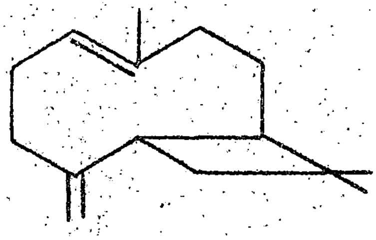
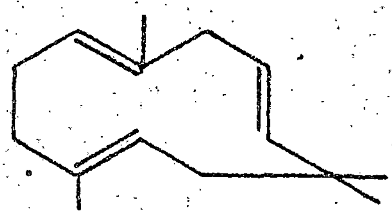
PART-I

The discovery in nature of polyethenoid mono-and di-carbocyclic sesquiterpenes derived from cyclononane to cyclo undecane e.g. Caryophyllene, Germacrone, Humulene etc. (Chart I), came as a great surprise since earlier large carbocyclic compounds have been found in nature only in the macrocyclic fragrant Ketones[1,2,3]. The difficult access to the synthesis of these ring systems had earlier favoured the view that compounds of this type were purely products of human thought and labour. The structural elucidation of these compounds by classical chemical and modern instrumental methods is definitely an achievement on the part of an organic chemist. The synthesis of these "medium ring" compounds pose certain difficulties and not many methods are available for the synthesis of these systems.

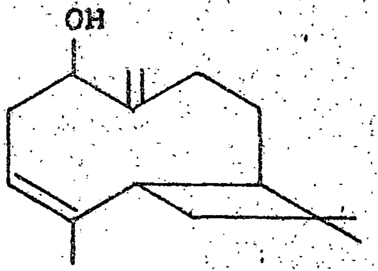
At this juncture it will be appropriate to consider the thermodynamics of ring formation vis-a-vis the stability and formation of medium rings.



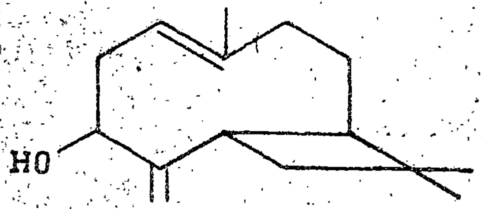
CARYOPHYLLENE



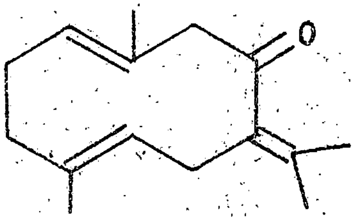
beta- HUMULENE



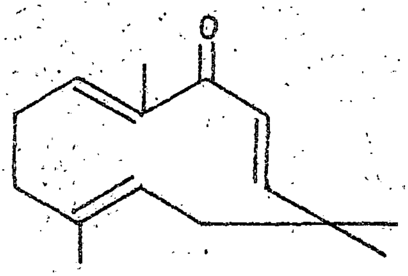
alpha- BUTULENOL



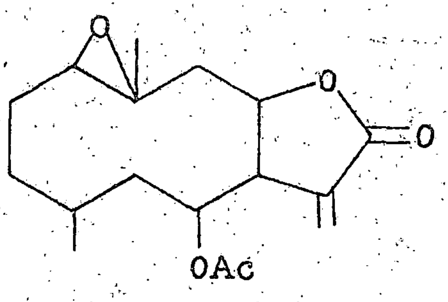
beta - BUTULENOL



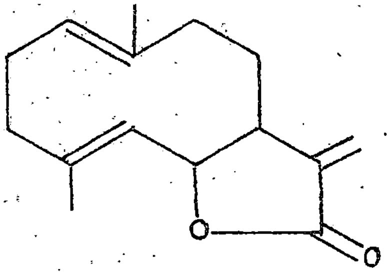
GERMACRONE



ZERUMBONE



PYRETHROSIN



COSTUNOLIDE

Chart- 1

Compounds with medium size ring (8 to 11 - membered) are not simple intermediates between common and large rings. While common and large rings generally differ little in chemical behaviour from their aliphatic counter parts, both saturated and unsaturated, the medium rings have specific features that are characteristic only of them and are not encountered in any other class of organic compounds. Detailed reviews on medium rings are available in literature[4,5,6,7].

A study of the molecular models of these ring systems shows that there is no angle strain and Pitzer strain. The factors responsible for the increased energy content [Fig. I] of such rings is the intramolecular over crowding, as a result of which non-bonded atoms are forced to arrange themselves at distances smaller than the sum of their Van der Waals radii. One of the important distinctive feature of medium size rings is the possibility of existence of conformation in which some of the bonds of carbon atoms are directed into the ring. Such bonds are termed intra-annular bonds; the bonds that are arranged outside the ring are called extra-annular or peripheral, e.g., in cyclodecane, in its most favoured conformation there are six intra-annular and 14-peripheral hydrogen atoms [Fig. 2]. It follows, therefore, that the methylene groups in cyclodecane are stereochemically non-equivalent. The situation is further

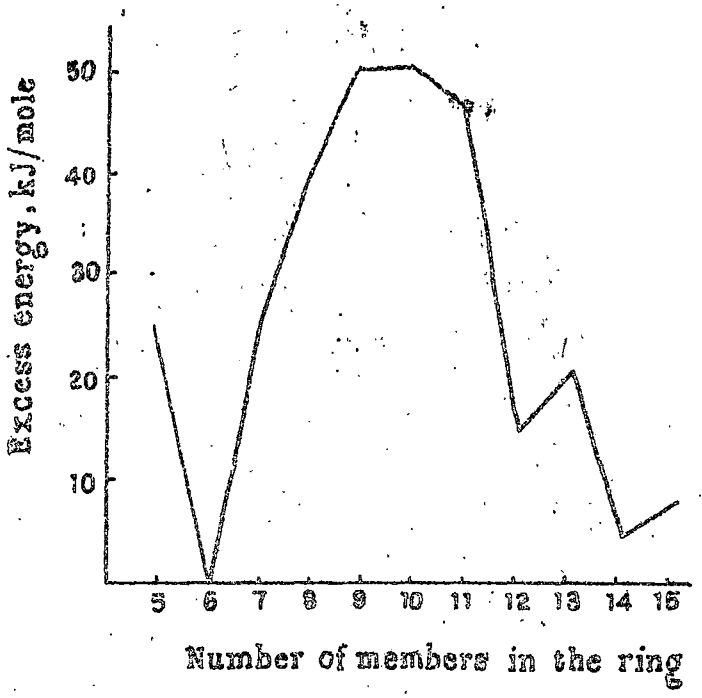

Excess energy, kJ/mole
50
40
30
20
10
5
6
7
8
9
10
11
12
13
14
15
Number of members in the ring

Fig. 1

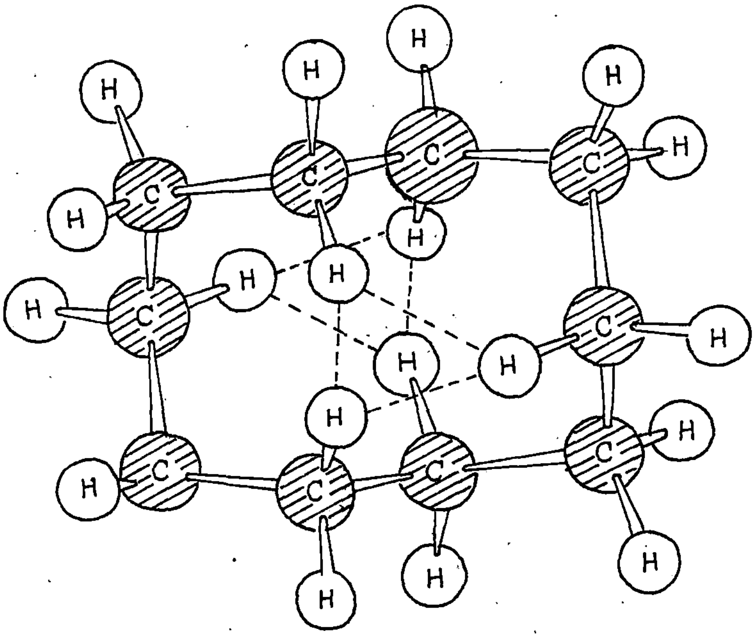


Fig. 2

complicated because both the hydrogens of some methylene are peripheral or one hydrogen atom is peripheral and the other intra annular. Further depending upon whether the peripheral hydrogen is equatorial or axial, we have total three different types of methylenes in cyclodecane. The structural parameters of trans cyclodecane-1,6-diol according to X-ray difraction data are shown in fig. 3.

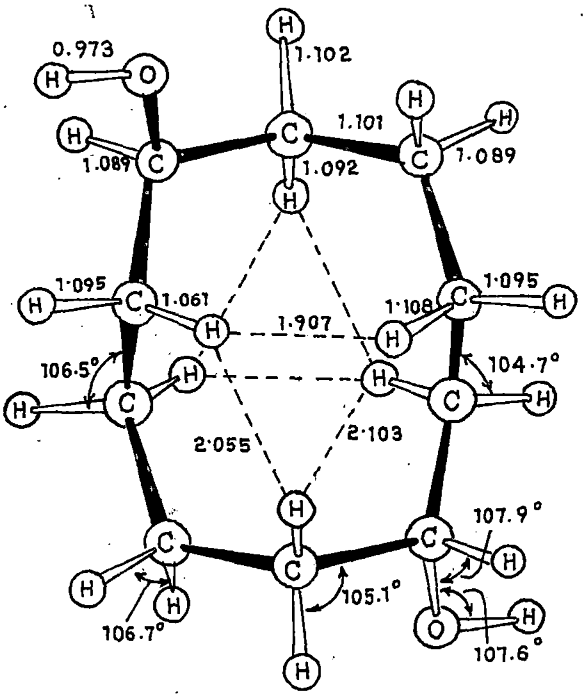
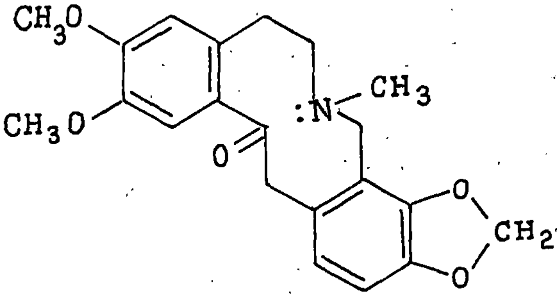


Fig. 3.

The most interesting distinctive feature of the medium sized rings is the manifestation of trans-annular effects and the occurence of trans-annular reactions. These effects and reactions do not occur at the carbon chain and do not involve neighbouring atoms. They take place between atoms across the ring.

The trans-annular interaction are especially prominent in those compounds in which units of electrophilic and nucleophilic nature are opposed in the ring e.g., the Carbonyl absorption in the molecule of the alkaloid Cryptopine (I)



I

disappears on protonation. Analogous phenomenon has been detected in some medium ring aza-acyloins.

A number of interesting studies correlating stability of rings with ring size are available. It must be pointed out that the ease of ring formation, which is a matter of kinetics and depends on the difference in free energy between the acyclic starting material, and the transition state for ring closer is not necessarily related to the stability of the product. Very little information is available about the position of equilibrium in a reaction in which an open chain and cyclic compound are equilibrated; the most informative studies are thermochemical in nature. The heat of combustion of methylene group is high in cyclopropane, drops to a minimum in cyclohexane, rises to a maximum in cyclononane and then drops again to reach the n-alkane value at about cyclotetradecane. Fig. 4 shows the heat of combustion per methylene as a function of ring size.

On the basis of the heat of combustion per methylene ring compounds are classified into four categories, namely, small rings (3 and 4), common rings (5,6 and 7), medium rings (8 to 11) and large rings (12 and above). The heat of combustion of small rings has been attributed to angle deformation strain. The high heat of combustion of medium size ring is due to some amount of angle strain and the existence of unfavourable conformational strain. There is also some over crowding of atoms and groups accross the rings. Equilibrium studies measuring thermodynamic stability of rings are unfortunately almost nonexistent.

We have so far considered saturated acyclic rings. Introduction of elements of unsaturation, hetero atoms or other structural elements will definitely alter the situation. Very little thermochemical information on this point is available. As an approximation one may consider a few systems that have been synthesized and therefore stable enough to exist. Some of these

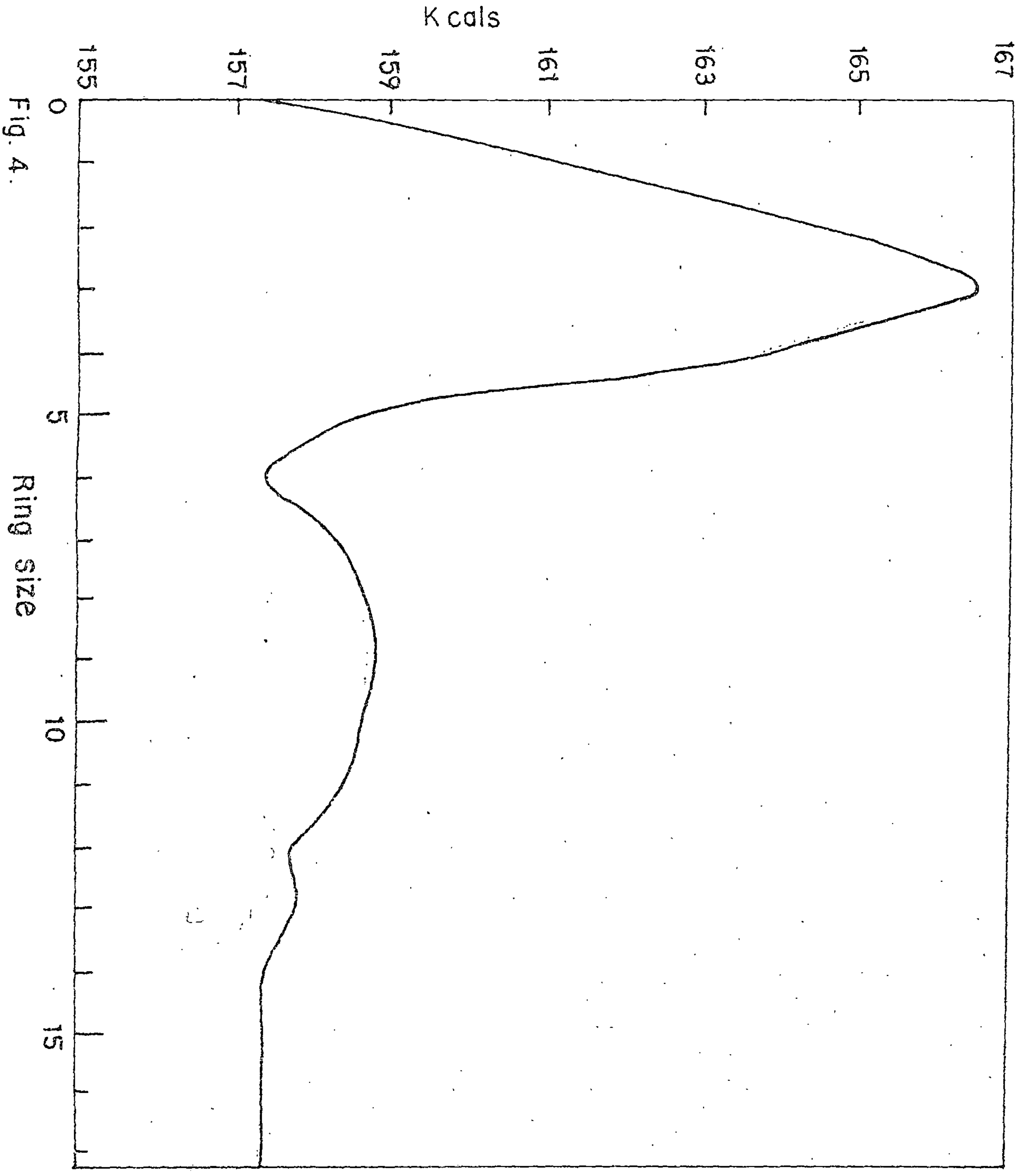


Fig. 4.

systems are obviously quite strained, some systems could not be synthesized inspite of several attempts. It will be wrong however to infer that such failures indicate that such systems are too strained to exist. The Chart-2 contains some unsaturated systems synthesized.

Ease of ring formation, it has already been pointed out is not synonymous with ring stability where as activation energy for ring closure might be expected to reflect the stability of the ring form to some extent. Other factors enter as well. The most important of these involves the probability of having the ends of the ring forming chain approach each other. This probability decreases as the ring size increases and reflects itself in an unfavourable activation entropy for the formation of medium and large rings. The over all ease of ring closure thus may be derived from two factors : a monotonous decrease in the case of having the ends of the ring size increases from three to six membered, then less favourable as it increases further upto nine membered, and then more favourable again for larger rings. In the over all result, ease of ring formation is relatively high for three-membered rings (because of the high probability factor; three atoms are necessarily in the optimum position for ring formation). It drops sharply for the four membered ring (if four atoms are arranged in the most stable conformation, as in trans-butane, they cannot form a ring; the best conformation for

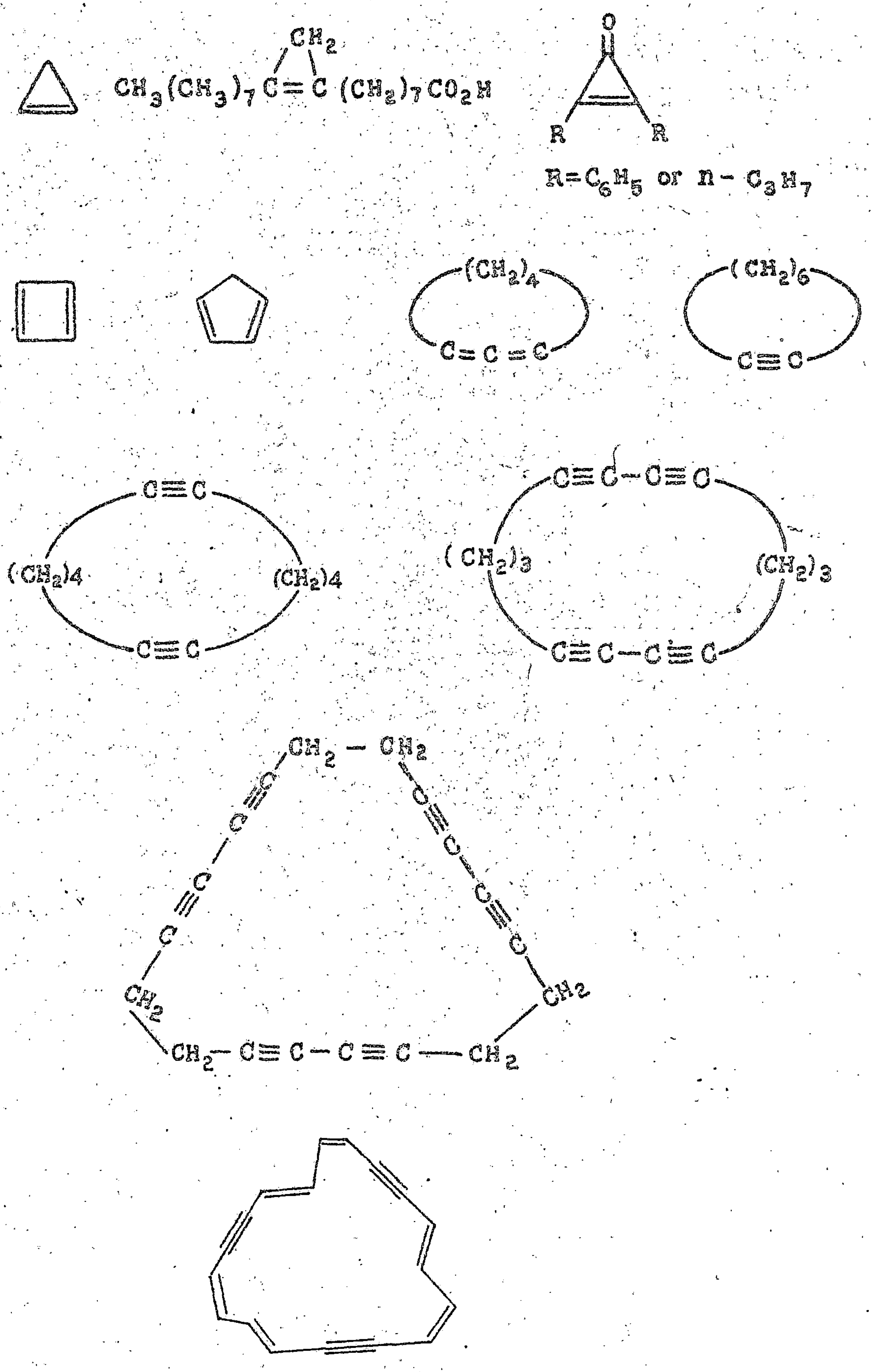
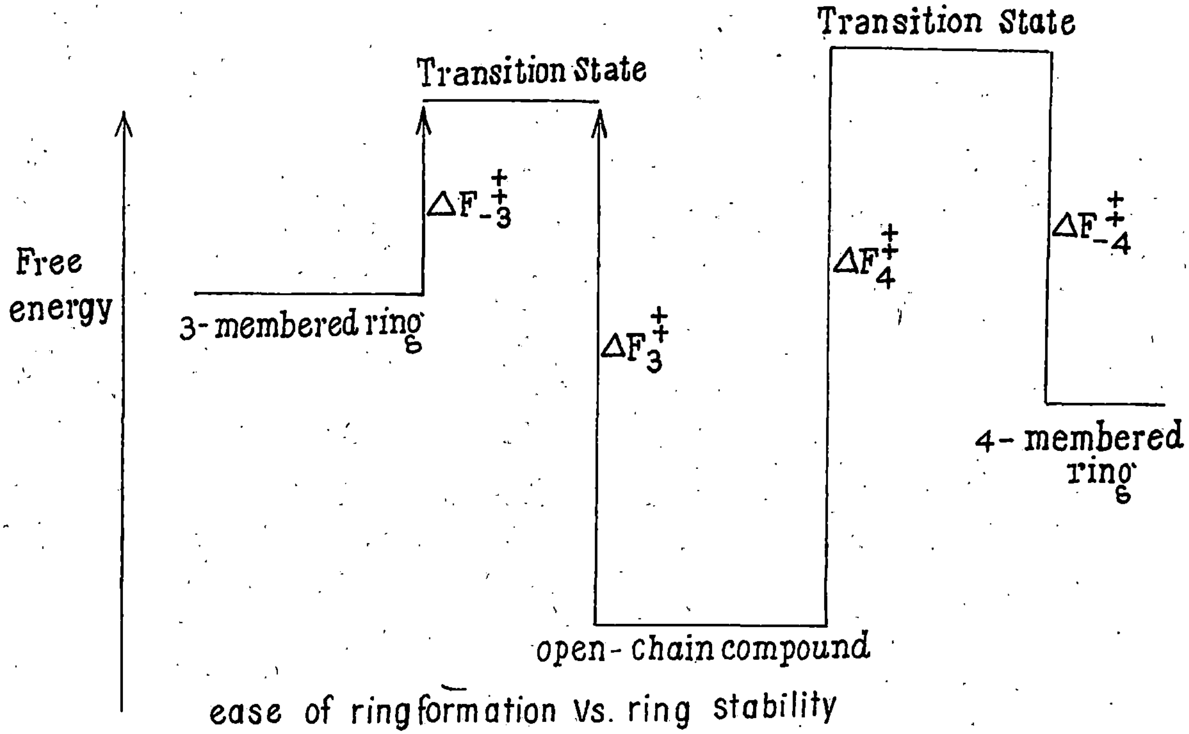

CH3(CH3)7C=C(CH2)7CO2H
CH2
O
R
R
R=C6H5 or n-C3H7
(CH2)4
C=C=C
(CH2)6
C≡C
C≡C
(CH2)4
(CH2)4
C≡C
C≡C-C≡C
(CH2)3
(CH2)3
C≡C-C≡C
CH2 - CH2
C≡C
C≡C
C≡C
C≡C
CH2
CH2
CH2-C≡C-C≡C-CH2

Chart- 2

for ring formation is the very unfavourable cis-conformation). For the five-membered ring there is a sharp rise because of the considerable reduction in the strain factor. The ease of formation of a six-membered ring is less than for a five-membered one because the slight improvement in the strain factor is out weighed by a deterioration in the distance factor. There is a sharper drop for the seven membered ring (both strain and distance factor become worse) and an even sharper drop for the eight membered ring (where non-classical strain sets in).

