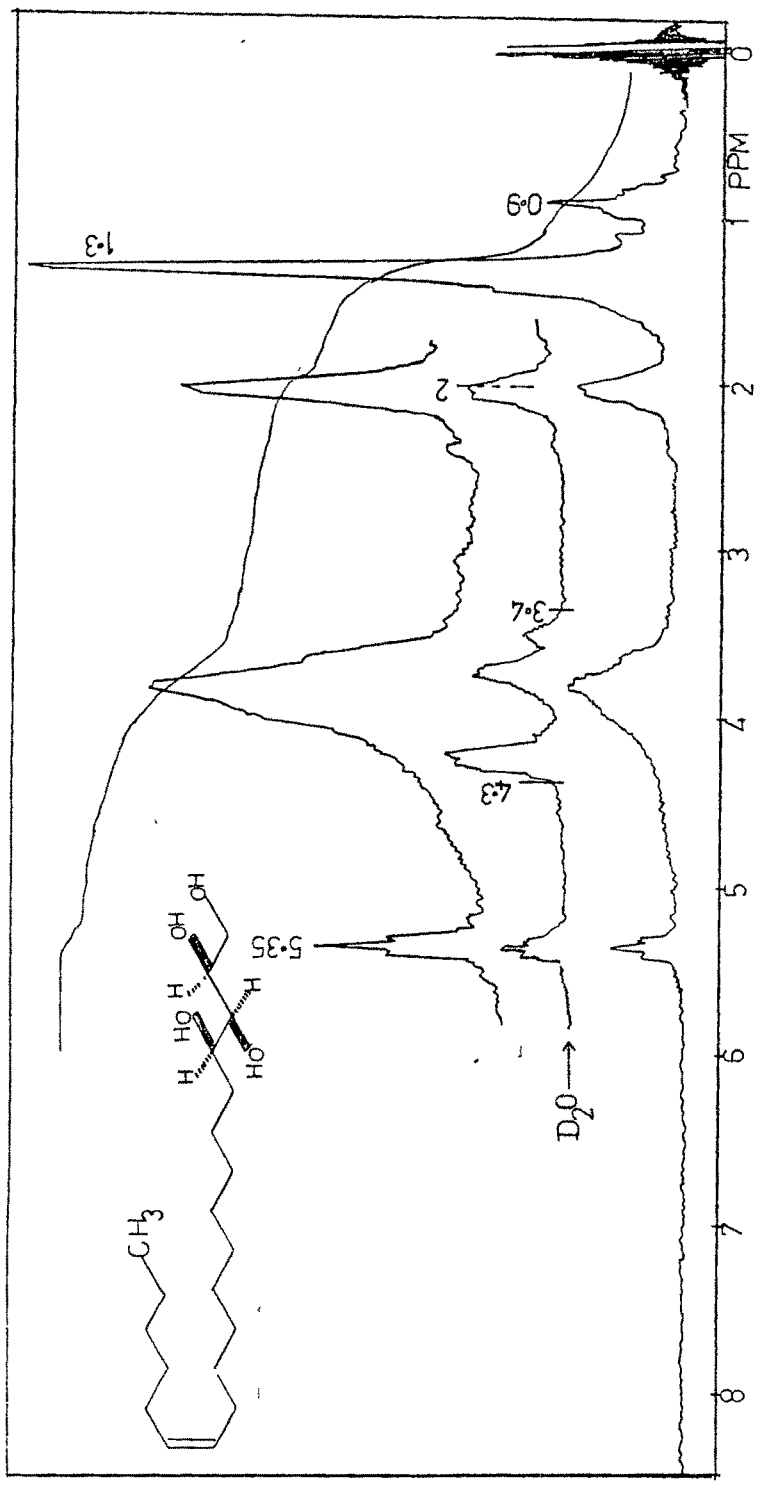


FIG. 21 : PMR SPECTRUM OF D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL (MAJOR ISOMER).