After that, the distance factor has become about constant and the ease of forming larger rings reflects the strain factors: low ease of ring formation for 9- and 10- membered rings (because of non-classical strain), improving for 11-and 12 - membered rings and levelling off for still larger cycles.



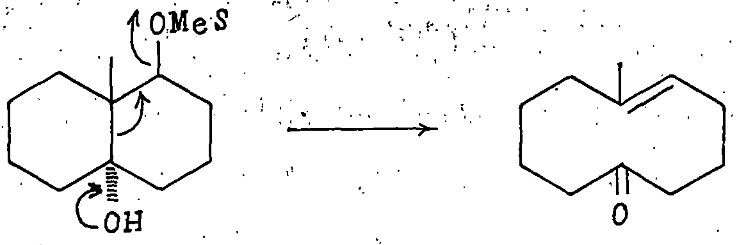
ease of ring formation vs. ring stability

The easier closure of three-membered rings as compared with four-membered ones is well illustrated by the ready formation of epoxides from 1,2-halohydrins in contrast to the difficulty in preparing trimethylene oxides from 1,3-halohydrins. Yet the epoxides, once formed, are much more easily opened than the trimethylene oxides, reflecting the lesser stability of the three-membered ring.

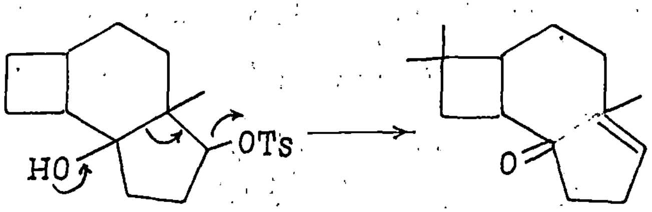
The above discussion clearly shows that the synthesis of medium rings is not easy, more so, when the rings are unsaturated because of pronounced transannular interactions. This is true especially if one starts from acyclic precursors. Even the very advantageous acyloin synthesis of Prelog and Stoll[1,8] which allows the preparation of ring compounds having more than 8-membered in good yields has limited applicability for the synthesis of unsaturated cyclic compounds with one or more multiple bonds in the ring, so highly characteristic of the naturally occurring medium ring compounds. Thus search for newer methods promising adoptability, slectivity and general usefulness is on and newer methods are appearing in literature continuously.

The use of metal carbonyls[8a] and other organometalic reagents is a pointer in this direction. Choosing bicyclic systems as precursors to medium ring compounds is a very attractive approach and has been recognised as such. In his pioneering work, on <u>beta</u>-ketotosylates and <u>beta</u>-hydroxytosylates

Eschenmoser[9] has shown how an intramolecular elimination can lead to the formation of larger ring compounds by the rupture of appropriate carbon-carbon single bonds. This principle has been extended by Wharton[10] and Corey[11] in their synthesis of methyl cyclodecenone (II) and Caryophyllene (III)



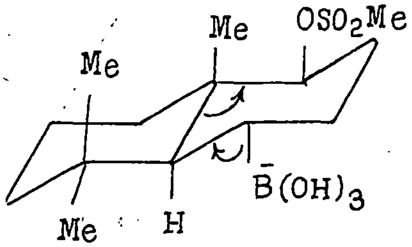
II



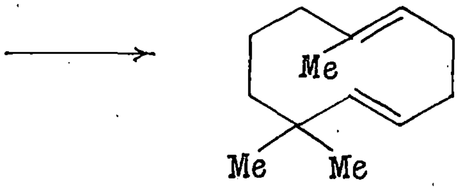
III

Elimination of halogen from properly substituted dihalide is also useful method for the synthesis of larger rings from bycyclic precursors. Variations of this method are known, e.g., Miyashita et. al.,[12] have prepared in 60% yield 1,7,7-trimethyl-trans, trans-1,5-cyclodecadiene (V) by treating the product of hydroboration of 5,5,9-trimethyl - Δ^4 - octalin-1-yl methanesulfonate

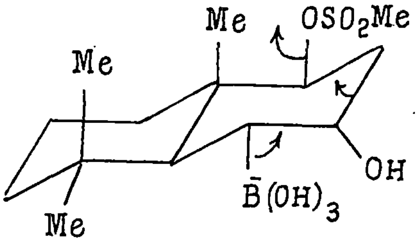
(IV) with 10% aqueous sodium hydroxide - Tetrahydrofuran solution at room temperature for 20 hrs. In contrast, the 3-hydroxy derivative (VI) gave peripheral bond cleavage product only, in 40% yield.



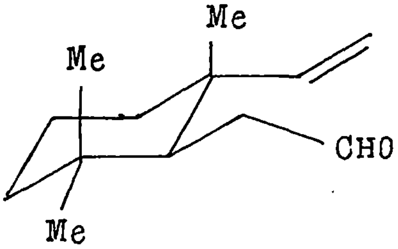
IV



V

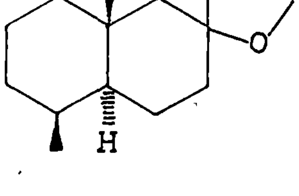


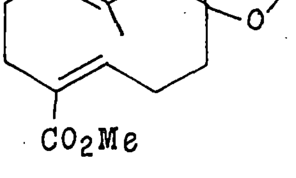
VI



VII

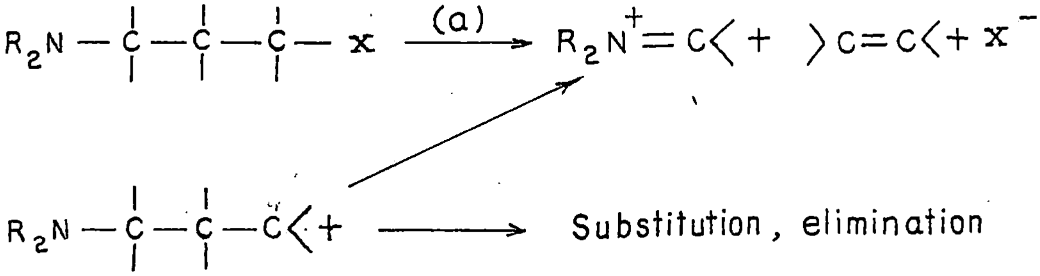
Mander[13] et. al., have succeeded in preparing a cyclodecadiene derivative (VIII) by Lithium-diisopropylamine treatment in tetrahydrofuran.





VIII

The starting ester tosylate was conveniently prepared from 5-methoxy- α -tetralone. This method is suitable for the synthesis of highly functionalized 9-methyl-1-decalones suitable for the synthesis of Germacrane and related sesquiterpenes. The stereochemical requirements for this type of reactions has been discussed by Grob et. al.,[14]. In the case of Gamma - aminohalide and aryl sulfonate they had predicted[15] that a synchronous or one step mechanism (a) would be favoured over a two-step mechanism (b) if the C_α - X bond and the free electron pair of the nitrogen atom were both oriented anti and parallel (anti periplanar) with respect to C_β - C_γ bond which undergoes cleavage.

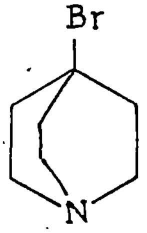


$$R_2N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-X \xrightarrow{(a)} R_2\overset{+}{N}=C\langle + \rangle C=C\langle + X^-$$

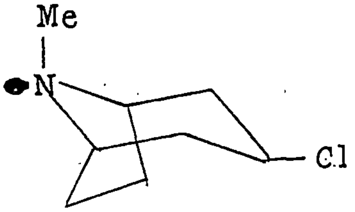
$$R_2N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-C\langle^{+} \longrightarrow \text{Substitution, elimination}$$

$x = Cl^-$, $Ar\,SO_3^-$

Compounds such as 4-Bromoquinuclidine (IX) and 3β-Chlorotropane (X), which meet these requirements, actually fragment by the synchronous mechanism (a) as shown by their enhanced reactivity when compared with

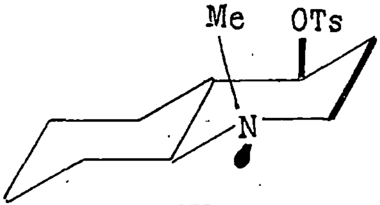


IX

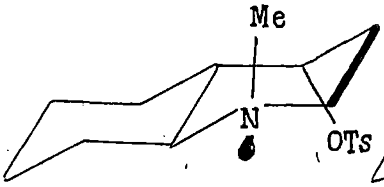


X

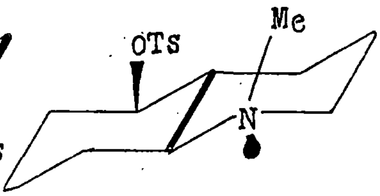
structurally similar cyclic halides not containing nitrogen atom.



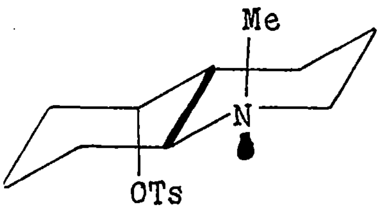
XI



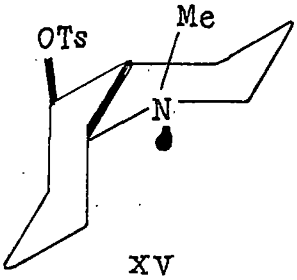
XII



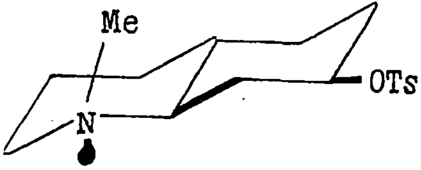
XIII



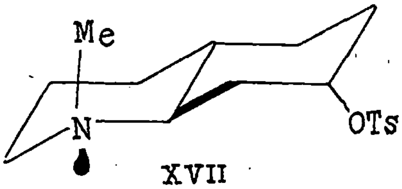
XIV



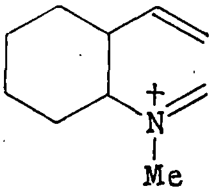
XV



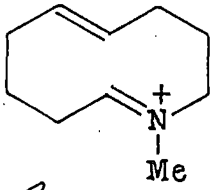
XVI



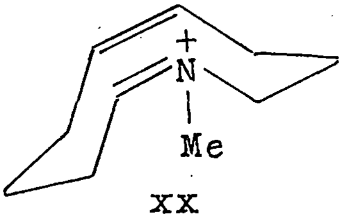
XVII



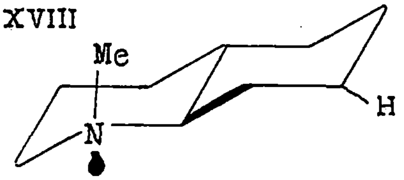
XVIII



XIX



XX



XXI

It remained to be shown that the synchronous mechanism would not be observable in cases where either the C_α - X bond or N-electron pair or both are prevented from adopting the required orientation.

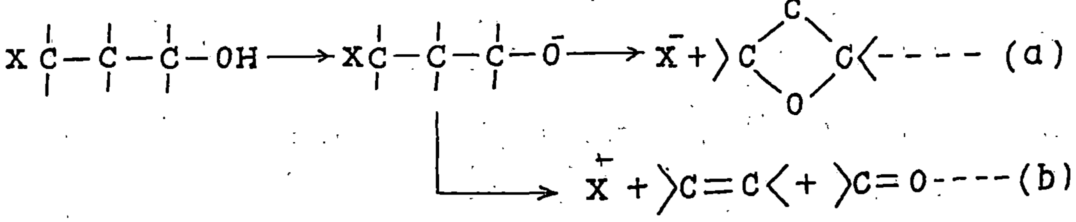
This has now been demonstrated by studying the solvolysis rates and the products of the stereoisomers of 4,5-and 7-tosyloxy N-methyl decahydroquinonaline (XI) - (XVII) in 80% (V/v) ethanol and by comparing their first order rate constants with these of the corresponding 1 - and 2-decalyl tosylates.

Thus the equatorial tosylates (XI), (XIII) and (XV), in which all three electron pairs involved in the synchronous process (a) are able to adopt anti-parallel orientations (indicated in the formulas by heavy lines or spots) afford exclusively the corresponding fragmentation products (XVIII), (XIX) and (XX) respectively. Furthermore, the solvolysis rates of (XI), (XIII) and (XV) are 4870, 46 and 86 times those of the corresponding α-decalyl tosylates respectively. The synchronous nature of the fragmentation process is also reflected in the stereospecific formation of a trans and a cis-olefinic bond in the strained products (XIX) and (XX) from (XIII) and (XV), respectively.

Conversely, the axial tosylates (XII) and (XIV) in which the C_α- OTs bond is no longer anti and parallel to the $C_\beta-C_\gamma$ bond, react at rates comparable to those of the corresponding axial 1-decalyl tosylates. In accordance with a reaction by way of a carbonium ion, the tosylate (XII) yields elimination product ($\Delta^{4,10}$ N-Methyl octahydroquinoline) besides fragmentation product (XVIII), where as the tosylate (XIV) affords substitution (alcohol and ether) and elimination products ($\Delta^{5,10}$ N-Methyl octahydroquinoline) only.

In the equatorial 7-tosyloxy derivative (XVI) the N-electron pair is unable to adopt a position anti-periplanar with the $C_\beta - C_\gamma$ bond, since it is constrained to oscillate in a plane perpendicular to the ring. In the case of the axial 7-tosyloxy derivative (XVII) the C_α - OTs bond as well as the N-electron pair are no longer anti-periplanar with respect to the $C_\beta - C_\gamma$ bond. Both tosylates, are predicted on stereo-electronic grounds, react more slowly than the corresponding α-decalyl tosylates and afford substitution and 1,2-elimination products only. Therefore, even in two step process via the carbonium ion (XXI) fragmentation is prevented by a departure from an anti-periplanar orientation of the N-electron pair with respect to the $C_\beta - C_\gamma$ bond.

In reaction of the type (a) and (b) proceeding via an intermediate anion fission is the preferred reaction in the

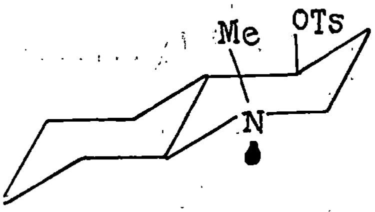


cyclohexane series.

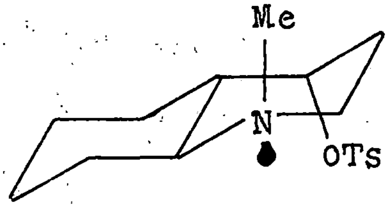
The difficulty in forming 1,3 - epoxy cyclohexane may be due to the additional steric strains which have to be created; the four membered oxide ring is approximately perpendicular to the reminder of the cyclohexane ring which becomes altered so that the atoms C_1 to C_5 become nearly co-planar and roughly in position to those incomparison to a cyclopentane ring. This distortion of the normal chair form of the cyclohexane ring causes increased hydrogen eclipsing, especially in the C_2, C_3 and C_4 groups. Such eclipsing probably contributes largely to the greater heat of combustion per methylene in cyclopentane (158.7 K cal/mole) than of cyclo hexane[16,17] . (157.4 K cal/mole).

Grob et. al[18] have discussed the stereochemical requirement in heterolytic fragmentation reaction of the type a - b - c - d - x $\longrightarrow$ a - b + c = d + : X ; the geometry of the d - X bond and that of the electrodonation group "a" relative to the b - c bond are critical. They arrived at this conclusion from a study of solvolysis rates and products of stereoisomeric 1-methyl-4,5 and -7-decahydroquinolyl p-toluene sulphonates in 80% ethanol.

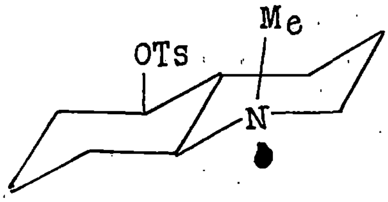
The equatorial 4α- and 5α -trans tosylates (XXII) and (XXIV) in the equatorial 5α - cis tosylate (XXVI) the C_α - OTs bond and free electron pair on nitrogen are fixed in an antiperiplanar with respect to the $C_\beta - C_\gamma$ bond. All three compounds undergo quantitative and stereospecific fragmentation. Since they also react more rapidly than "homomorphous" 1-decalyl tosylates a synchronous mechanism is indicated. The rate of enhancement due to the synchronous mechanism (fragomeric effect) varies with the stability of the fragmentation product formed in the transition state.



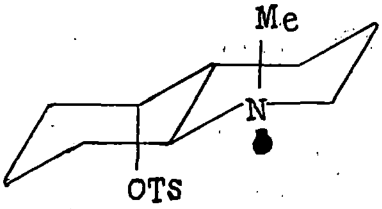
XXII



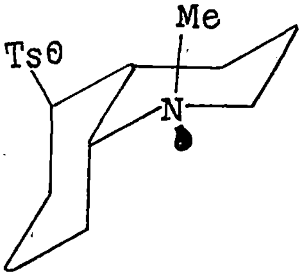
XXIII



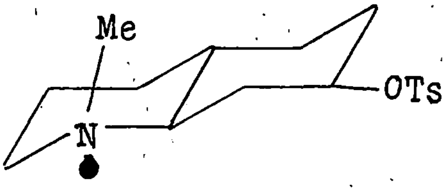
XXIV



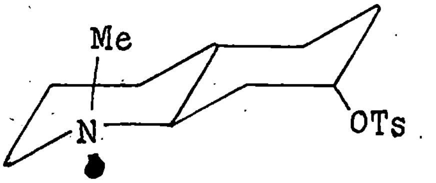
XXV



XXVI



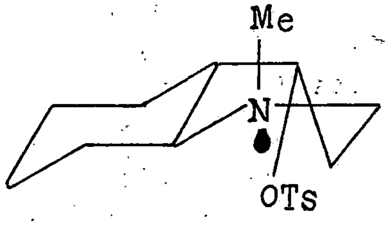
XXVII



XXVIII

By contrast, the axial 5β and 7β-tosylates (XXV) and (XXVIII) as well as the equatorial 7α-tosylate (XXVII), in which an antiperiplanar alignment of the electrons on nitrogen and in the C – OTs and C_β – C_γ bonds is sterically excluded, react by the unimolecular substitution and elimination mechanism (S_N1 – E1) only. Ionisation rates are 2 to 8 times lower than those of "homomorphous" 1- and 2- decalyl tosylates due to the rate decreasing inductive effect of nitrogen.

The 4β-trans tosylate (XXIII) is exceptional in that fragmentation is accompanied by elimination. The rate-product relationship indicates concurrent unimolecuar elimination (E_1) by

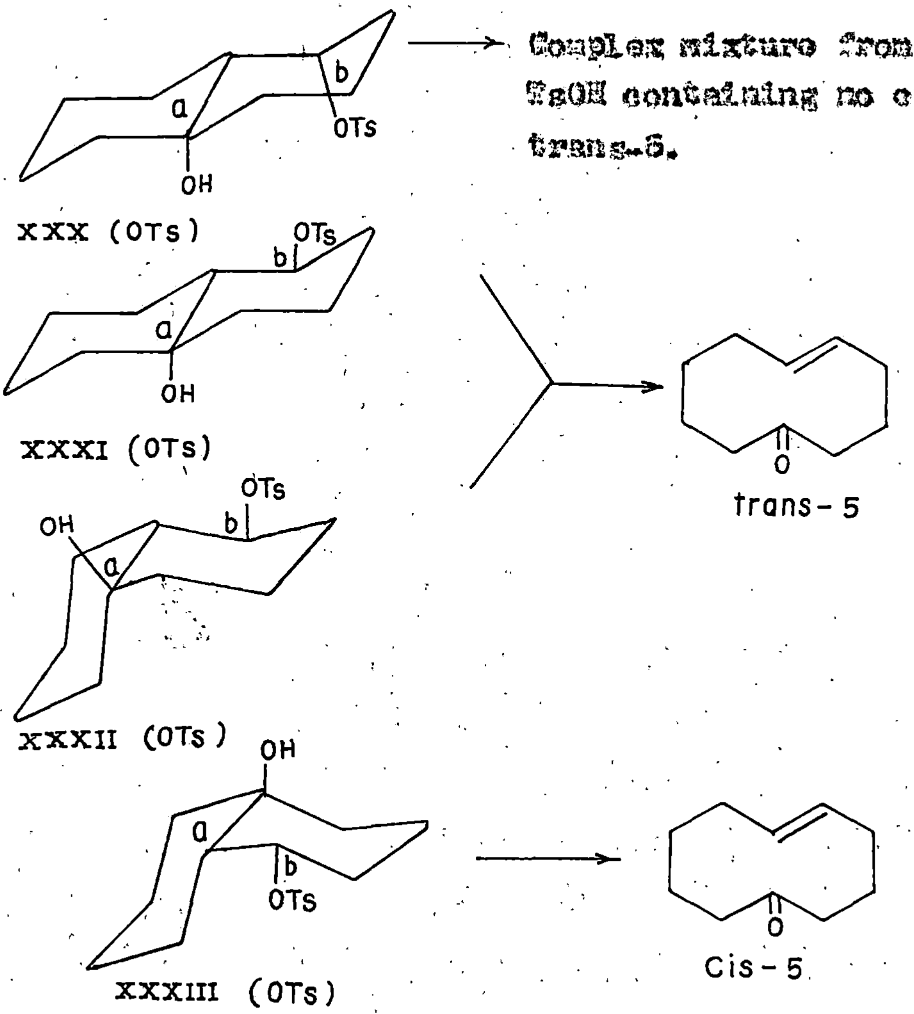


XXIX

way of the predominant all-chair conformation (XXIII), and synchronous fragmentation via the skew boat conformation (XXIX) of piperidine ring.

Wharton and Hiegel[19] had studied the stereochemical requirement for the fragmentation reaction of 1,10-decalindiol monotosylate leading to the formation of cis-and transcyclodecenones.

The four 1,10 - decalindiol monotosylates (XXX) -- (XXXIII) (OTs) were subjected to the action of potassium t-butoxide in t-butanol for 1 hr. at 40°. Monotosylates (XXXI) and (XXXII) (OTs) were individually converted in high yield (Ca. 90%) to trans cyclodecenone (trans-5)[20,21], and (XXXIII) (OTs) was converted in similar yield to cis-5-cyclodecenone (cis-5)[21a]. The results are in accord with concerted breakage of antiperiplanar (180°) bonds



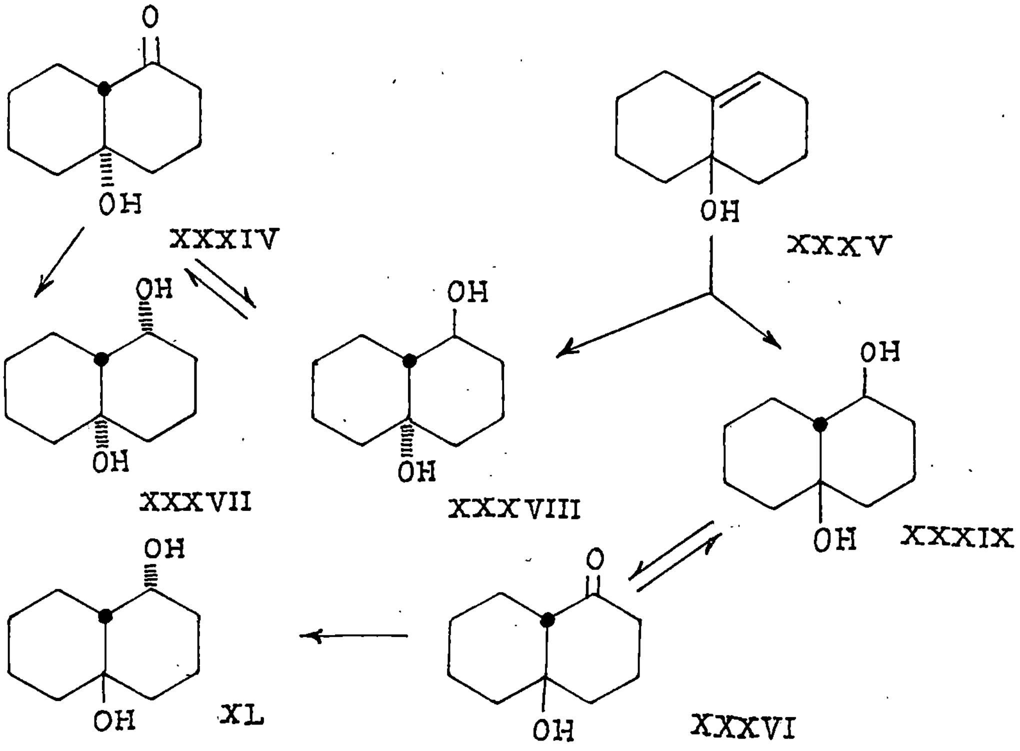
Complex mixture from elimination of TsOH containing no cis-5 and 6% of trans-5.

"a" and "b" in the conformations of (XXXI) - (XXXIII) (OTs) drawn. The stereospecificity of each reaction is evident from the detection by capillary vapour phase chromatography of no more than 0.1% of the unexpected isomer of 5-cyclodecenone in each product.

The importance of geometry is also emphasized by the different behaviour on treatment with base of (XXX) (OTs) in which bonds "a" and "b" are necessarily syn-clinal[22] (60°), subjected to the same condition used to fragment (XXXI) - (XXXIII) (OTs), (XXX) (OTs) yielded a product which contained much unreacted tosylate. Under more drastic conditions sodium methyl sulfinyl carbanion[11] or prolonged t-butoxide treatment (XXX) (OTs) disintegrated with loss of tosylate to a mixture of products containing no detectable cis-5, the product expected from a concerted, albeit difficult, fragmentation. Analyses of the product by infrared spectroscopy and capillary V.P.C. were, however, consistent with the presence of 6% of trans-5 which might be expected from nonconcerted fragmentation via a carbonium ion.

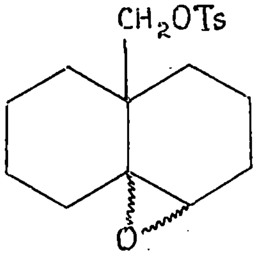
Note should be made of the characterisation of new compounds involved in this work. Diol monotosylates (XXXI) - (XXXIII) (OTs) were prepared by tosylating the corresponding diols in pyridine. Monotosylates (XXX) (OTs) could not be prepared in pyridine but was obtained by treatment of the diol in ether solution first with sodium hydride and then with tosylchloride[23]. The 1,10 -decalindiols were synthesized by methods which allowed configurational assignments to be made without difficulty.

Hydroboration of allylic alcohols gave the previously reported[20] mixture of two diols which was resolved into its components, one oily, the other crystalline, by p-nitrobenzoylation of the p-nitrobenzoates, and saponification of the isolated pure-p-nitrobenzoates. Assignments of configuration (XXXI) to the crystalline diol and (XXXII) oily diol were made after examining the infrared spectra of the two diols in dilute carbon tetrachloride solution[24], intramolecular hydrogen bonding was apparent only in the spectrum of the oily diol. The two diols were related structurally by oxidation of two different ketols which both yielded the expected ultraviolet spectrum of Δ^{9} - 1 -cotalone when subjected to mild alcoholic acid or base treatment. Sodium borohydride reduction of the oily Keto (XXXVI) obtained from (XXXIX) gave a crystalline diol mixture from when a new diol (XL) was obtained in 50% yield

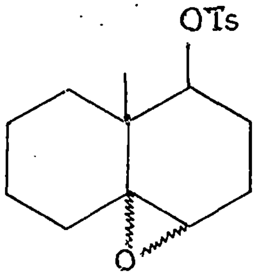


by simple crystallization. As expected, intramolecular hydrogen bonding was not detected in the I.R. spectrum of this diol. Aluminium Lithium hydride reduction of the crystalline Ketol (XXXIV), obtained from (XXXVIII) gave an oily diol mixture from which another new diol (XXXVII) and showing strong intramolecular hydrogen bonding in its I.R. spectrum was obtained by a sequence involving p-nitrobenzoylation of the diol mixture, crystallisation of a new p-nitrobenzoate in 50% yield, and saponification of the pure p-nitrobenzoate. It is a curious fact that the p-nitrobenzoates of (XXVII) to (XXXVIII) were both found to be dimorphic with identical double melting points 106° and 113°C.

A survey of the fragmentation reactions of hydroxy-tosylates in literature shows that the mono-tosylates have been prepared from the corresponding diols. Reactions of epoxy-tosylates of the type (XLI) and (XLII) under fragmentation conditions have not been studied.

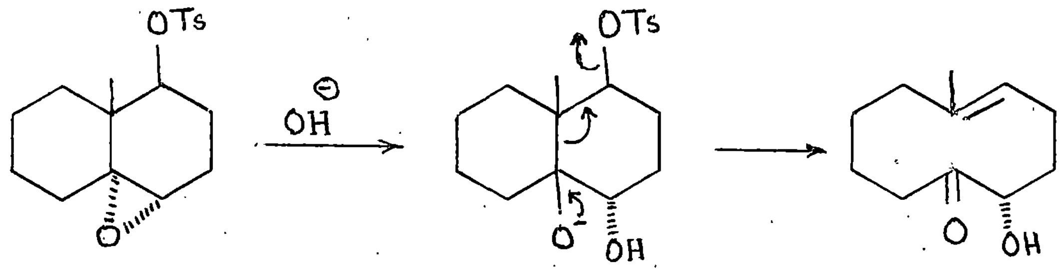


XLI



XLII

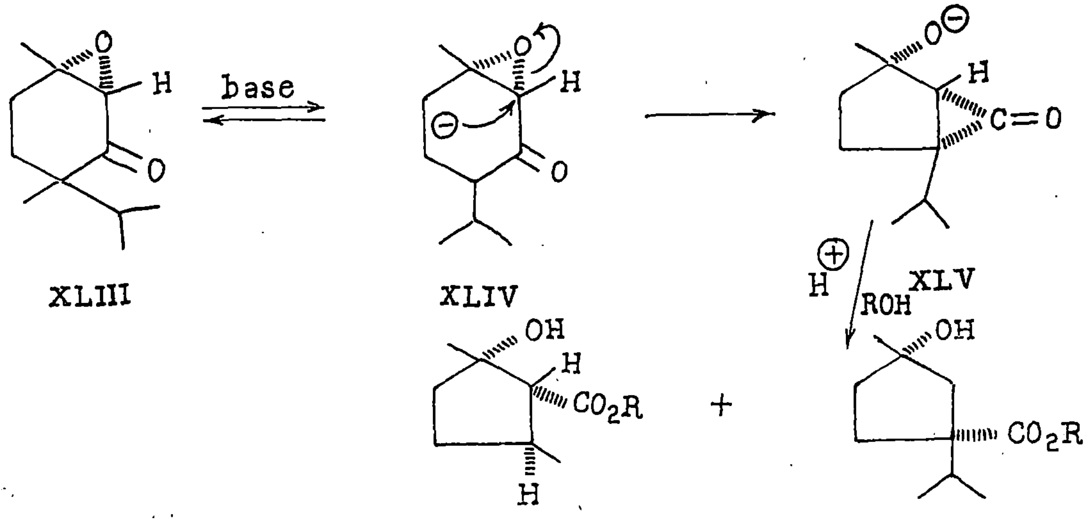
Action of base on these systems is likely to proceed as shown below:



The attack of base on the epoxide ring will generate the alkoxide ion which in an Eschenmoser - Wharton-Corey fragmentation will lead to the formation of the monocyclic unsaturated acyloin.

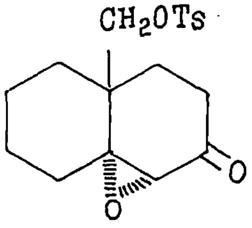
An oxo-group in conjugation with the epoxide ring can lead to Favorskii type reaction. House and Gilmore[26] have studied the Favorskii rearrangement of 2,3-expoxicyclohexanones to determine the stereochemistry of Favorskii rearrangement in cyclic systems in which the group being displaced was not bonded to a tertiary carbon atom.

When piperitone oxide was treated with base ring contraction product could be isolated from the reaction mixture. The rearrangement was postulated as proceeding through the following mechanism:

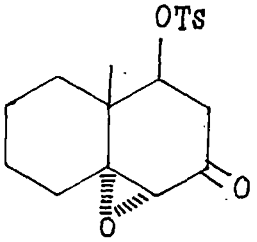


XLIII XLIV XLV XLVII XLVI

We wondered whether a similar rearrangement would occur if a carbonyl group is present in (XLI) and (XLIX) as shown below:



XLVIII



XLIX

The enols (L) and (LI) in a similar fashion can release the alkoxide ions which in an Eschenmoser - Wharton - Corey fragmentation may lead to the formation of bicyclodecenones and cyclononanones as shown in chart - 3.

The presence of the carbonyl and carboxyl functions in

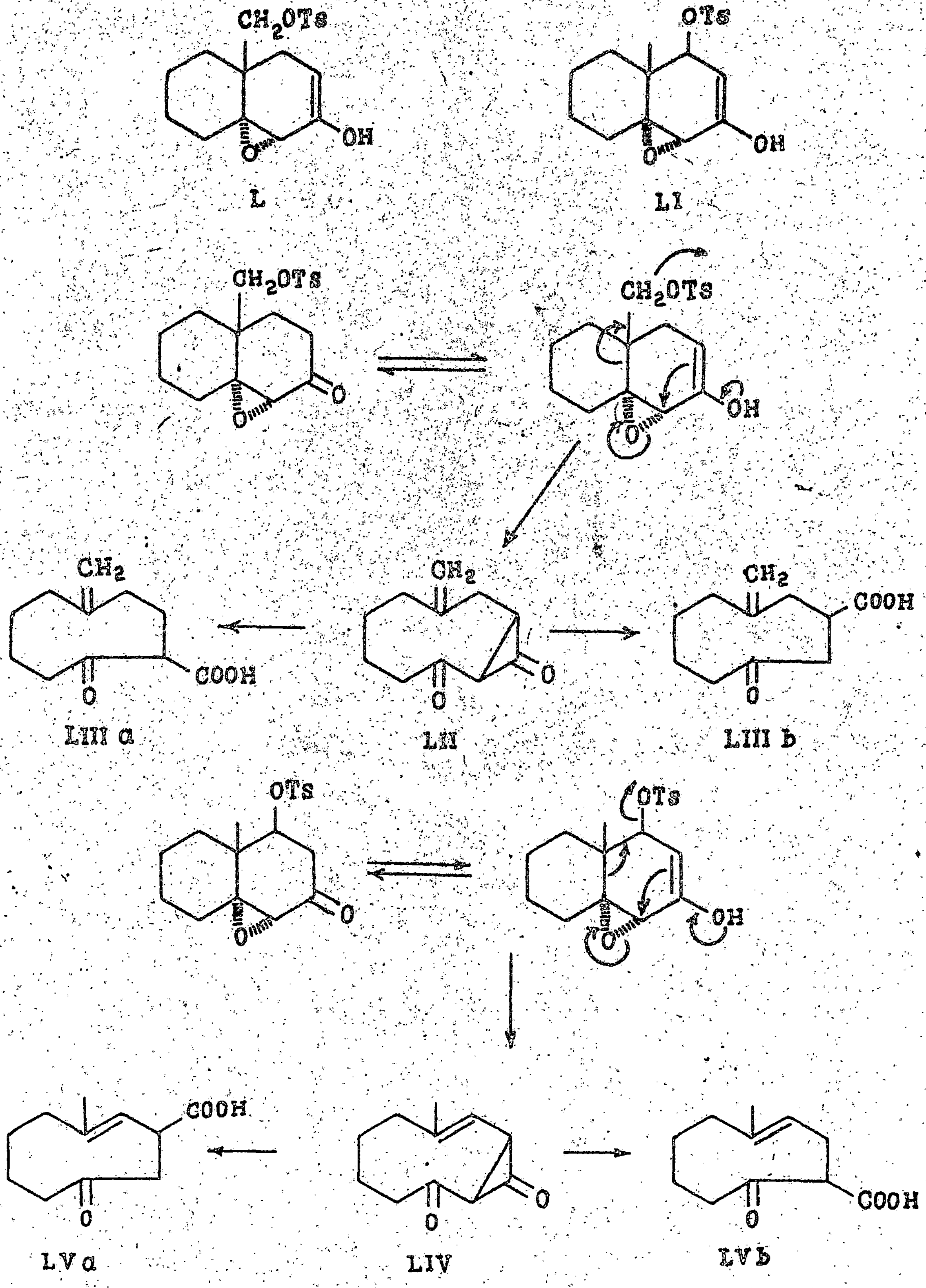
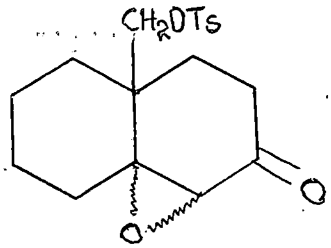

CH$_2$OTs
OTs
OH
O
L
LI
CH$_2$OTs
O
CH$_2$OTs
OH
O
CH$_2$
COOH
O
LIII a
CH$_2$
O
O
LII
CH$_2$
COOH
O
LIII b
OTs
O
O
OTs
OH
O
COOH
O
LVa
O
O
LIV
COOH
O
LVb

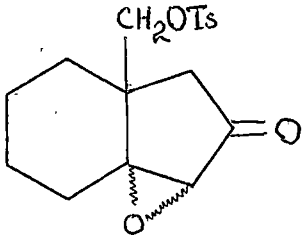
Chart - 3

(LIIIa) and (LIIIb), (LVa) and (LVb), it was felt, could be exploited for the introduction of other functionalities.

In order to test whether such a Favorskii ≠ Eschenmoser-Wharton-Corey rearrangement fragmentation reaction could be realised, we prepared 4,10-epoxy-9-tosyloxymethyl-3-decalone (XLVIII) and 3,9-epoxy-8-tosyloxymethyl-2-hydrindone (LVII) as follows:



XLVIII



LVII

Cyclohexanone-2-Carboxylate (LVIII) was prepared by condensing diethyl oxalate with cyclohexanone in presence of sodium ethoxide followed by decarbonylation. Condensation with diethylaminobutanone methoiodide with the enolate of ethyl cyclohexanone-2-carboxylate gave in 75% yield ethyl-2-(3'-oxobutyl) cyclohexanone-2-carboxylate (LIX). The cyclisation of the diketone to 10-carboethoxy-$\Delta^{1,9}$-octal-2-one (LX) was effected by sodium ethoxide in ethanol in about 66% yield (2;4-dinitrophenylhydrazone derivative, m.p. 118°C[26]). Ketalisation of the octalone according to Dreiding and Tomasewski[26] led to the formation of a lot of high boiling material and the desired Ketal was obtained in about 50% yield as reported by the workers.

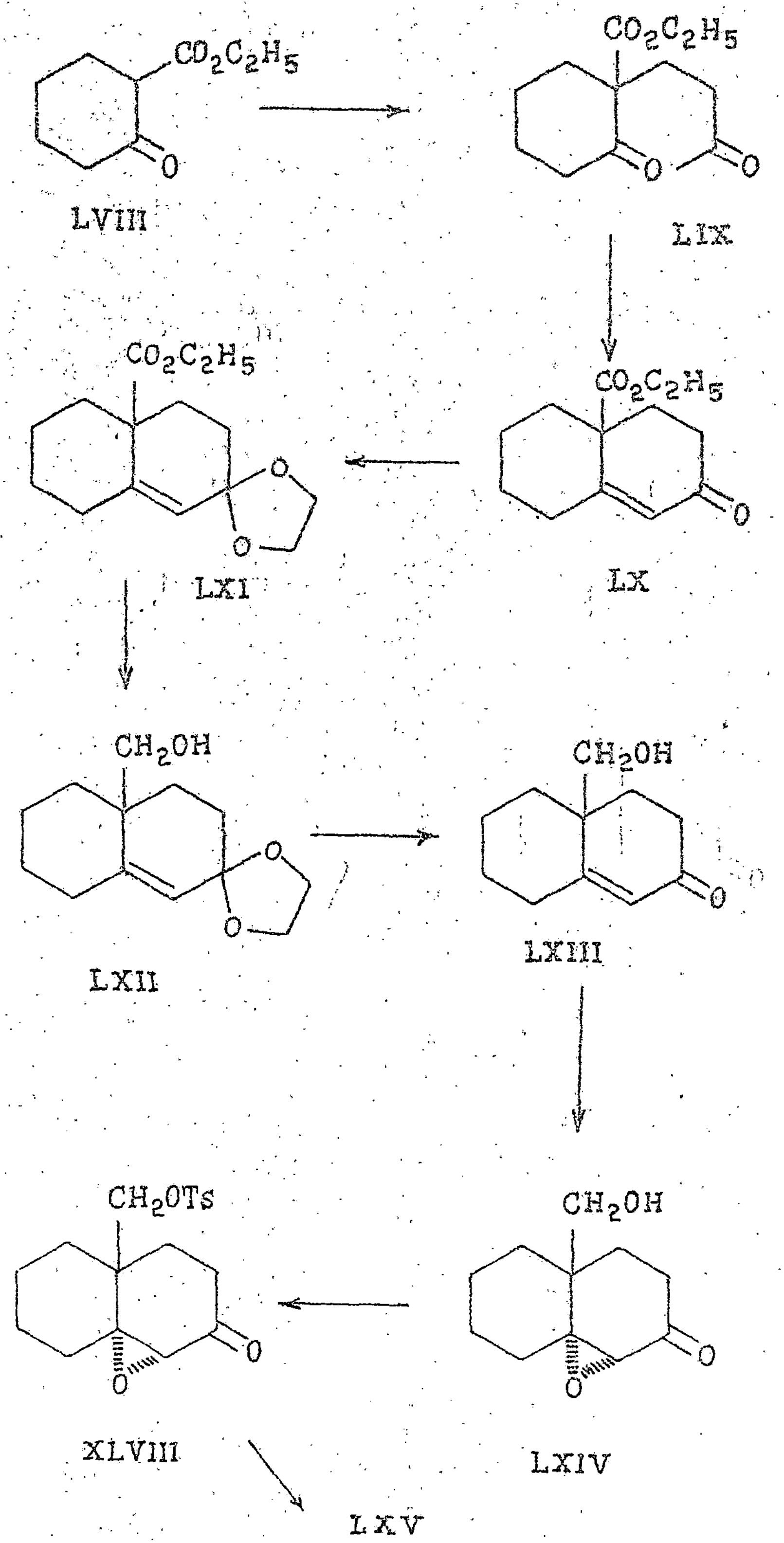
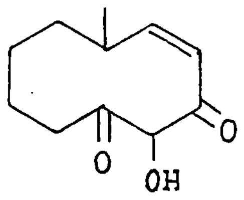

$CO_2C_2H_5$
O
LVIII
$CO_2C_2H_5$
O
O
LIX
$CO_2C_2H_5$
O
O
LXI
$CO_2C_2H_5$
O
LX
CH_2OH
O
O
LXII
CH_2OH
O
LXIII
CH_2OTs
O
O
XLVIII
CH_2OH
O
O
LXIV
LXV

Chart- 4

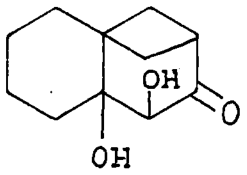
Use of just 1.2 equivalent ethane diol and a catalytic amount of p-toluenesulfonic acid, the yield of the Ketal was greatly improved. Reduction of the Ketal with Aluminium Lithium hydride gave the Ketal alcohol (LXII) (m.p. 70°C). De-Ketalisation by refluxing with MeOH - HCl gave the unsaturated Keto alcohol (2:4 - D.N.P. m.p. 155°C). Treatment with alkaline hydrogen peroxide gave the epoxy-keto-alcohol (LXIV) (I.R. 3480 cm^{-1}, 1720 cm^{-1}) and NMR) (m.p. 80°C). Careful treatment with redistilled p-toluenesufonyl chloride in Pyridine at 0°C gave epoxy-keto-tosylate (XLVIII) (I.R. 1720 cm^{-1}) (m.p. 98°C).

The compound was treated with sodium hydroxide at 0°C for three hours gave a mixture of products from which could be isolated a liquid (b.p. 145°/2m.m.) (LXV)[m/e 196].

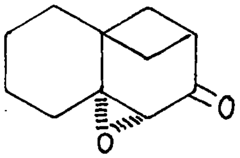
The compound which was isolated may have any one of the following structures (LXV), (LXVI), (LXVII), (LXVIII), (LXIX), (LXX), (LXXI), (LXXII).



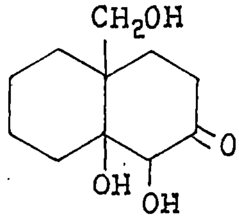
LXV



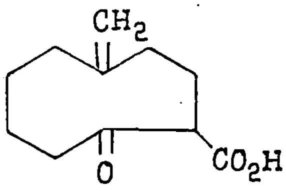
LXVI



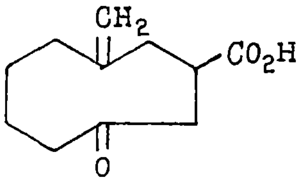
LXVII



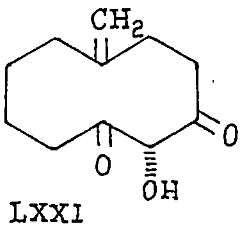
LXVIII



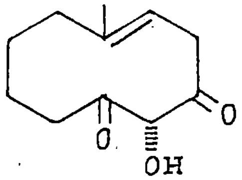
LXIX



LXX

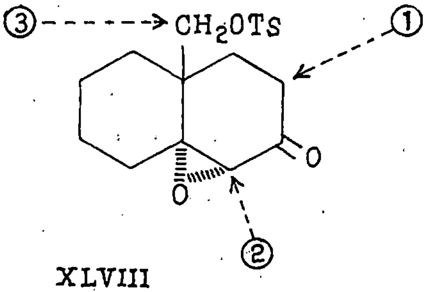


LXXI



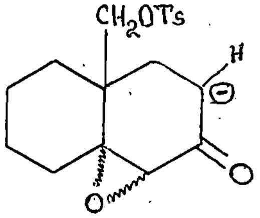
LXXII

A base may attack any or all of the indicated positions simultaneously or discretely depending upon its size, concentration and other reaction conditions.

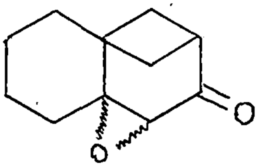


XLVIII

Attack of the base on 2 and 3 positions will result in the formation of the trihydroxy compound (LXVIII) by (a) opening of the epoxide ring and (b) nucleophilic displacement of the tosyloxy groups. Attack on position (1) will generate a carbanion as shown below:

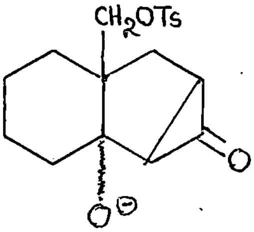


The carbanion may attack position (3) to give the tricyclic compound (LXVII).

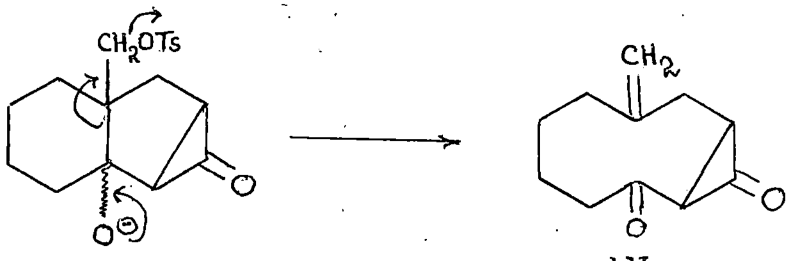


LXVII

On the other hand the attack of the carbanion on position (2) may release the alkoxide ion which may trigger the

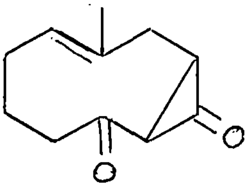


rupture of the central bond and consequent elimination of the tosyloxy group to yield(LII).



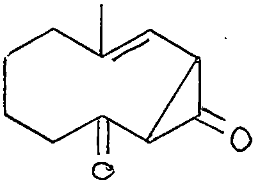
LII

The exo double bond may rearrange to endo double bonded structure (LXXIII) or (LXXIV)



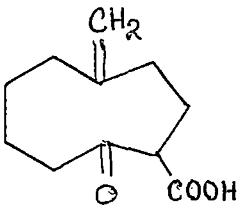
LXXIII

or

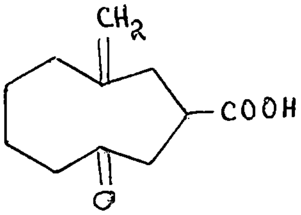


LXXIV

The cyclopropene ring of the above compounds may open up to give the acids (LXIX) or (LXX).