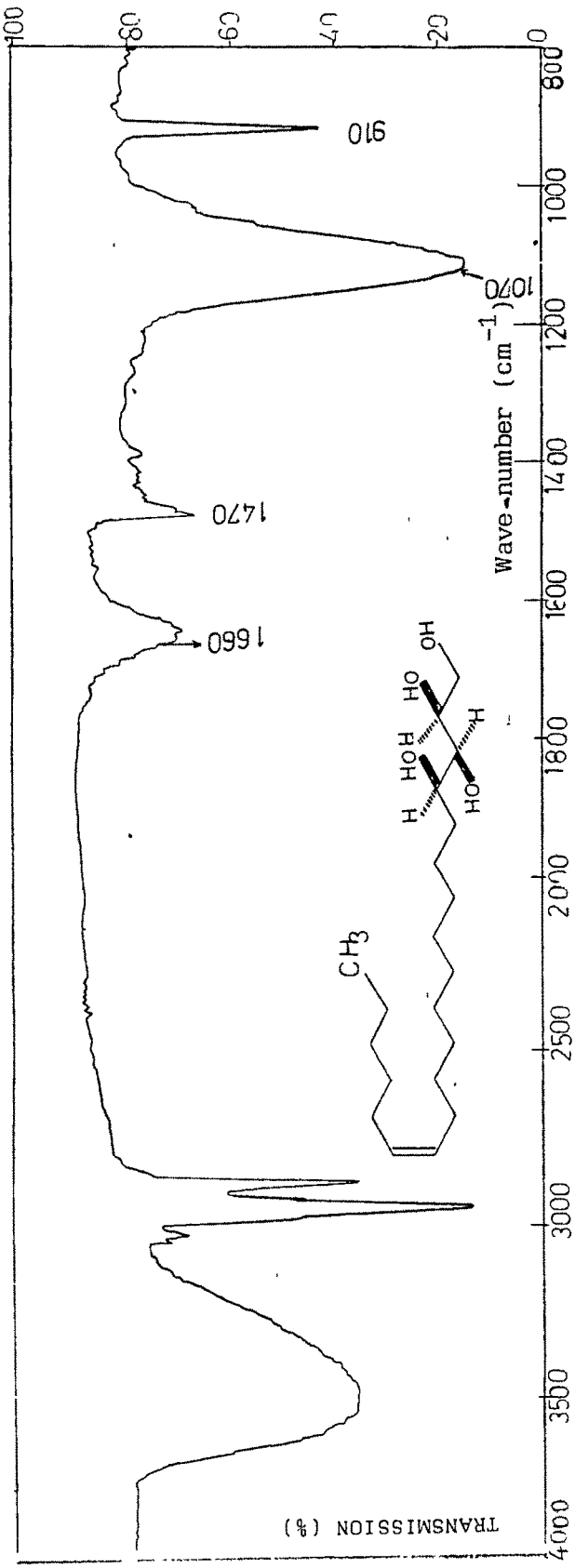


FIG. 22 : IR SPECTRUM OF D-XYLO-EICOS-14(Z)-ENE-1,2,3,4-TETROL (MAJOR ISOMER).

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ABSTRACT

The chemistry, medicinal properties and pharmacological activities of Commiphora mukul gum-resin is discussed. Methods for segregation of gum-resin into acids, bases, neutral, ketonic, non-ketonic, pet.ether-soluble, benzene-soluble and 50% MeOH-soluble fractions are discussed. Methods for separation of long chain homologous tetrols are also described. Two types of saturated tetrols with ribo and D-xylo configurations were isolated in pure form. C_{18} and C_{20}-ribo tetrols and C_{18}, C_{19} and C_{20} D-xylo unsaturated tetrols (as bis-acetonides) were separated by prep. GLC. Ribo tetrols were identified as (1) ribo-eicosane-1,2,3,4 tetrol and (2) ribo-octadecane-1,2,3,4-tetrol by spectral techniques. Unsaturated tetrols were identified as (1) D-xylo-octadec-8(Z)-ene-1,2,3,4-tetrol (2) D-xylo-nonadecene-1,2,3,4-tetrol and (3) D-xylo-eicos-14(Z)-ene-1,2,3,4-tetrol by degradation and spectral studies.