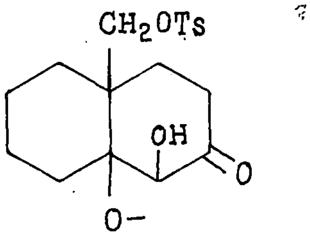


LXIX

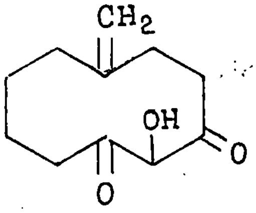


LXX

Attack of the base on position (2) may take a different course. The alkoxide released may trigger the Eschenmoser-

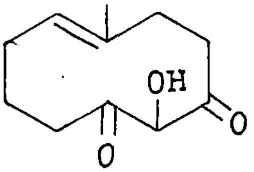


Wharton-Corey fragmentation to give (LXXI) which may rearrange

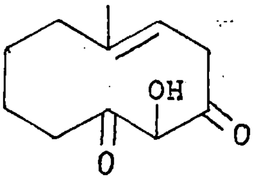


LXXI

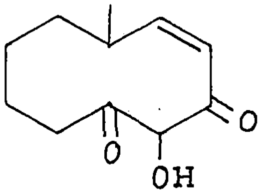
to the endo double bond structures.



or



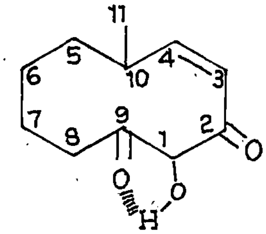
(LXV) is likely to rearrange to the thermodynamically more stable structure.



LXV

The method of isolation followed, clearly rules out the acids (LXIX) and (LXX).

Infrared spectral analysis of the compound showed absorption band at 3570 cm^{-1} ~ 3350 cm^{-1} (broad) due to intramolecular hydrogen bonding between carbonyl and the hydroxyl group. The strong absorption band at 1665 cm^{-1} indicates the presence of α,β-unsaturated carbonyl systems. This band would be expected in any one of the structures (LXV), (LXVI), (LXVIII), (LXXI) and (LXXII), but the second absorption band would remain absent for structures (LXVI), (LXVII), (LXVIII), (LXXI), (LXXII). The free carboxylic carbonyl stretching band between 1725 cm^{-1} ~ 1700 cm^{-1} remained absent in the present i.r. analysis. Though the α,β-unsaturated ketonic system is only possible for the isomeric structure (LXV) the observed hydrogen bonding stretching vibration may arise from the two adjacent ketones. Since the $>C = O$ stretching vibration for the free ketone at C - 9 has shifted to the lower energy region [1700 cm^{-1} (W)] and



the α,β -unsaturated ketonic stretching vibration at C - 2 remain at the expected region [1665 cm^{-1} (S)], it is resonable that the hydrogen bonding would arise from the Ketonic oxygen at C - 9 with hydroxyl group at C - 1.

The compound absrobed at 236 nm (ϵ=3475) and 281 (ϵ= 116) in ultraviolet. This indicates the probable presence of an α,β -unsaturated Ketone and a Ketone system in the present structure (Fig. 8).

In the PMR spectrum of this compound the proton signal due to the methyl group held on C - 10 was observed at 1.18 ppm (3H,S), which indicates that no double bond is attached to the methyl group. No evidence for the exo-cyclic double bond exists in the present systems. Accordingly, the double bond can be located between C - 3 and C - 4, the position of which is also supported by the fact the proton signal attributed to C - 3 and C - 4 position appeared at 5.72 ppm (1H, S) and 6.01 ppm (1H,d) respectively. The C - 8 methylene group of our expected structure can be accounted for from the proton signal at 2.29 ppm (2H,T). The other three methylene groups at C - 5, C - 6, C - 7 quadruplet centered from 1.41 to 1.90 ppm (6H). The proton signal due to the -CH held on C - 1 was observed at 3.99 (1H,d).

The molecular weight of the compound is 196. The probable mass fragmentation is outlined in Chart-5.

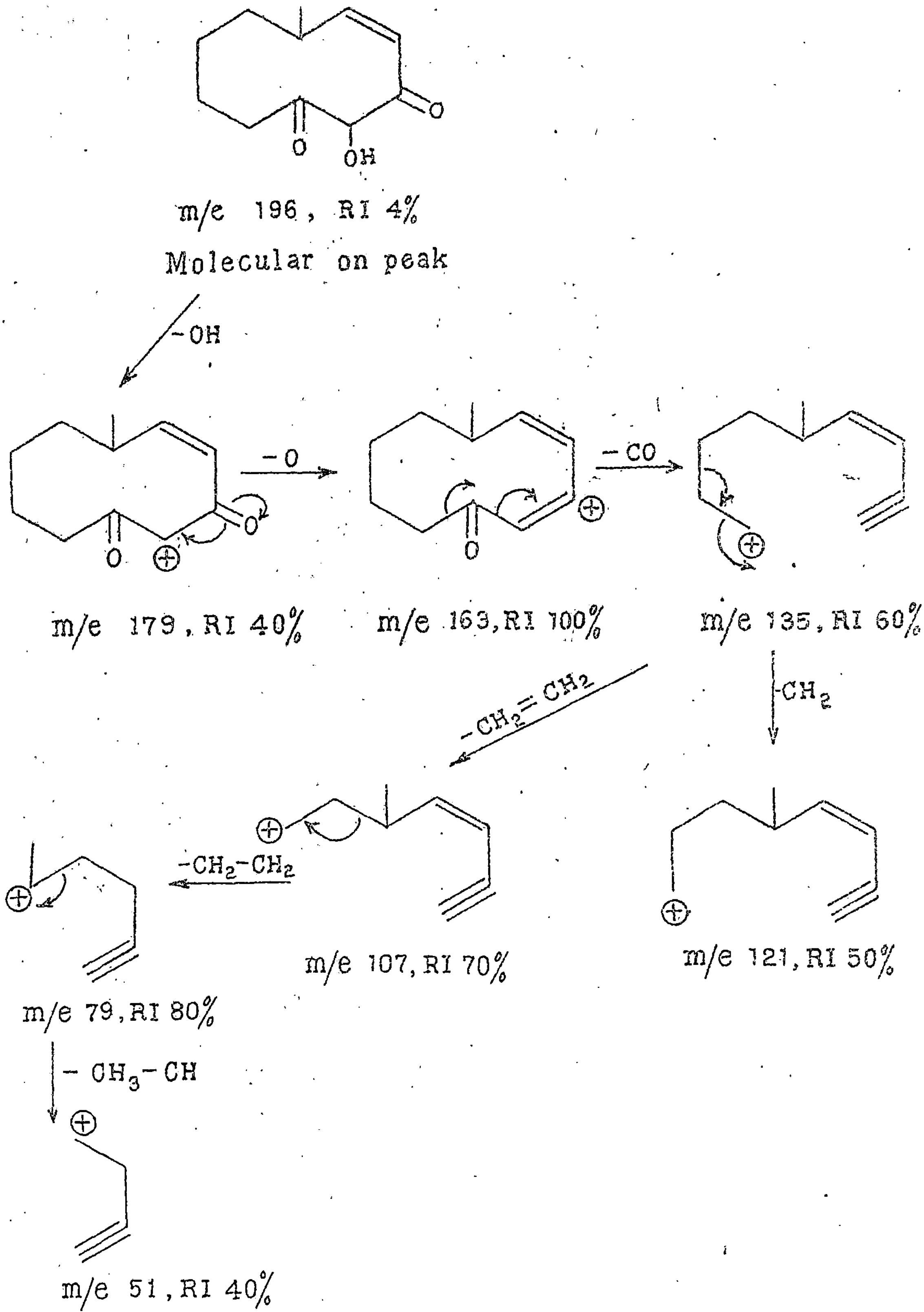

m/e 196, RI 4%
Molecular on peak
-OH
-O
-CO
m/e 179, RI 40%
m/e 163, RI 100%
m/e 135, RI 60%
-CH2=CH2
-CH2
-CH2-CH2
m/e 107, RI 70%
m/e 121, RI 50%
m/e 79, RI 80%
- CH3-CH
m/e 51, RI 40%

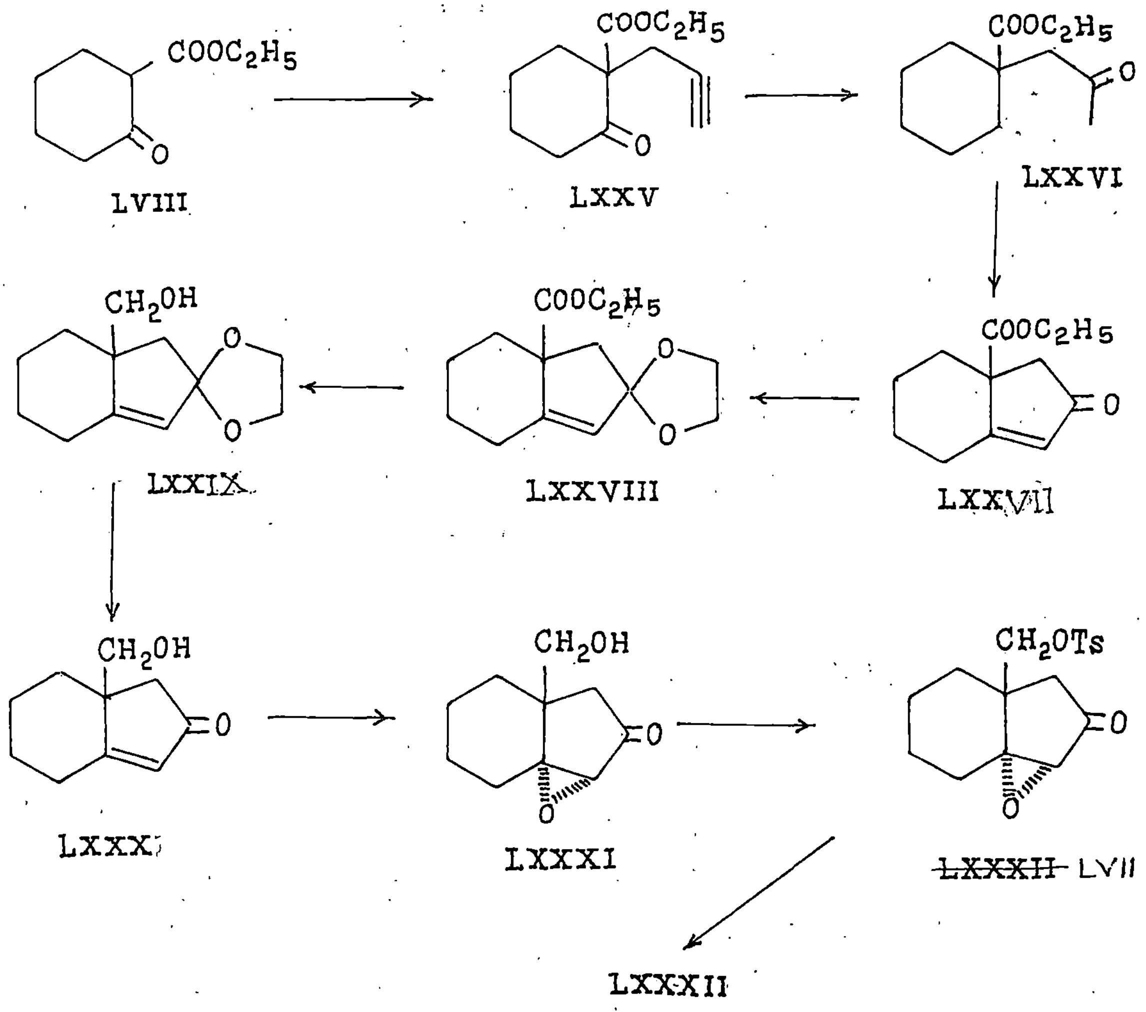
Chart - 5

On the basis of the above evidences, we have tentatively assigned the structure (LXV) to the compound. As we have no GLC facilities in our laboratory, we could not identify any other compound present in the product. However, further work is in progress in our laboratory to identify and completely characterise the fragmentation products.

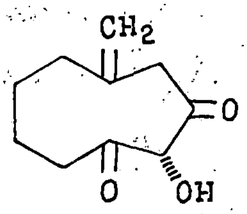
Sodioderivative of ethylcyclohexanone-2-carboxylate (LVIII) was condensed with propargyl bromide to give acetylenic compound (LXXV) as a major product. Hydration of the acetylenic compound to the acetonyl derivative (LXXVI) [b.p. 135°/ 1 mm; Disemicarbazone derivative m.p. 216°, Lit.[28] records 195.5° - 195.6°; 214°[29], i.r. 1720 cm^{-1} 1695 cm^{-1} (broad)] and subsequent ring closure by potassium tert. butoxide gave the unsaturated bicyclo Keto ester (LXXVII) [b.p. 132.5°/2.9 mm; semicarbozone derivative m.p. 202°, Lit.[28] records 202.6 - 202.8°; i.r. 1730 cm^{-1}, 1670 cm^{-1}]. Use of just 1.2 equivalent ethanediol and a catalytic amount of <u>para</u>-toluene sulfonic acid yielded Ketal (LXXVIII) [b.p. 140°/.5 mm, i.r. 1720 cm^{-1}]. Reduction of the Ketal with Aluminium Lithium Hydride gave the Ketal alcohol (LXXIX) [p.b. 145°/.5 mm]. Deketalisation by refluxing with MeOH - HCl gave the unsaturated Keto alcohol (LXXX) [b.p. 135°/.5 mm.; 2:4 Dinitrophenylhydrazone derivative m.p. 152°; i.r. 3520 cm^{-1} 3480 cm^{-1} (broad), 1670 cm^{-1}]. Treatment of alkaline hydrogen peroxide gave epoxy-keto-alcohol (LXXXI) [m.p. 72°, i.r. 3420 cm^{-1}

3340 cm^{-1} (broad), 1720 cm^{-1}]. Careful treatment with redistilled *para* - toluene - sulphonyl chloride in pyridine at 0°C gave epoxy-Keto-tosylate (LVII) [gummy mass, i.r. (crude): 1715 cm^{-1}].

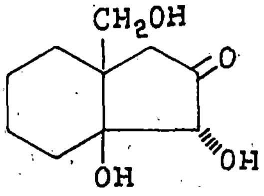
The compound was treated with sodium hydroxide at 0°C for three hours gave a mixture of products from which could be isolated a viscous liquid (b.p. 135°/.5 mm) (LXXXII).



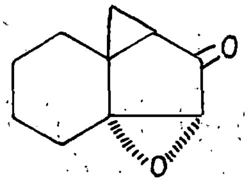
The compound which was isolated may have any one of the following structures (LXXXII), (LXXXIII), (LXXXIV), (LXXXV), (LXXXVI), (LXXXVII), (LXXXVIII), (LXXXIX).



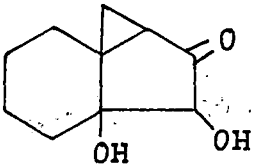
LXXXII



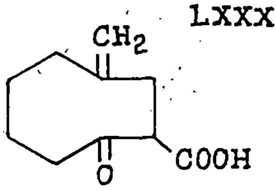
LXXXIII



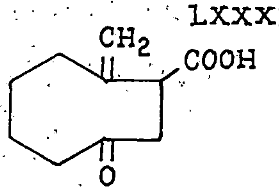
LXXXIV



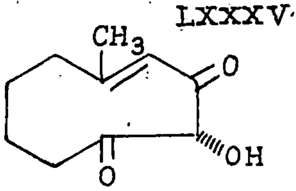
LXXXV



LXXXVI

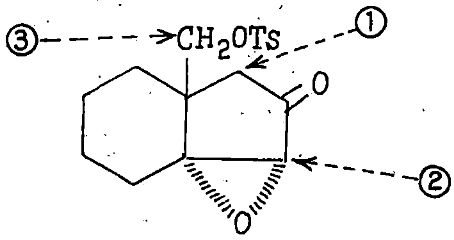


LXXXVII

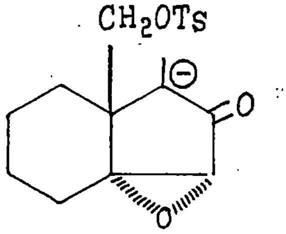


LXXXVIII

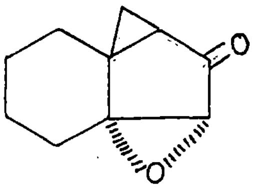
A base may attack any or all of the indicated positions simultaneously or discretely depending upon the size, concentration and other reaction conditions.



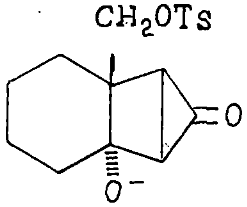
Attack of the base on (2) and (3) positions will result in the formation of the trihydroxy compound (LXXXIII) by (a) opening of the expoxide ring (b) nucleophilic displacement of the tosyloxy group. Attack on position (1) will generate a carbanion as shown below:



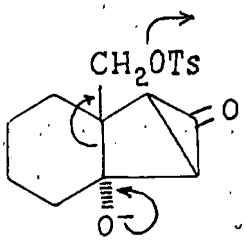
The carbanion may attack position (3) to give tricyclic compound (LXXXIV). The formation of such cyclopropane ring has been reported.[31]

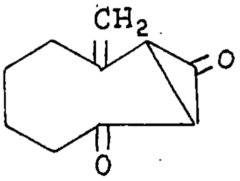


On the other hand the attack of the carbanion on position (2) may release the alkoxide ion which may trigger

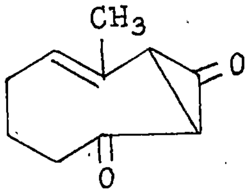


the rupture of the central bond and consequent elimination of the tosyloxy group to yield (LXXXIX).





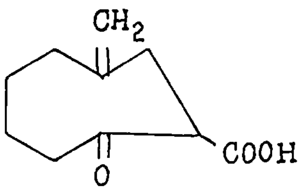
LXXXIX



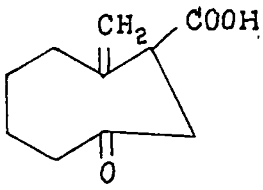
XC

The exo double bond may rearrange to endo double bonded structure (XC).

The cyclopropane ring of the above compounds may open up to give the acids (LXXXVI) or (LXXXVII)

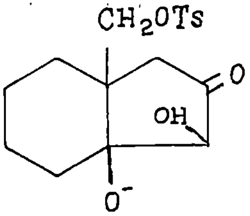


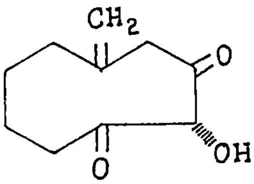
LXXXVI



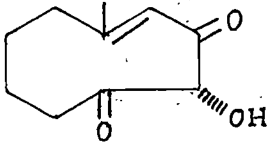
LXXXVII

Attack of the base on position (2) may take a different course. The alkoxide released may trigger the Eschenmoser - Wharton - Corey fragmentation to give (LXXXII) which may rearrange to the endo double bond structures (LXXXVIII) or (XCI).



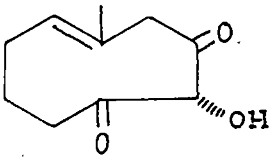


LXXXII



LXXXVIII

or



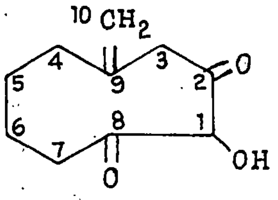
XCI

The method of isolation followed, clearly rules out the acids (LXXXVI) and (LXXXVII).

Infrared spectral analysis of the compound showed absorption band at 3450 ~ 3360 cm^{-1} due to the presence of hydroxyl group. The strong absorption band at 1720 cm^{-1} indicates the presence of carbonyl system. The i.r. band clearly rules out the structure (LXXXVIII).

The compound absorbed at 282 nm (ϵ 117) in ultraviolet. This indicated the probable presence of a Ketone system in the present structure (Fig. 19).

In the PMR spectrum of this compound, the proton signal due to the methylene group held on C - 9 was observed at 4.52 ppm (2H,d), which indicates the presence of exocyclic double bond.



The proton signal at 2.55 ppm (2H,d), 2.26 ppm (2H,d) and 2.39 ppm (2H,s) are probably due to C - 3, C - 4 and C - 7 methylene group respectively. The other two methylene groups at C - 5, C - 6 quadruplet centered from 1.5 to 1.9 ppm (4H). The proton signal

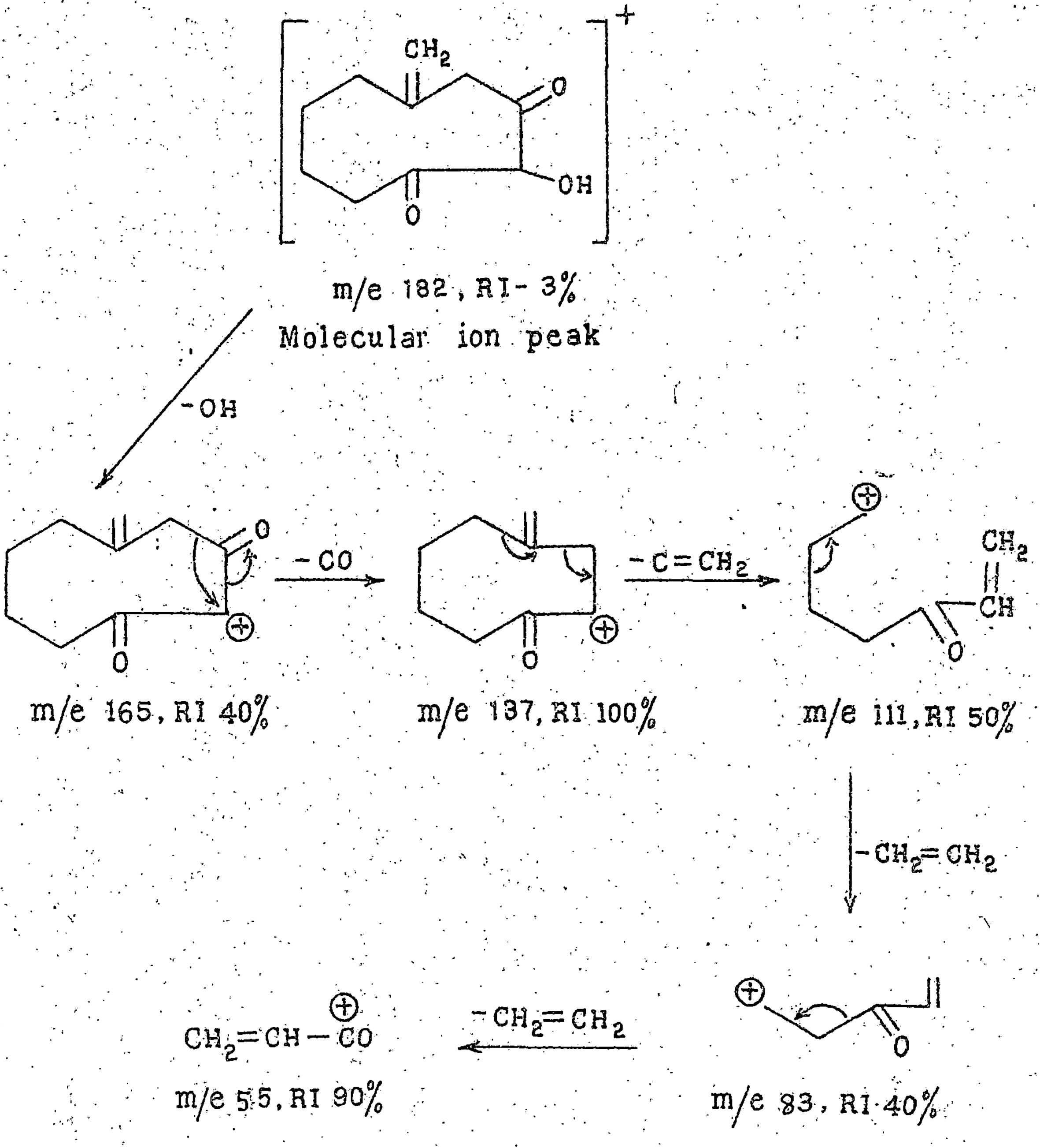

CH2
O
OH
O
+
m/e 182, RI- 3%
Molecular ion peak
-OH
O
O
m/e 165, RI 40%
- CO
O
m/e 137, RI 100%
- C=CH2
CH2
CH
O
m/e 111, RI 50%
- CH2=CH2
O
m/e 83, RI 40%
- CH2=CH2
CH2=CH—CO
m/e 55, RI 90%

Chart - 6

due to the $-\overset{|}{\underset{|}{C}}H$ held on C - 1 was observed at 3.99 ppm (1H,d).

The molecular weight of the compound is 182. The probable mass fragmentation is outlined in Chart-6.

On the basis of the above evidences, we have tentatively assigned the structure (LXXXII) to the compound. As we have no GLC facilities in our laboratory, we could not identify any other compound present in the product. However, further work is in progress in our laboratory to identify and completely characterise the fragmentation products.

EXPERIMENTAL

The melting and boiling points are uncorrected. The solvent extracts were dried over anhydrous sodium sulphate. Alumina used for chromatographic adsorption was E. Merck Aluminium oxide standardised for chromatography according to Brockmann. Infrared and PMR spectra were recorded on Beckmann - 20 IR spectrophotometer and varian EM.390 90 Mhz spectrometer respectively. The symbol S, M and W represent the strong, medium and weak band respectively in IR absorption.

Ethyl Cyclohexanone-2-Carboxylate (LVIII)

A solution of sodium ethoxide was prepared by the cautious addition of clean sodium (23 g, 1 gm mole) to anhydrous ethanol (300 ml) and cooled to 0°C in an ice salt bath. A mixture of redistilled cyclohexanone (98 g, 1 mole) and diethyl oxalate (146 g, 1 mole) was then added in one lot and after thorough mixing left overnight in an ice bath. The following day the reaction mixture was diluted, acidified with 10 (N) Sulphuric acid and extracted with ether. The extract was washed until neutral, dried and the solvent was removed.

To the residue soft glass powder was added and heated it in an oil bath at about 180°C, until no more carbon monoxide evolved. The residue on distillation gave ethyl cyclohexanone-2-carboxylate (180 g) b.p. 110/10 mm.

Ethyl-2-(3'-oxobutyl)-cyclohexan-1-one-2-Carboxylate (LIX)

Diethyl aminobutan-3-one methiodide prepared from methyl iodide (10 ml) and diethylaminobutanone (17 g; 0.12 mole) was covered with anhydrous benzene (100 ml.). Ethyl-cyclohexanone-2-carboxylate (17 g; 0.1 mole) was added in one lot followed by dropwise addition of sodium ethoxide in ethanol prepared from sodium (2.3 g; 0.1 g. atom) and anhydrous ethanol (40 ml) with continuous cooling and stirring. After the addition, the reaction mixture was stirred for an additional hour and left overnight. The following day, the reaction mixture was refluxed for an hour, cooled and diluted. The benzene layer was separated and the aqueous layer extracted once with ether. The combined extracts were washed, dried and concentrated. Distillation of the residue gave ethyl-2-(3'-oxobutyl)-cyclohexan-

-1-one-2-carboxylate (18 g), b.p. 138°/0.5 mm. It was used such as in the next step.

10-Carboethoxy-$\Delta^{1,9}$-octal-2-one (LX)

To a solution of sodium ethoxide in ethanol [prepared from sodium 3.1 g; 0.135 g. atom and anhydrous ethanol (160 ml)] was added under an atmosphere of nitrogen ethyl-2-(3'-oxobutyl)-cyclohexane-1-one-2-carboxylate (25 g; 0.104 mole) and the reaction mixture left at room temperature for 2 hrs. and then acidified with glacial acetic acid. Sodium acetate was filtered off and alcohol removed under reduced pressure. The residue was taken up in benzene, washed with brine, saturated sodium bicarbonate solution and brine, dried and the solvent distilled off. The residue on distillation gave 10-Carboethoxy-$\Delta^{1,9}$-octal-2-one (17 g) b.p. 136°/2 mm.

I.R. (Liquid) [in cm^{-1}]

2920 (s), 2840 (s), 1720 (s), 1670 (s), 1630 (s), 1450 (s), 1370(M), 1350 (M), 1340 (M), 1325 (W), 1300 (M), 1260 (s), 1220 (s), 1190 (s), 1180 (M), 1150 (M), 1140 (W), 1095 (s), 1060 (M), 1040 (M), 1020 (M), 980 (W), 950 (M), 930 (W), 905 (W), 880 (M), 860 (M), 835 (W), 780 (W), 760 (M). (Fig.)

The 2:4-dinitrophenylhydrazone prepared in the usual way crystallised as crimson plates from ethyl acetate-ethanol m.p. 117°C (literature[26] records 117-118°C).

Anal. Calcd. for $C_{19}H_{22}O_6N_4$: C = 56.71%, H = 5.47%,
N = 13.93%,

Found C = 56.70%, H = 5.46%, N = 13.90%.

Semicarbazone prepared in the usual way on crystallisation from ethanol melted at 208°C (lit.[27] records 186-188°C).

Anal. Calcd. for $C_{14}H_{21}O_3N_3$: C = 60.21%, H = 7.52%,
N = 15.05%,

Found C = 60.20%, H = 7.50%, N = 5.04%.

10-Hydroxymethyl-$\Delta^{1,9}$-octal-2-one (LXIII)

10-Carboethoxy-$\Delta^{1,9}$-octal-2-one (22.1 g, 0.1 mole) was refluxed with ethane diol (7.5 g, 0.12 mole), para-toluene sulphonic acid (50 mg) and dry benzene (200 ml) using a water separator until no more water separated. The reaction mixture was cooled, washed with saturated sodium bicarbonate solution and brine, dried and concentrated. Distillation of the residue afforded the ethylene Ketal of 10-carboethoxy-$\Delta^{1,9}$-octal-2-one (LXI) (24 g.) b.p. 142°/2 mm.

The above Ketal (5.7 g) was hydrolysed by refluxing with 65% methanol (60 ml) containing conc. hydrochloric acid (4 ml) for 1 hour. The product was isolated by ether. The ether extract was washed with brine, saturated sodium bicarbonate solution and water, dried and concentrated. The residue on distillation gave 10-hydroxymethyl- $\Delta^{1,9}$ -octal-2-one (LXIII) b.p. 136°/0.6 mm. I.R. (Liquid) [in cm^{-1}]

3420 ~ 3380 (broad), 2840 (s), 1665 (s), 1470 (M), 1455 (s), 1360 (M), 1340 (M), 1310 (W), 1240 (M), 1210 (W), 1170 (W), 1140 (M), 1080 (s), 1030 (s), 990 (M), 970 (M), 940 (M), 910 (W), 870 (M), 850 (W), 840 (M), 790 (M), 740 (W), 680 (M). (Fig.).

It formed a 2:4-dinitrophenylhydrazone which on crystallisation from ethanol had m.p. 155°C.

I.R. (nujol) [in cm^{-1}]

3300 (s), 3100 (W), 1610 (s), 1590 (s), 1540 (M), 1500 (s), 1430 (M), 1380 (M), 1360 (M), 1330 (s), 1305 (s), 1290 (M), 1260 (M), 1215 (M), 1125 (M), 1060 (M), 1050 (W), 1040 (W), 1015 (W), 980 (W), 920 (M), 860 (M), 835 (M), 825 (M), 820 (M), 760 (W), 735 (s), 690 (M). (Fig.).

4-10-epoxy-9-hydroxymethyl-3-decalone (LXIV)

A solution of 10-Hydroxymethyl- $\Delta^{1,9}$ -octal-2-one (1.7 g. .01 mole) and methanol (50 ml) was cooled to 0°C in an ice-salt bath. Then a mixture of 4(N) sodium hydroxide (10 ml) and 30% hydrogen peroxide (10 ml) was added with continuous stirring. After the addition, the reaction mixture was stirred for an additional hour and left for 72 hours in fridge. Methanol was removed on waterbath under reduced pressure. The residue was cooled and diluted with water (30 ml). The aqueous layer extracted with benzene. The extract was washed until neutral, dried and the solvent removed. The gummy mass on crystallisation from petroleum ether (60-80), gave the epoxy alcohol (LXIV) m.p. 80°C.

Anal. Calcd. for $C_{11}H_{15}O_3$; C = 67.69%; H = 7.69%;

Found C = 67.66%, H = 7.68%;

I.R. (nujol) [in cm^{-1}]

3480 (s), 1720 (s), 1450 (s), 1425 (s), 1370 (s), 1340 (s), 1310 (M), 1250 (s), 1210 (s), 1175 (M), 1140 (s), 1080 (s), 1025 (s), 970 (s), 940 (s), 910 (M), 890 (M), 870 (W), 860 (M), 840 (s), 790 (s), 760 (M). (Fig.).

4,10-epoxy-9-tosyloxymethyl-3-decalone (XLVIII)

4,10-epoxy-9-hydroxymethyl-3-decalone (2.0 g) was dissolved in absolute pyridine (3 ml) and cooled to -5°C. It was treated with freshly distilled para-toluene sulphonyl chloride (2.5 g) in absolute pyridine (4 ml) and left at 10° for 72 hours. The mixture was poured into a slurry of ice, the gummy white solid was extracted with chloroform. The extract was washed with ice cold water several times, dried and concentrated. The tosylate (3.0 g) was obtained as a white solid m.p. 98°C.

I.R. (nujol) [in cm^{-1}]

2920 (s), 2260 (s), 1720 (s), 1590 (M), 1460 (s), 1470 (M), 1370 (M), 1330 (s), 1290 (W), 1280 (W), 1255 (W), 1186 (M), 1170 (s), 1140 (W), 1120 (W), 1060 (W), 1030 (M), 1010 (M), 990 (M), 925 (s), 890 (W), 830 (M), 820 (M), 810 (M), 700 (M), 680 (M), 670 (M). (Fig.)

Action of base on (XLVIII)

To a solution of 4,10-epoxy-9-tosyloxy methyl-3-decalone (XLVIII) (1.0 g; 0.003 mole) in methanol (6 ml) at 0°C was added a methanolic solution of Sodium hydroxide (.5 g in 4 ml methanol) in one lot and left at 0°C for 3 hours. The reaction mixture was diluted with brine, extracted with ether, washed well with brine and finally with water, dried and the ether was distilled off. The viscouse liquid on distillation gave (LXV) b.p. 148°/1 mm.

I.R. (Liquid) [in cm^{-1}].

3670 ~ 3350 (broad), 2920 (s), 2860 (s), 1760 (W), 1665 (s), 1620 (M), 1460 (s), 1370 (W), 1350 (M), 1260 (s), 1200 (W), 1165 (M), 865 (S), 810 (s), 795 (s). (Fig.).

PMR:

1.18 (3H,S), 1.41 - 1.99 (6H,q), 2.29 (2H,t), 3.99 (1H,d), 5.72 (1H,s), 6.01 (1H,d). (Fig.)

Mass: m/e 196

The aqueous portion was acidified with dilute hydrochloric acid (1:1) and extracted with chloroform, washed until neutral, dried and concentrated. The gummy mass which did not solidify was not purified.

Ethyl-2-propargyl-cyclohexan-1-one-2-carboxylate (LXXV)

To sodio-derivative of ethyl-cyclohexanone-2-Carboxylate, prepared in the usual way from ethyl-cyclohexanone-2-Carboxylate (51 g. 0.3 mole) and sodium dust (7.6 g; 0.33 mole) in anhydrous benzene (200 ml), was added dropwise propargyl bromide (39.27 g; 0.33 mole) with cooling and stirring. The mixture was refluxed on a steam bath for 5 hours, cooled, washed well with water and concentrated. The residue on distillation gave ethyl-2-propargyl-cyclohexan-1-one-2-carboxylate (56 g) b.p. 136°/9 mm.

Semicarbazone prepared by sodium acetate method on crystallisation from aqueous ethanol melted 154°c (lit.[28] records 152.7 - 153.5°c).

Ethyl-2-(2'-oxopropyl)-cyclohexane-1-one-2-carboxylate (LXXVI)

A solution of ethyl-2-propargyl-cyclohexan-1-one-2-Carboxylate (58 g; 0.27 mole) in 100 ml methanol was added dropwise with stirring to the catalyst prepared by momentarily warming a mixture of red oxide of mercury (3.8 g), Borontrifluoride-Ether complex (3 ml), Trichloro acetic acid and 15 ml methanol. A slightly exothermic reaction ensued. After the addition the reaction mixture was stirred at room temperature for an additional two hours and poured in to very dilute cold sulphuric acid with stirring. The product was isolated with ether, washed with water, dried and the solvent distilled off. The residue on distillation gave ethyl-2-(2'-oxopropyl)-cyclohexan-1-one-2-carboxylate (45 g) b.p. 135°/1 mm.

I.R (nujol) [in cm^{-1}]:

2940 (s), 1720 ~ 1696 (broad), 1465 (M), 1450 (s), 1420 (M), 1400 (M), 1360 (s), 1340 (W), 1310 (M), 1255 (M), 1220 (s), 1196 (s), 1156 (s), 1140 ~ 1125 (s), 1080 (M), 1070 (M), 1050 (W), 1020 (M), 1010 (M), 975 (W), 950 (W), 910 (M), 850 (M), 820 (W). (Fig.).

Disemicarbazone prepared in the usual way had a crude melting point 216°C. It could not be purified due to its insolubility (Lit.[28] records 196.5°- 195.6°C, 214°C[29]).

Ethyl 2,4,5,6,7,8 hexahydroindene-2-one-8-Carboxylate (LXXVII)

Potassium (11.0 g; 0.282 g atom) was dissolved in 450 ml tertiary butyl alcohol by heating under reflux. When the solution had cooled to room temperature, ethyl-2-(2'-oxopropyl)-cyclohexan-1-one-2-Carboxylate (56 g; 0.243 mole) was added in one lot. A mild exothermic reaction ensued. After standing for 25 minutes at room temperature the reaction mixture was poured into 450 ml ice-water and 24 ml. of conc. hydrochloric acid was rapidly added. The product was isolated after saturation with sodium chloride with ether, dried, and the solvent distilled off. The residue on distillation gave ethyl 2,4,5,6,7,8 hexahydroindene-2-one-8-Carboxylate (LXXVII) (30 g) b.p. 132.5°/2.8 mm.

I.R. (Liquid) [in cm^{-1}]

2920 (s), 2840 (s), 1730 (s), 1670 (s), [illegible] (s), 1630 (s), 1450 (s), 1370 (M), 1350 (M), 1340 (W), 1300 (M), 1260 (s), 1240 (s), 1220 (s), 1190 (M), 1150 (M), 1095 (s), 1060 (M), 1040 (M), 1020 (M), 950 (M), 930 (W), 905 (W), 860 (s), 835 (W), 780 (W), 760 (M), 680 (W). (Fig. 13).

Semicarbazone prepared in the usual way on crystallisation from ethanol melted 202°C (Lit.[28] records 202.6°- 202.8°C).

Anal. Calcd. for $C_{13}H_{19}O_3N_3$; C = 58.86%; H = 7.16%;
N = 15.85%

Found C = 58.84%; H = 7.15%; N = 15.83%.

Ethylene Ketal of 8-hydroxymethyl 2,4,5,6,7,8 hexahydroindene-2-one (LXXIX)

A mixture of ethyl 2,4,5,6,7,8 hexahydroindene-2-one-8-Carboxylate (20.8 g; 0.1 mole), ethane diol (8.16 g; 0.13 mole), Para-toluene sulphonic acid (50 mg) and dry benzene (200 ml) was refluxed using a water separator for three hours after which time there was no more water separated. The reaction mixture was cooled, washed with saturated sodium bicarbonate solution and water, and concentrated. The residue on distillation gave 22 g, of ethylene ketal of 2,4,5,6,7,8 hexahydroindene-2-one-8-Carboxylate (LXXVIII) b.p. 140°/.5 mm.

I.R. (Liquid) [in cm^{-1}]

2920 (s), 1720 (s), 1620 (W), 1450 (s), 1370 (M),
1350 (W), 1260 (M), 1230 (M). (Fig.).

The solution of the above Ketal in anhydrous ether (100 ml) was added dropwise with stirring to a solution of Lithium aluminium hydride (3.66 g) in anhydrous ether (200 ml). After the addition, the mixture was gently refluxed for 12 hours. Excess of the hydride was decomposed by careful addition of water (2 ml) to the well cooled reaction mixture and the complex was decomposed by saturated sodium sulphate solution. Ether Layer was separated, dried and concentrated. The residue on distillation gave ethylene Ketal of 8-hydroxymethyl 2,4,5,6,7,8 hexahydroindene-2-one (LXXIX) (18 g), b.p. 145°/0.5 mm.

8-Hydroxymethyl 2,4,5,6,7,8 hexahydroindene-2-one (LXXX)

A solution of the ethylene Ketal of 8-hydroxy methyl 2,4,5,6,7,8 hexahydroindene-2-one (5 g) in methanol (30 ml) was warmed with 5% hydrochloric acid at 50°C for one hour, when the turbid reaction mixture became clear, the heating was stopped and the reaction mixture was cooled, diluted with brine, extracted with ether and the extract washed well with brine and concentrated. Distillation of the residue 8-hydromethyl 2,4,5,6,7,8 hexahydro-indene-2-one (2.5 g) (LXXX) b.p. 135°/0.5 mm.

I.R. (Liquid) [in cm^{-1}]:

3520 ~ 3480 (broad), 2900 (s), 1670 (s), 1610 (M),
1440 (s), 1410 (W), 1280 (M), 1230 (W), 1190 (M),
1160 (M), 1080 ~ 1055 (M), 1025 (M), 940 (M), 840 (W),
850 (M), 750 (W). (Fig.).

2:4 - Dinitrophenyl hydrazone prepared by sulphuric acid method on crystallisation from dilute ethanol separated as red crystals m.p. 152°C.

Anal. Calcd. for $C_{16}H_{18}O_5N_4$: C = 55.65%,

H = 4.92% ; N = 16.23%

Found C = 55.62% ; H = 4.91% ; N = 16.21%.

I.R. (nujol) [in cm^{-1}] :

3300 (s), 3100 (s), 2920 (s), 2860 (s), 1610 (s),
1585 (s), 1540 (W), 1500 (M), 1460 (M), 1430 (W),
1410 (W), 1380 (M), 1360 (M), 1340 (s), 1310 (s),
1275 (M), 1220 (M), 1190 (W), 1130 (M), 1065 (M),
1040 (W), 920 (M), 830 (M). (Fig.).

3,9-epoxy-8-hydroxymethyl-2-hydroindene (LXXXI)

To a solution of 8-hydroxy methyl 2,4,5,6,7,8-hydroindene-2-one (1.66 g; 0.01 mole) in methanol (50 ml) cooled to 0°c was added a mixture 4(N) Sodium hydroxide (10 ml) and hydrogen peroxide (10 ml) in one lot with continuous stirring. After the addition the reaction mixture was stirred for an additional hour and left it for 72 hours in fridge. Methanol was removed on water bath under reduced pressure. The residue was cooled and diluted with water (50 ml). The aqueous layer was extracted with benzene, washed until neutral, dried and the solvent distilled off. The gummy mass was crystallised from pet-ether (60-80) to give the epoxy alcohol (LXXXI) m.p. 72°c.

Anal. Calcd. for $C_{10}H_{14}O_3$; C = 65.93%; H = 7.69%

Found C = 65.90% ; H = 7.68%.

I.R. (nujol) [in cm^{-1}]

3420 ~ 3340 (broad), 2920 (s), 2840 (s), 1700 (s), 1470 (s), 1450 (s), 1410 (W), 1380 (M), 1290 (M), 1240 (M), 1210 (W), 1190 (M), 1140 (M), 1090 ~ 1060 (broad), 1030 (M), 1010 (M), 970 (W), 850 (M), 810 (W), 790 (W). (Fig.).

3,9-epoxy-8-tosyloxymethyl-2-hydroindone (LVII)

To a solution of epoxy alcohol (LXXXI) (3.32 g; 0.02 mole) in absolute pyridine (5 ml) cooled to -10°C was added a solution of freshly distilled para-toluene sulphonyl chloride (4.5 g; 0.21 mole) in absolute pyridine (5 ml) in one lot and left at 5°C for 48 hours. The reaction mixture was poured into slurry of ice and extracted with chloroform. The extract was washed consecutively with water, dried and concentrated. The crude gummy tosylate (4.5 g) which did not solidify on tituration, was used as such in subsequent steps.

I.R. (gummy mass) [in cm^{-1}] :

2920 ~ 2840 (broad), 2670 (W), 1715 (s), 1660 (M), 1620 (W), 1590 (s), 1470 (s), 1440 (s), 1420 (s), 1390 (W), 1370 (s), 1325 (s), 1280 (M), 1260 (W), 1240 (M), 1205 (M), 1180 (s), 1160 (s), 1130 (W), 1110 (W), 1080 (M), 1020 (M), 1010 (M), 980 (s), 940 ~ 900 (broad), 860 (s), 840 (M), 830 (M), 810 (M), 780 (M), 700 (s). (Fig.).

Action of base on (LVII)

To a solution of 3,9-epoxy-8-tosyloxymethyl-2-hydroindone (LVII) (0.99 g; 0.003 mole) in methanol (4 ml) at 0°C was added a methanolic solution of sodium hydroxide (0.5 g in 4 ml.

methanol) in one lot and left at 0°C for 3 hours. The reaction mixture was diluted with brine, extracted with ether, washed well with brine and finally with water, dried and the solvent distilled off. The viscous liquid on distillation gave (LXXXII) b.p. 142°/ 1 mm.

I.R. (Liquid) [in cm^{-1}]

3450 - 3360 (broad), 1720 (s), 1605 (M), 1490 (W), 1460 (M), 1370 (s), 1290 (M), 1230 (W), 1175 (s), 1090 (s), 1040 - 1015 (broad), 950 (M), 900 (M), 840 (M), 810 (s). (Fig.).

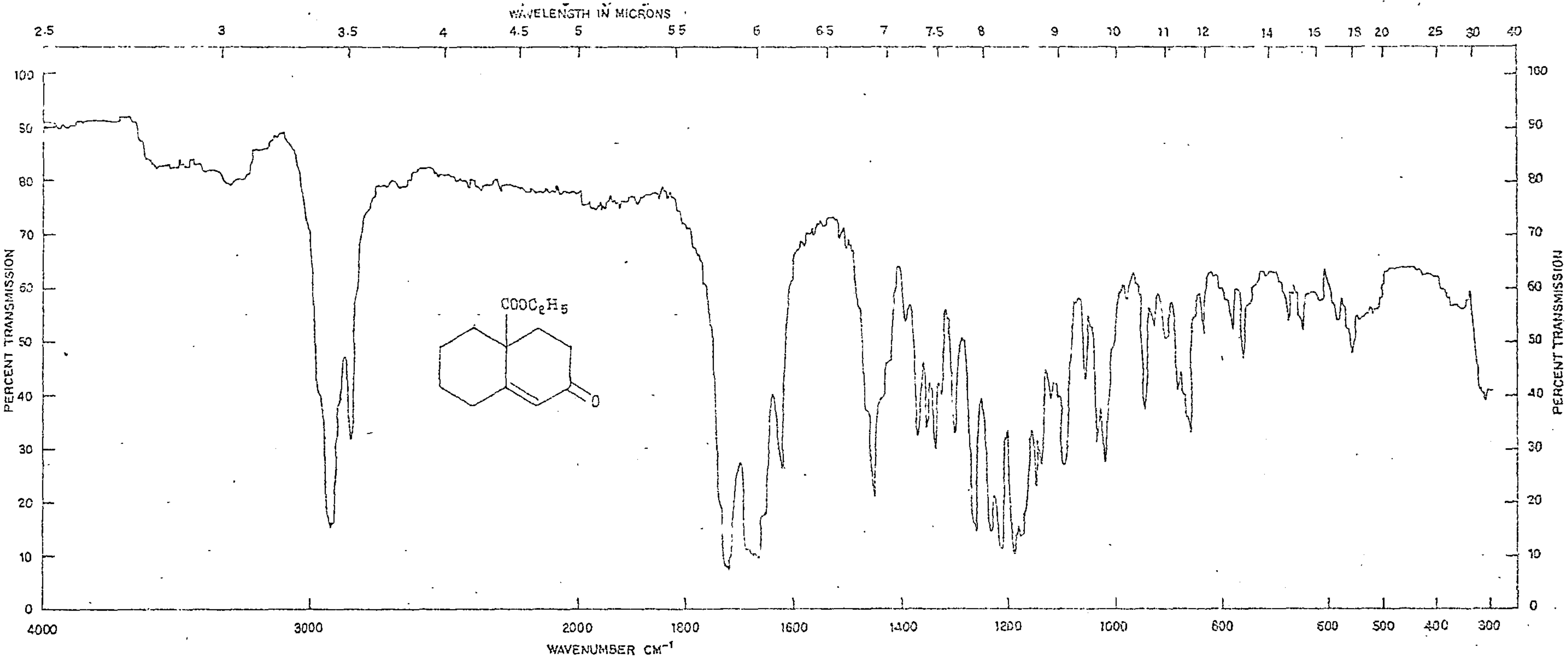
PMR :

1.5 - 1.9 (4H,q), 2.25 (2H,d), 2.55 (2H,d), 2.39 (2H,s), 3.99 (1H,d), 4.52 (2H,d). (Fig.).

Mass: m/e 182

The aqueous portion was acidified with dilute hydrochloric acid (1:1) and extracted with chloroform, washed until neutral, dried and concentrated. The gummy mass which did not solidify could not be purified.

SPECTRA



WAVELENGTH IN MICRONS
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3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
COOC$_2$H$_5$
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3000
2000
1800
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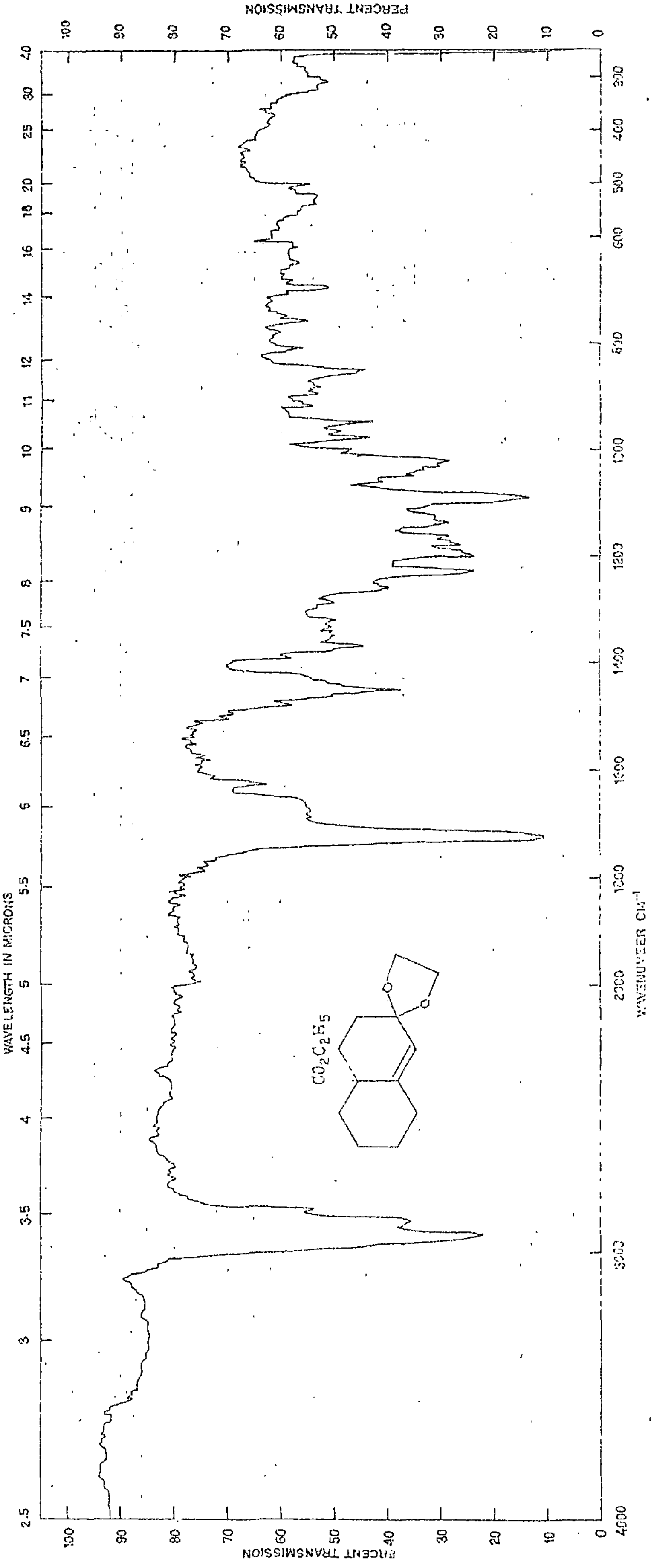
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM^{-1}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6.5
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7.5
8
9
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11
12
14
16
18
20
25
30
40
WAVENUMBER CM⁻¹
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1800
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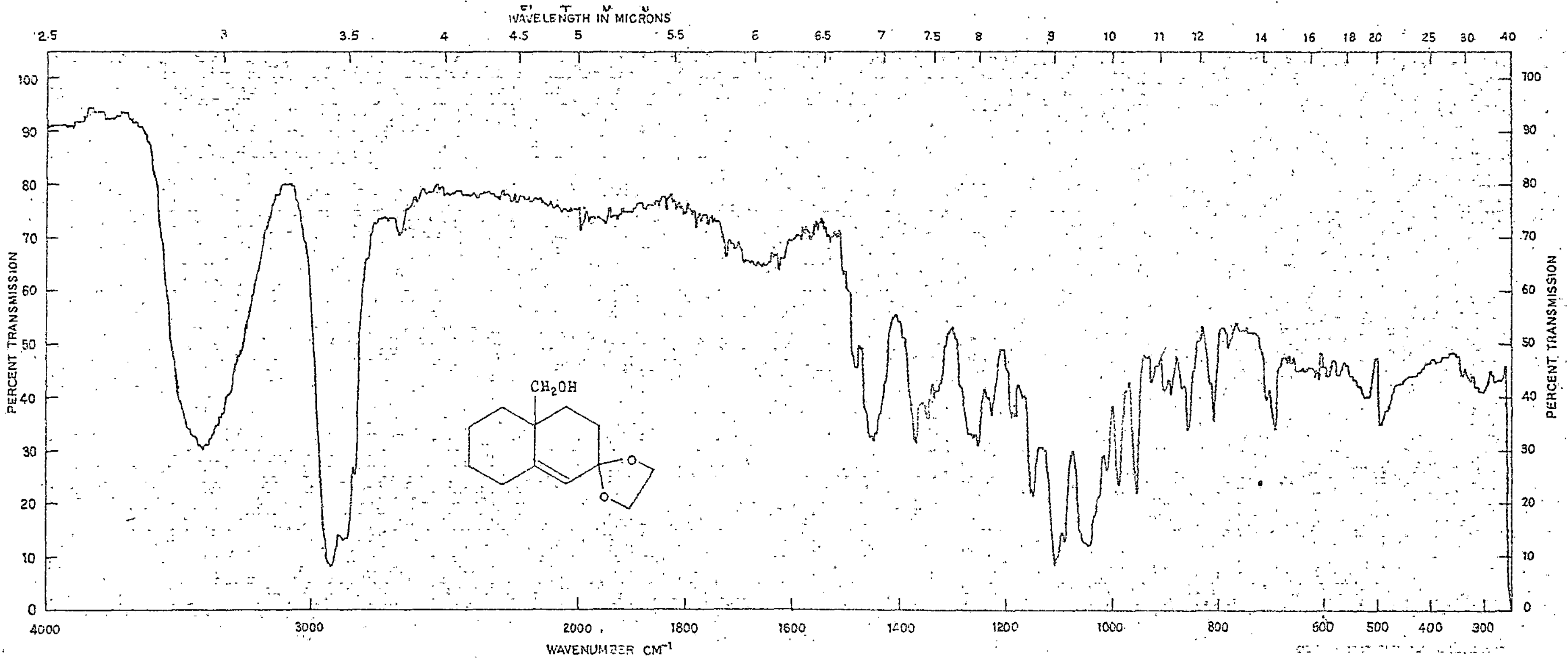
1400
1200
1000
800
600
500
400
300
O
O
CO2C2H5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7.5
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
0
10
20
30
40
50
60
70
80
90
100
4000
3000
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1400
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1000
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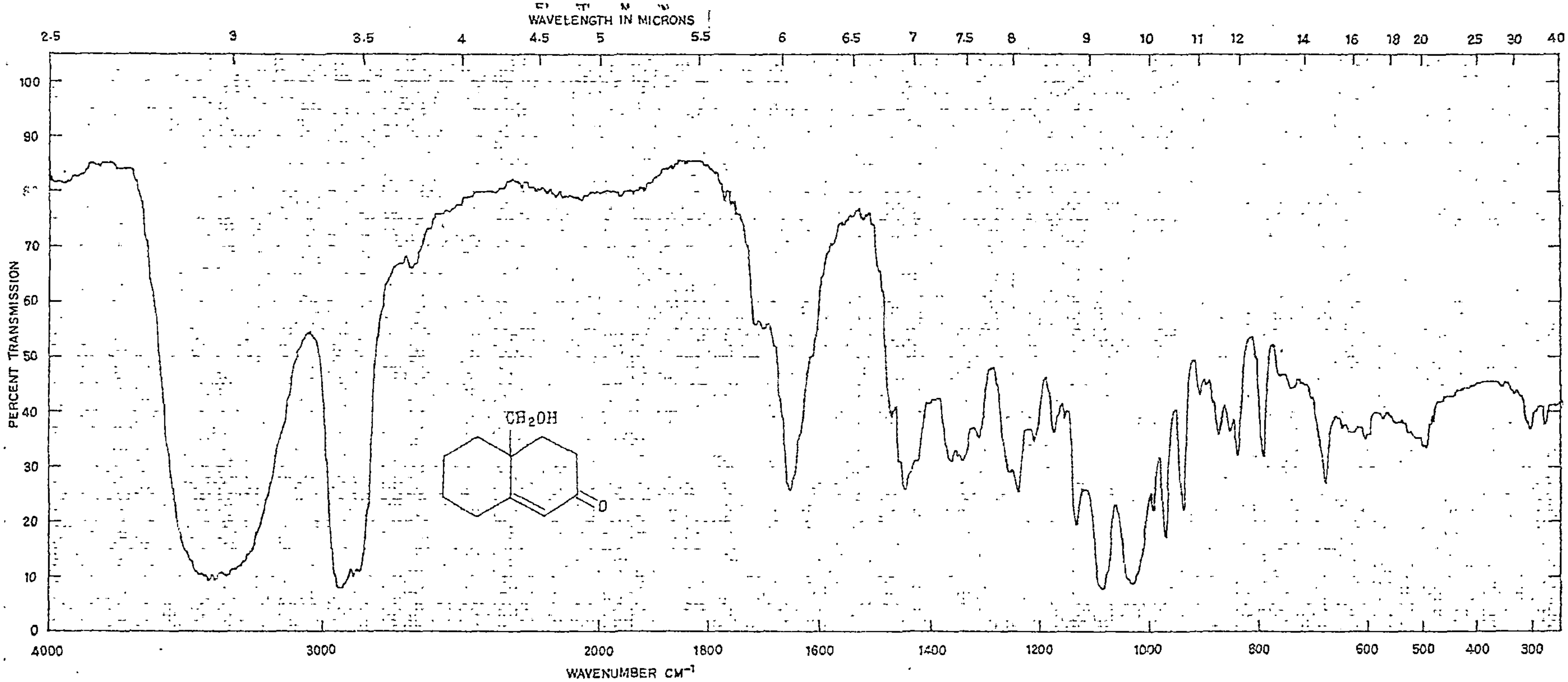
400
300
WAVENUMBER CM⁻¹
CH₂OH
O
O


WAVELENGTH IN MICRONS
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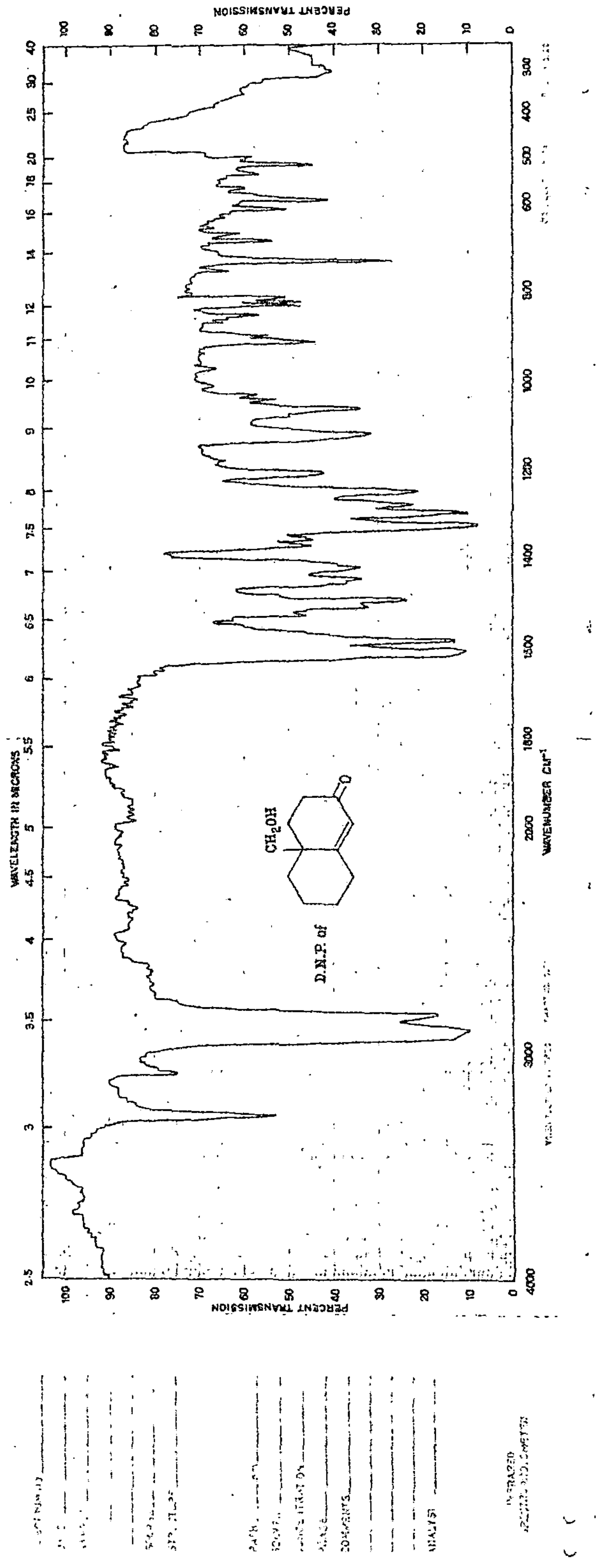
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
CH2OH
O
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM⁻¹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4.5
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5.5
6
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7.5
8
9
10
11
12
14
16
18
20
25
30
40
WAVENUMBER CM-1
4000
3000
2000
1800
1600
1400
1200
1000
800
600
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400
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100
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60
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10
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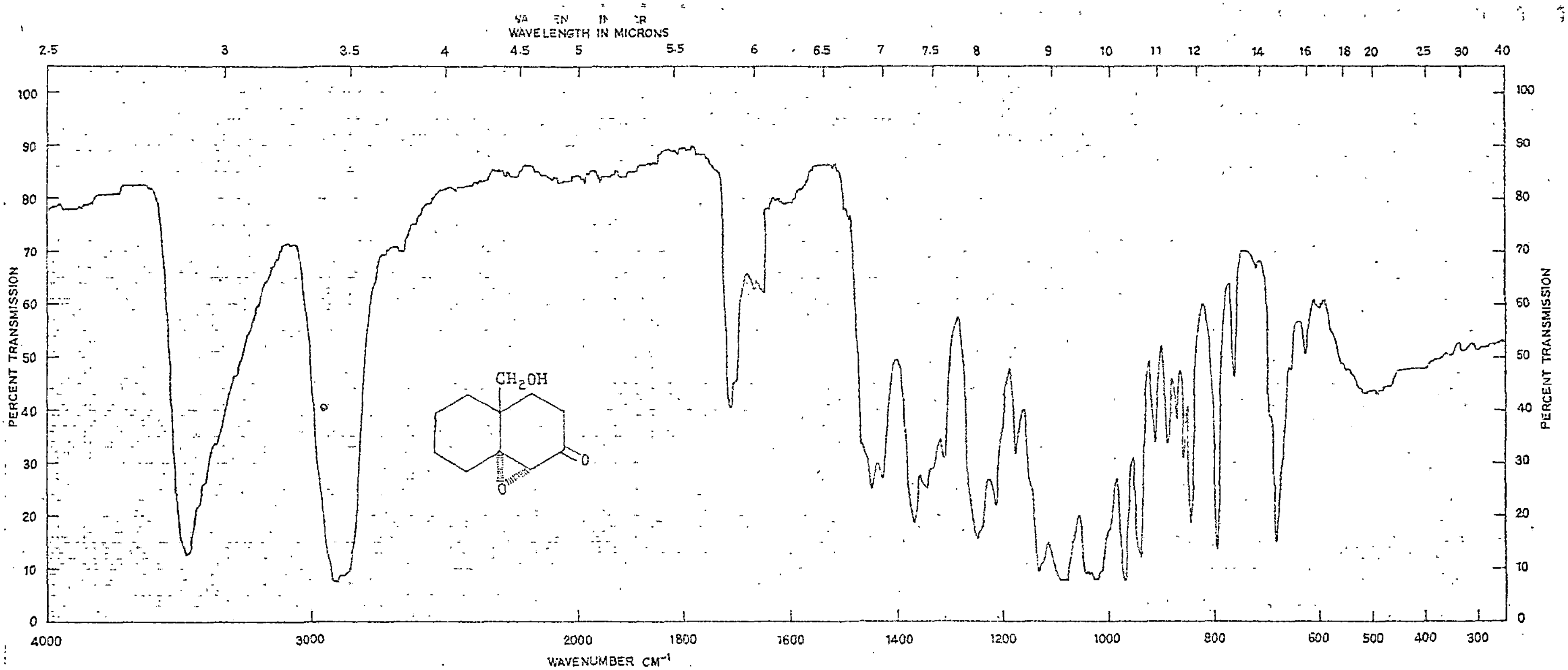
D.N.P. of
CH2OH
O
INFRARED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6
6.5
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8
9
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11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
CH$_2$OH
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3000
2000
1800
1600
1400
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1000
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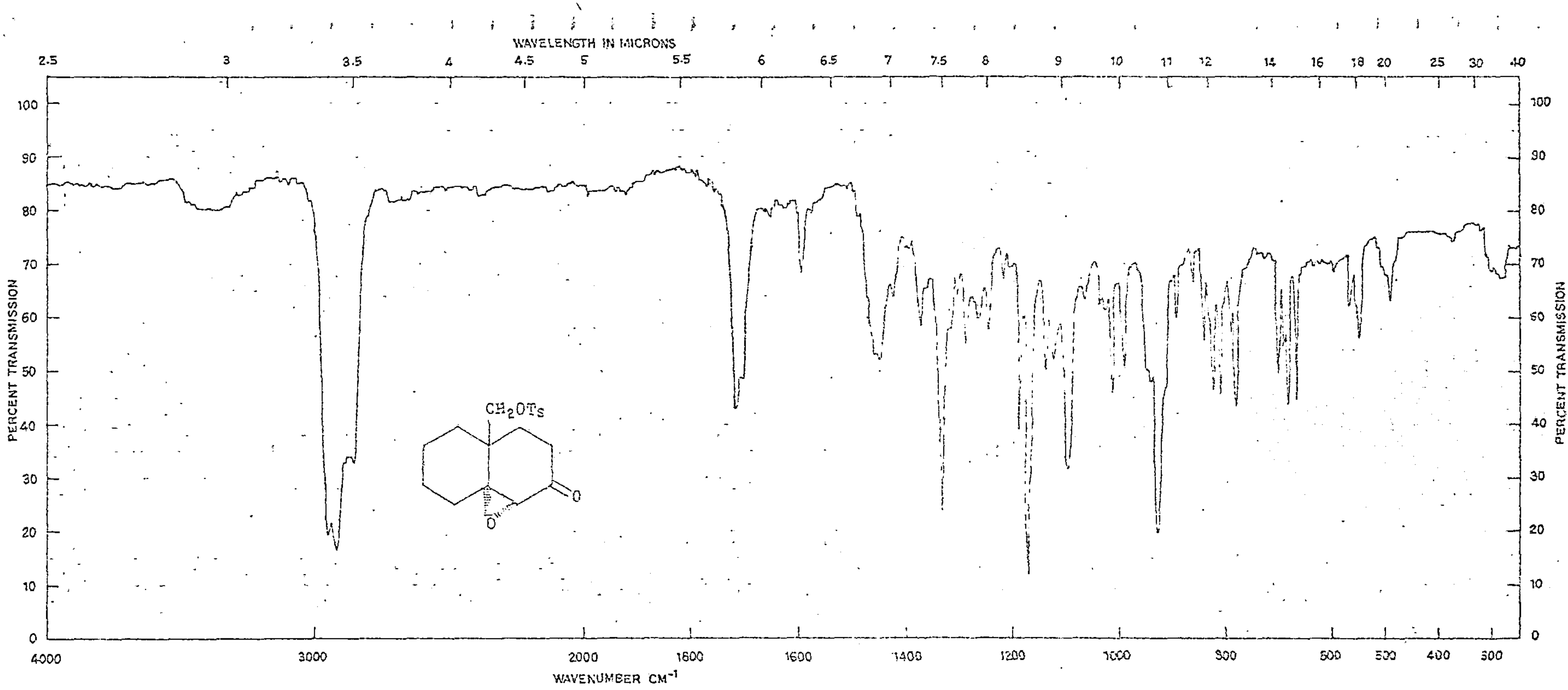
WAVENUMBER CM^{-1}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5.5
6
6.5
7
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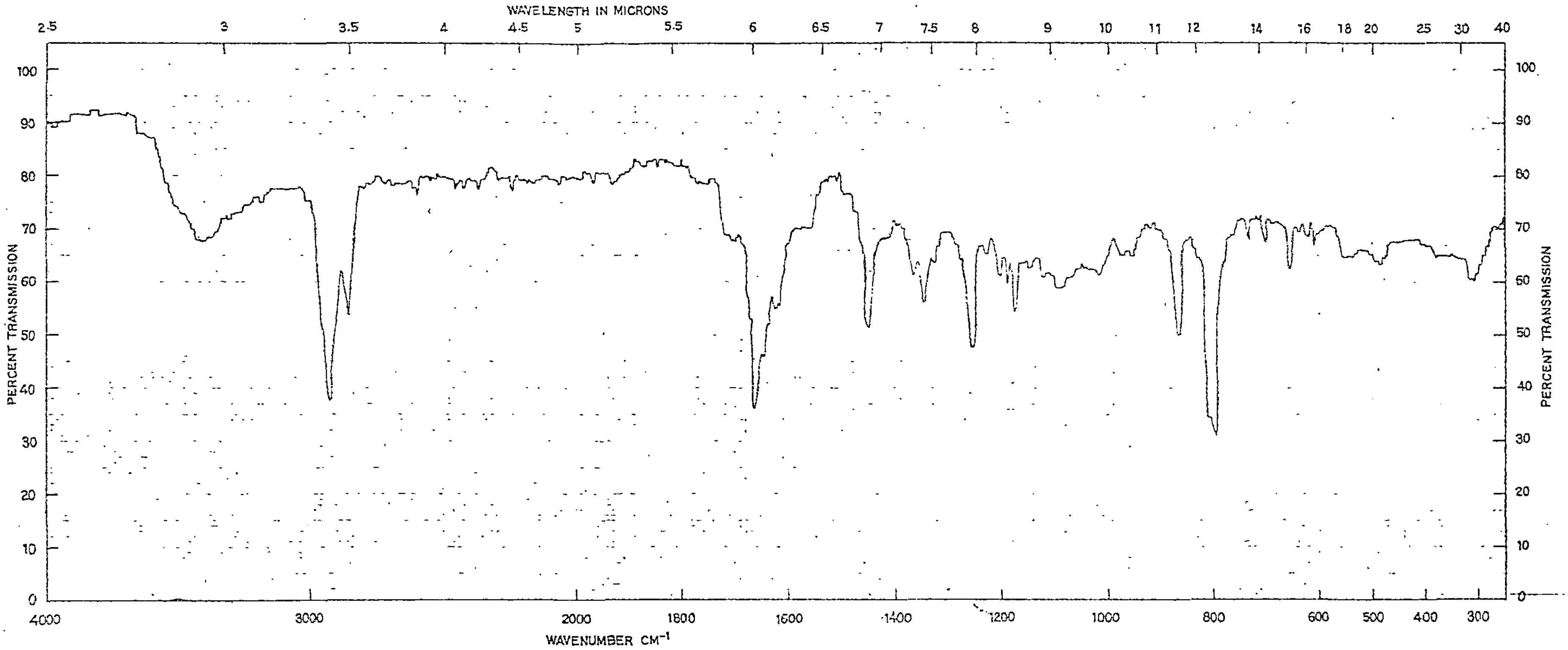
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM⁻¹
CH2OTs
O
O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6
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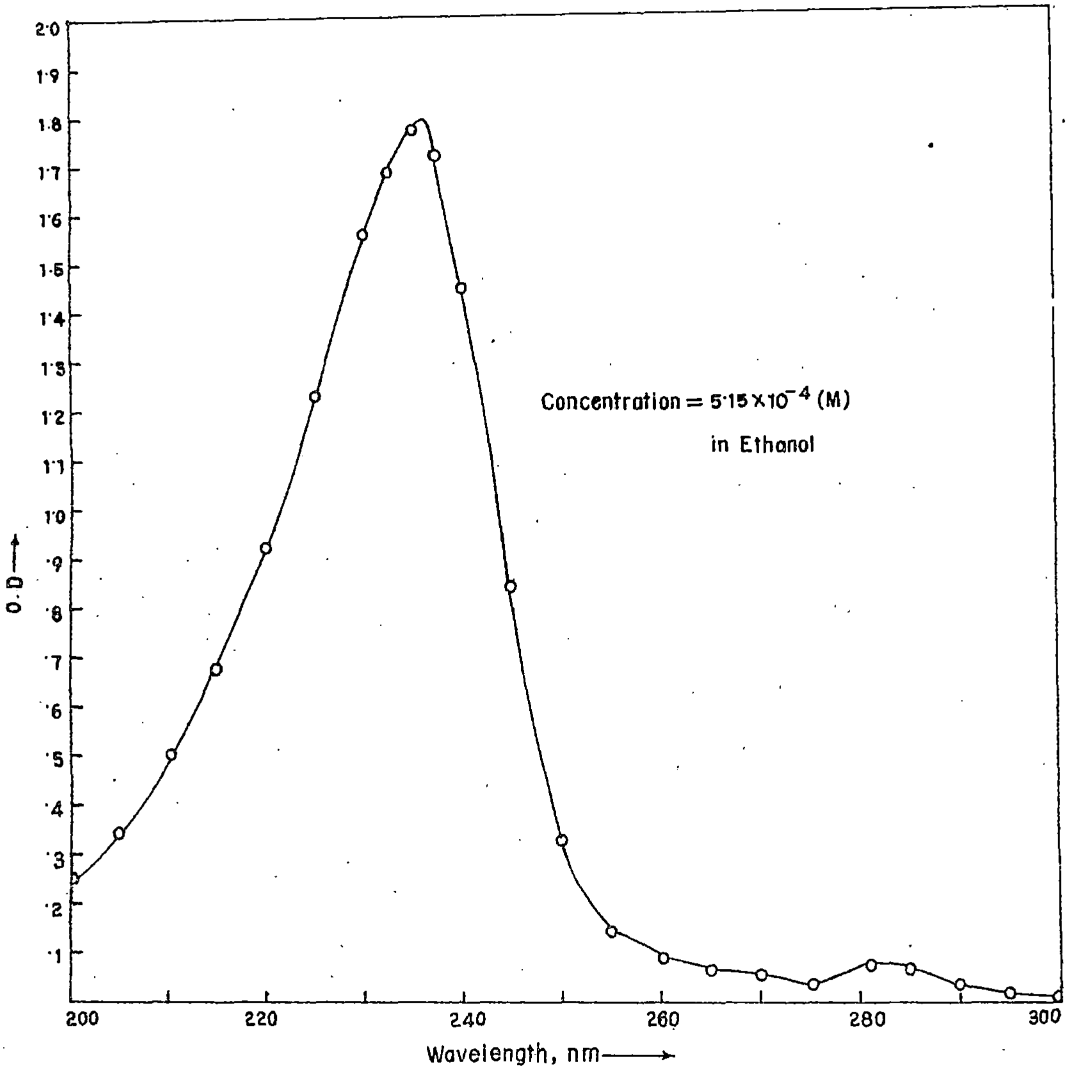
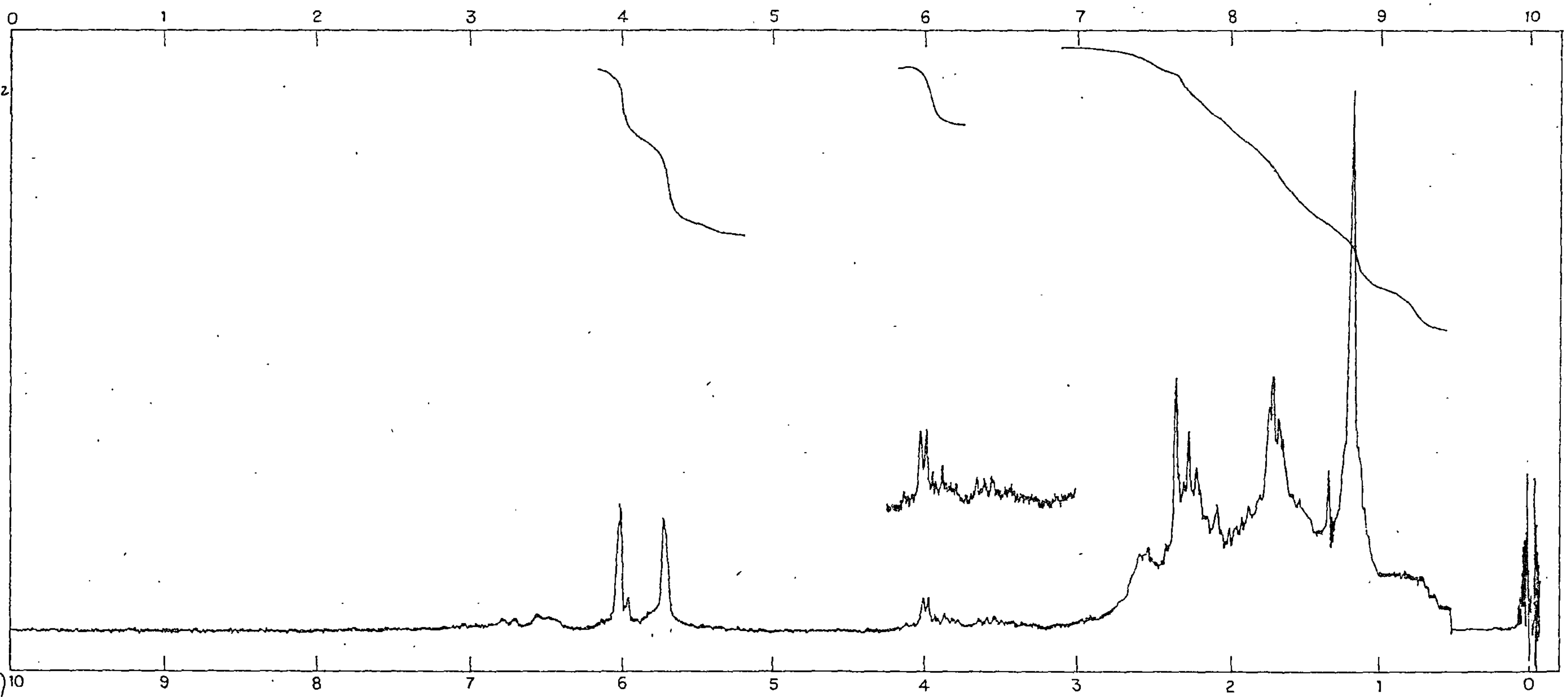
7.5
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM⁻¹


2·0
1·9
1·8
1·7
1·6
1·5
1·4
1·3
1·2
1·1
1·0
·9
·8
·7
·6
·5
·4
·3
·2
·1
O.D ⟶
Concentration = 5·15 × 10⁻⁴ (M)
in Ethanol
200
220
240
260
280
300
Wavelength, nm ⟶

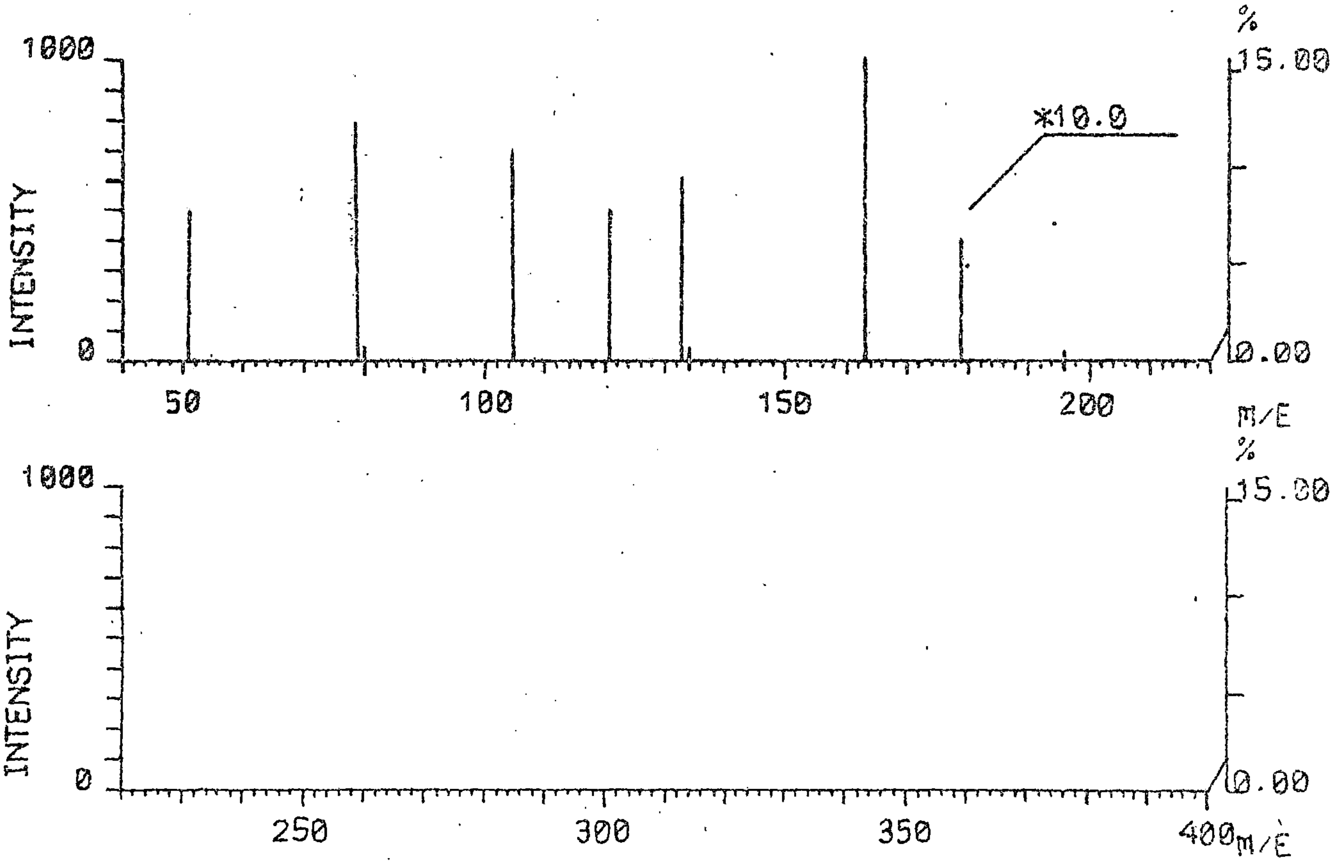
SPECTRUM No	RS2/652
DATE	2/8/82
OPERATOR	Klopsch
SAMPLE No	[illegible] 2
SUBMITTED BY	Dr Ghosh



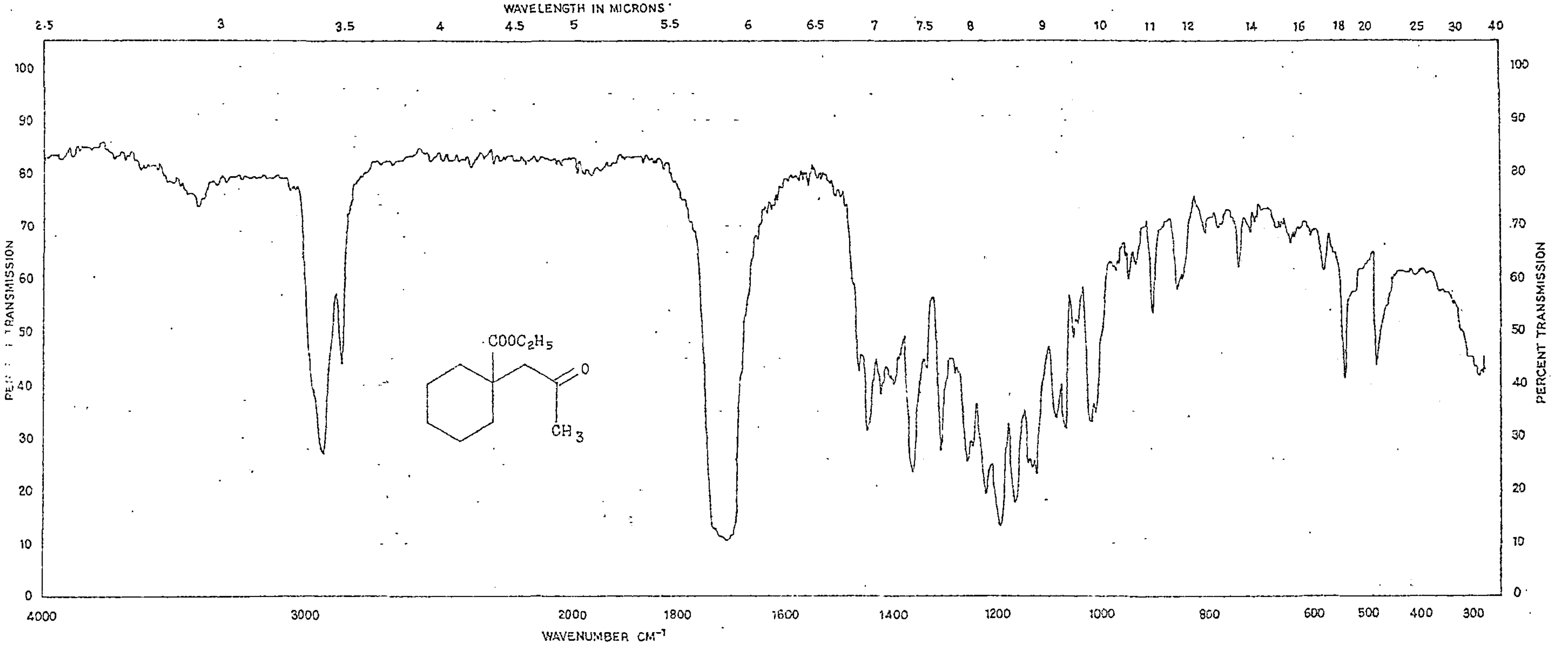
^1H	60	~~90~~	MHz
^{19}F	56.4	84.6	MHz

SOLVENT	$CDCl_3$
CONC	
TEMPERATURE	RT
REF. STD	TMS
LOCK SIGNAL	
SWEEP RANGE	10 PPM
SWEEP TIME	300 s
FILTER	2
OFFSET	—
H. LEVEL	5
SENSITIVITY	[illegible]

MASS SPECTRUM : (3 TO 4)
SAMPLE:AM/FR/S-3,DR.A.K.GHOSH,N.W.UNIVERSITY
NOTE : 4TH.AUG.82
BASE PEAK : M/E 163.0 INT. 446.0



Mass spectrum of LXV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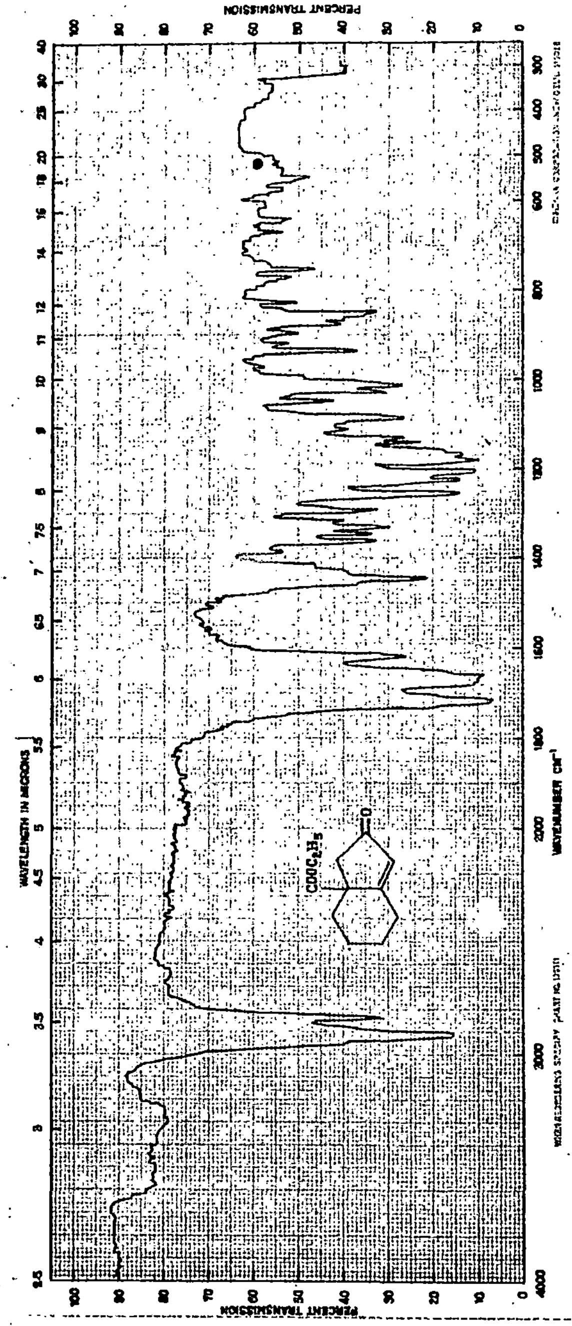
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM⁻¹
COOC₂H₅
O
CH₃



SPECTRUM NO. ______

DATE ______

SAMPLE ______

SOURCE ______

STRUCTURE ______

PATH ______ mm

SOLVENT ______

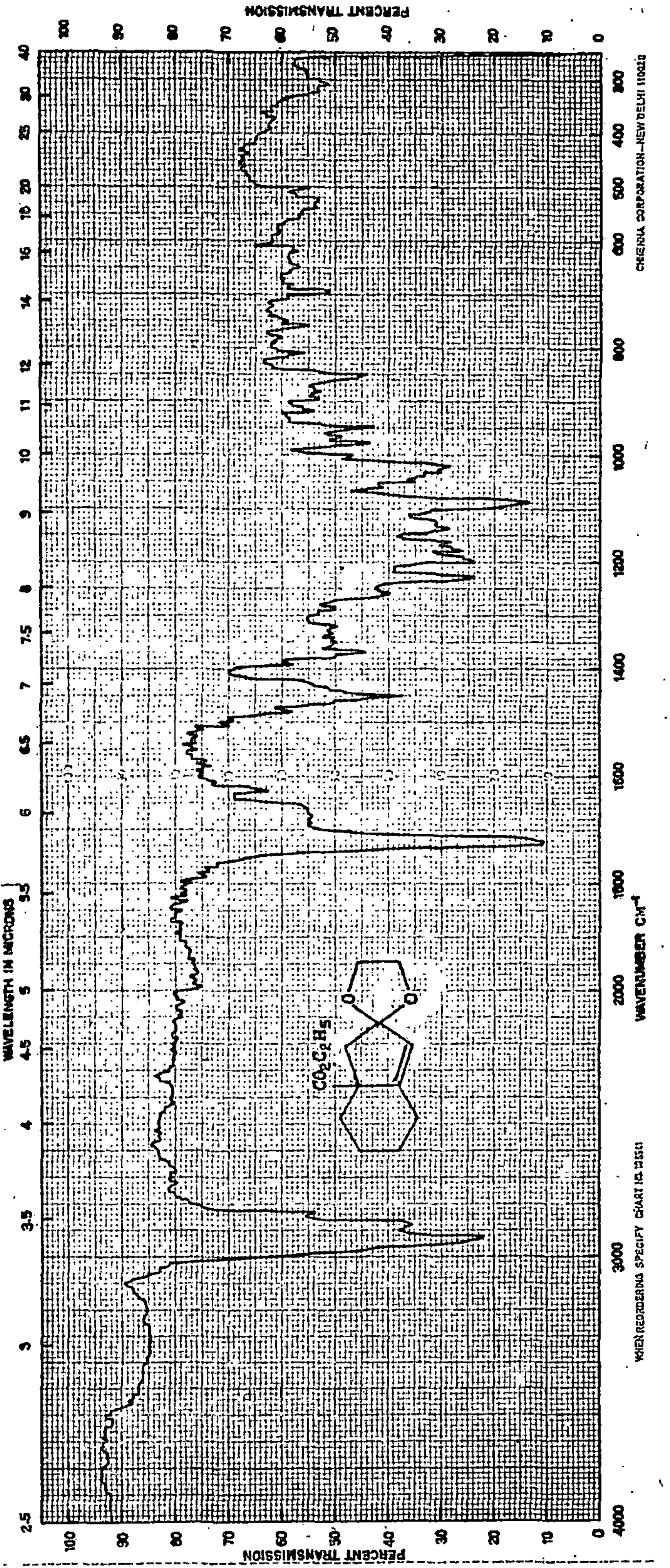
CONCENTRATION ______

PHASE ______

COMMENTS ______

ANALYST ______

INFRARED SPECTROPHOTOMETER


PERCENT TRANSMISSION
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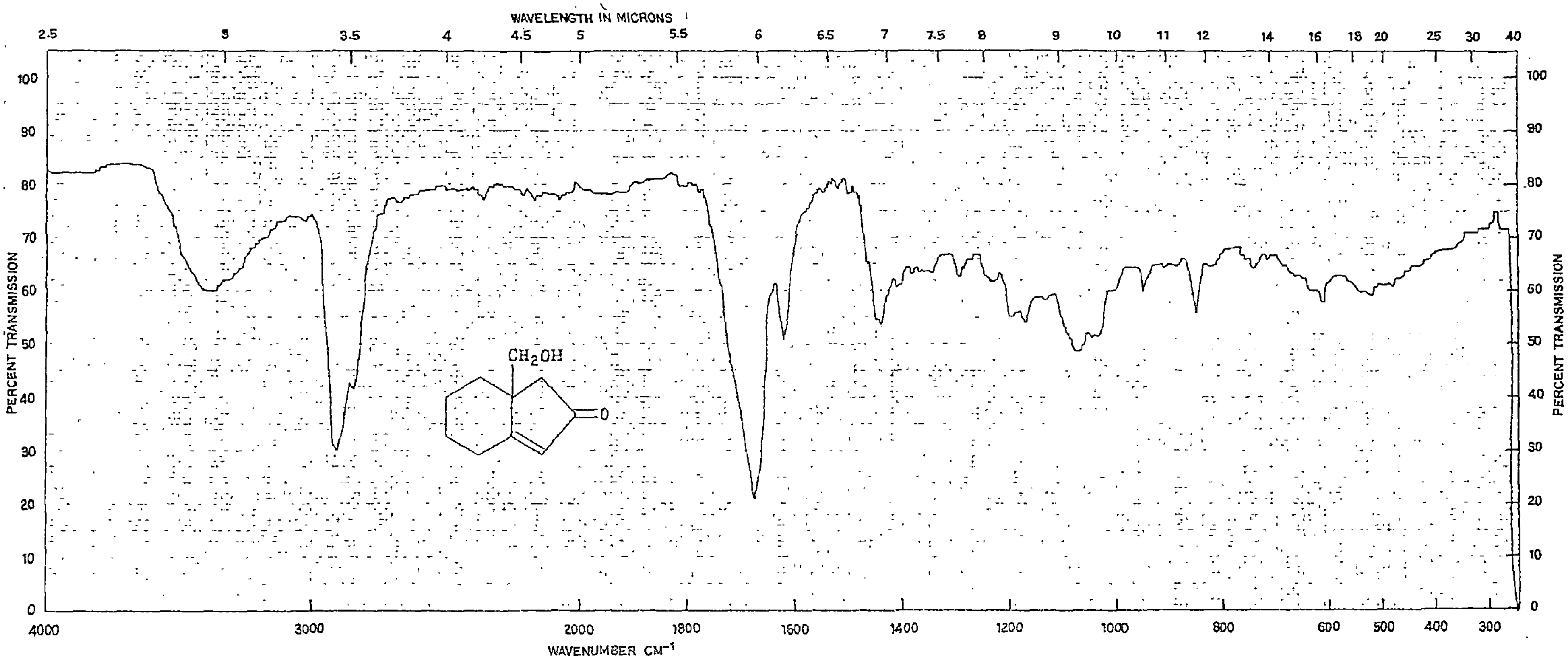
90
80
70
60
50
40
30
20
10
0
WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
WAVENUMBER CM⁻¹
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WHEN REORDERING SPECIFY CHART NO. 12550
CHEENA CORPORATION—NEW DELHI 110028
CO2C2H5
O
O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5.5
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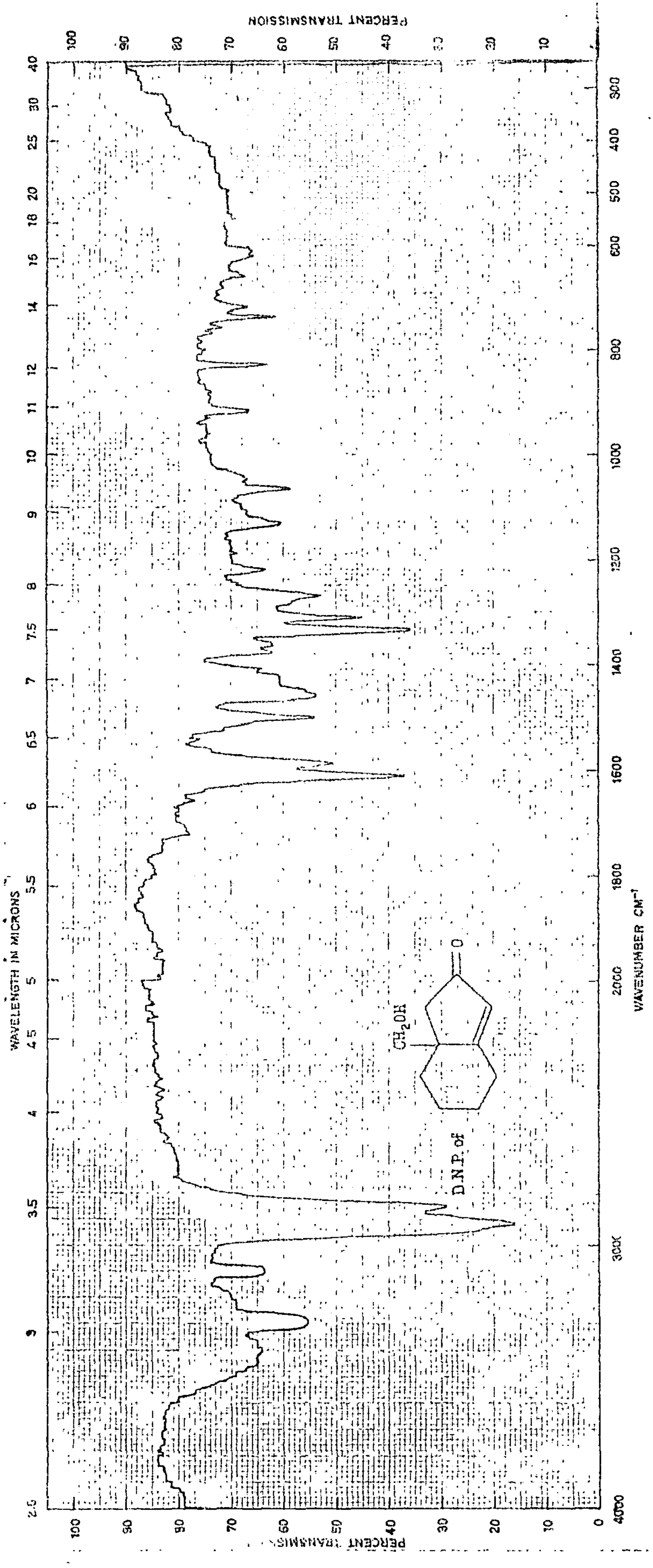
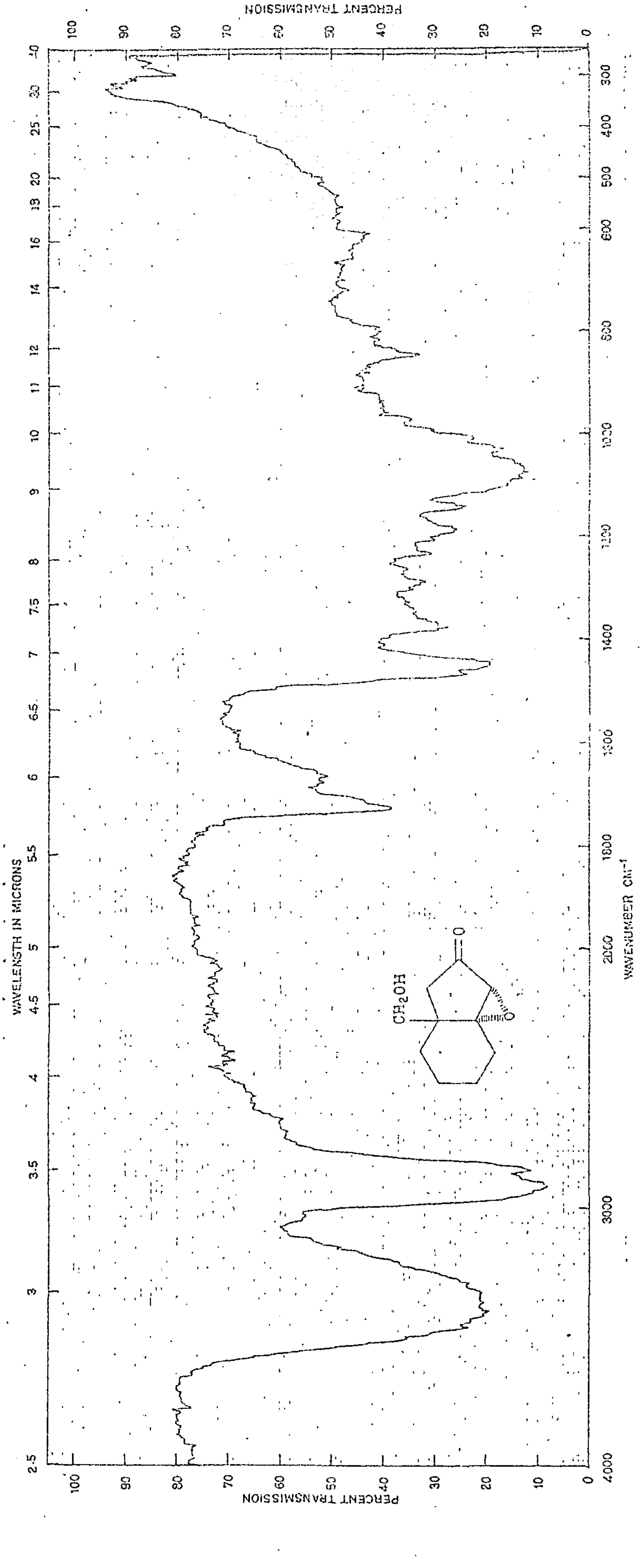
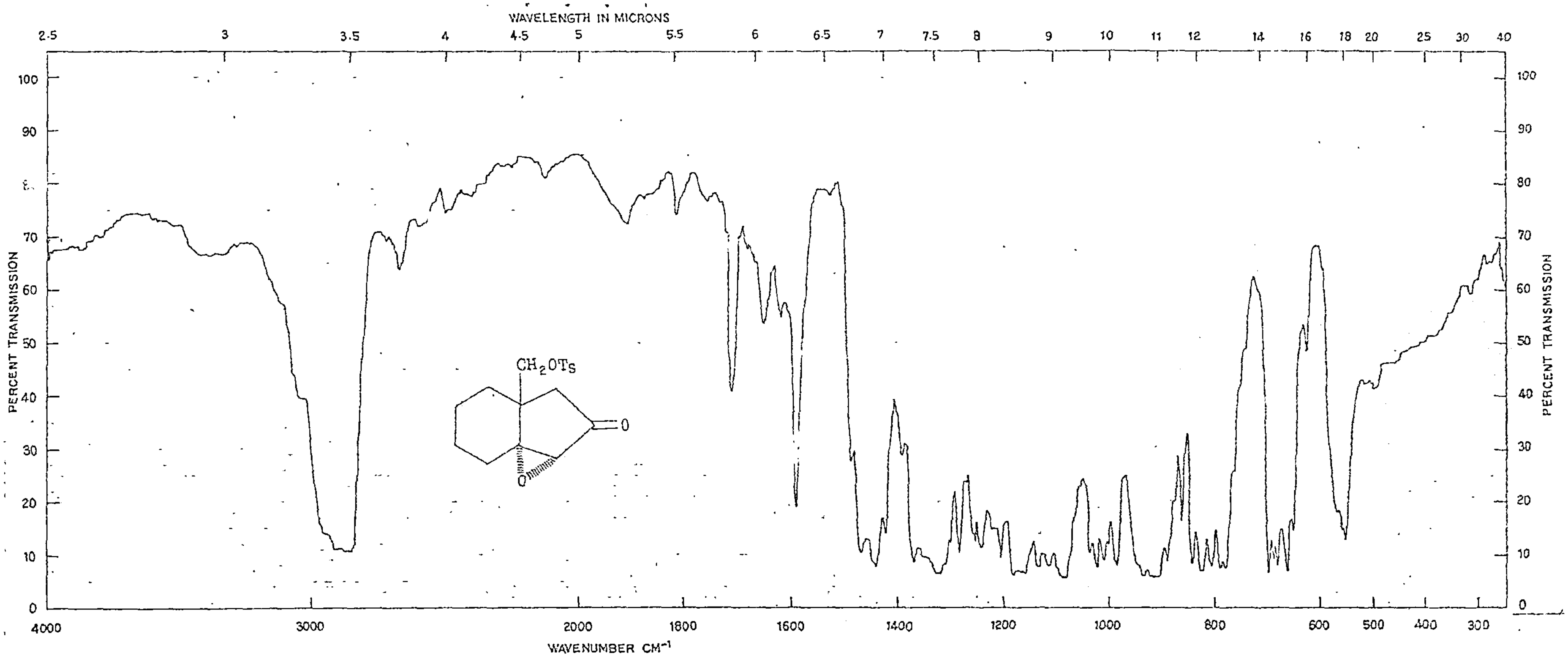
9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
CH2OH
O
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM-1


PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
WAVENUMBER CM⁻¹
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
D.N.P. of
CH₂OH
O


PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
20
25
30
40
WAVENUMBER CM⁻¹
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
CH₂OH
O
O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5.5
6
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9
10
11
12
14
16
18
20
25
30
40
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
500
400
300
WAVENUMBER CM⁻¹
CH₂OTs
O
O

[illegible]

PATH ____ mm

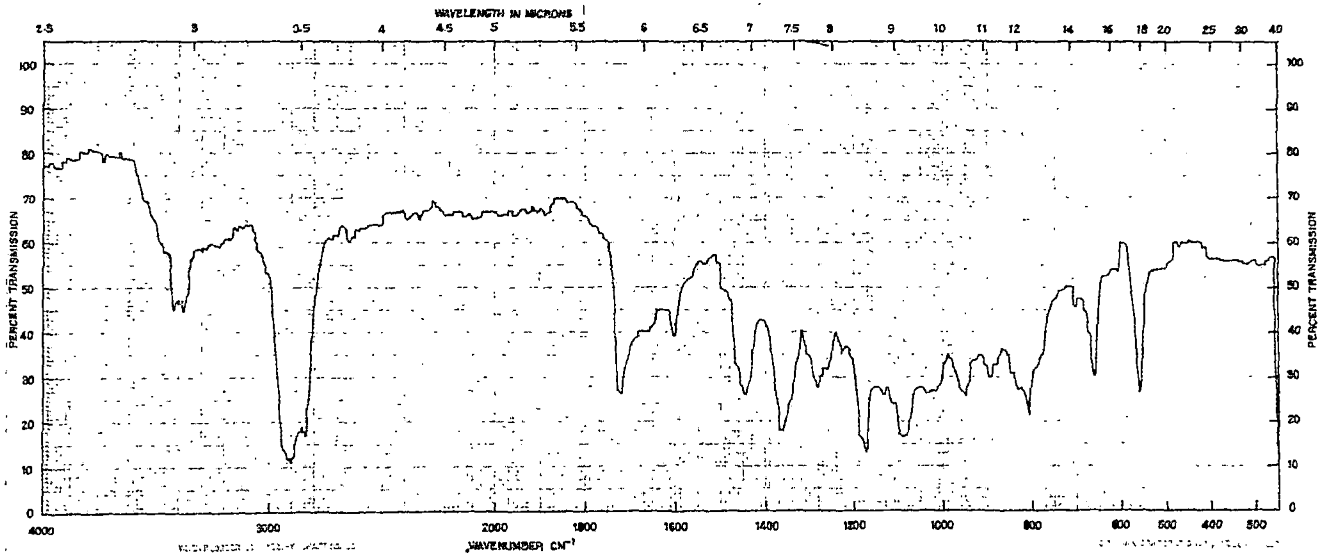
SOLVENT

CONCENTRATION

COMMENTS

ANALYST

INFRARED SPECTROPHOTOMETER



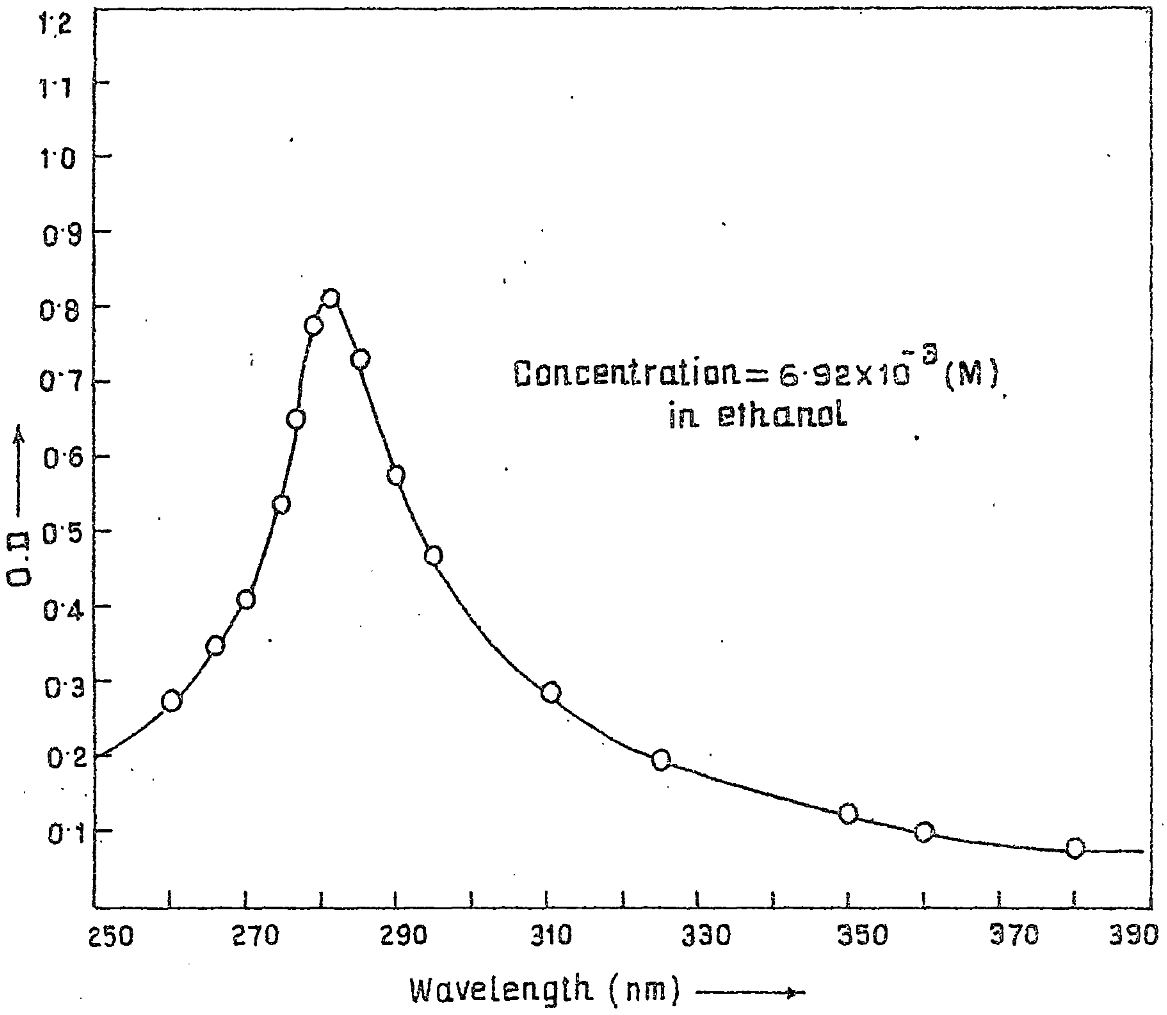
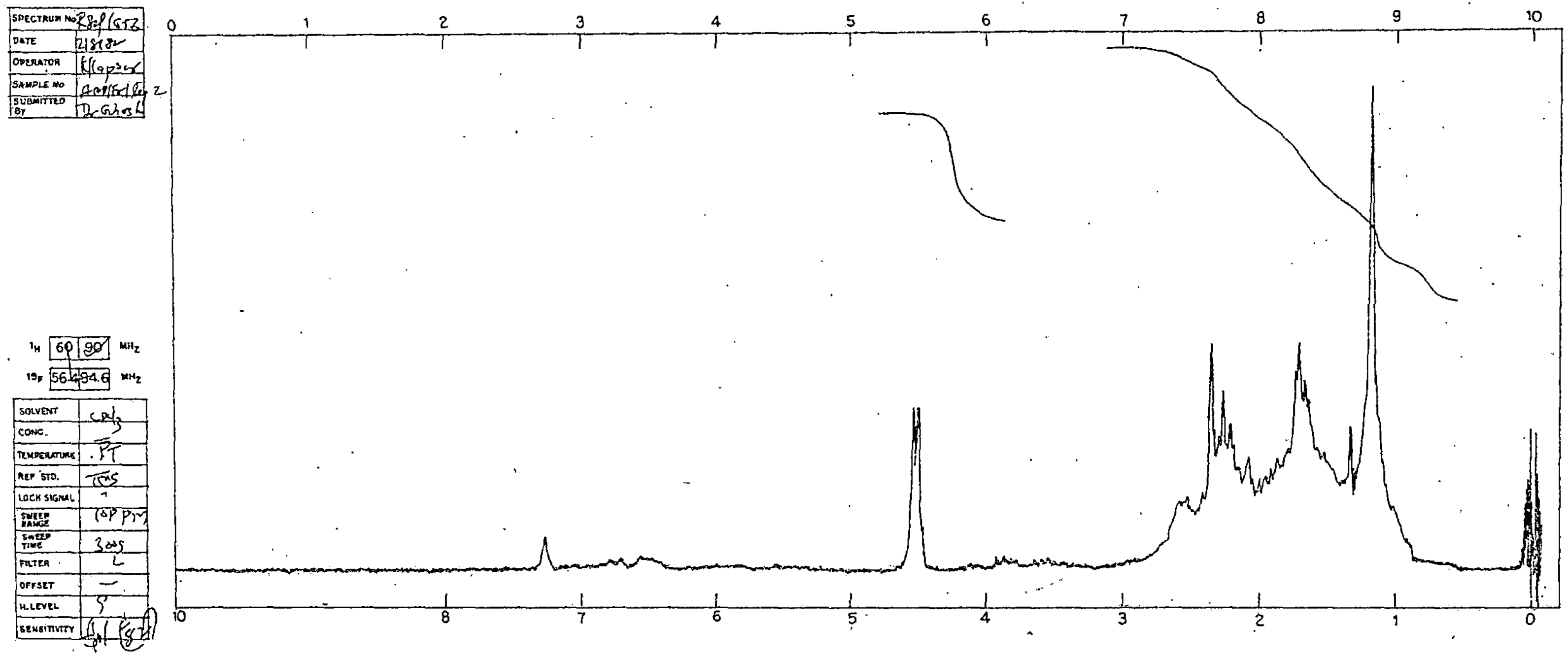

1·2
1·1
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
O.D ⟶
Concentration = 6·92×10⁻³ (M)
in ethanol
250
270
290
310
330
350
370
390
Wavelength (nm) ⟶

Fig.



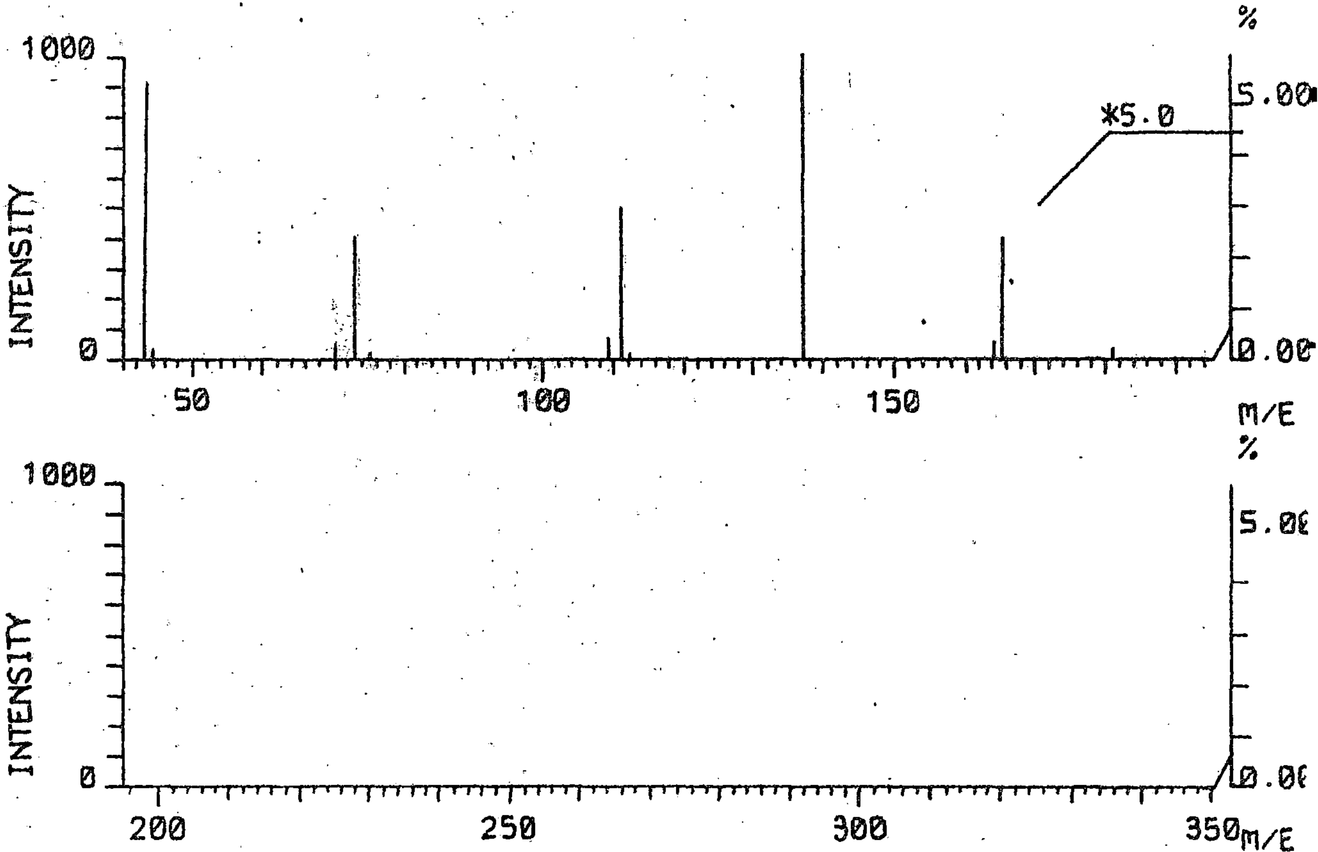
SPECTRUM No	R8of/GTZ
DATE	2/8/82
OPERATOR	[illegible]
SAMPLE No	[illegible] 2
SUBMITTED BY	Dr Ghosh

^1H 60 | ~~90~~ MHz

^{19}F 56.4 | 84.6 MHz

SOLVENT	$CDCl_3$
CONC.	
TEMPERATURE	RT
REF STD.	TMS
LOCK SIGNAL	-
SWEEP RANGE	10 ppm
SWEEP TIME	300s
FILTER	L
OFFSET	—
H. LEVEL	5
SENSITIVITY	5x1 (5x2)

MASS SPECTRUM : (4 TO 5)
SAMPLE:AM/FR/LIQ-1,DR.A.K.GHOSH,N.W.UNIVERSITY
NOTE : 4TH.AUG.82
BASE PEAK : M/E 137.0 INT. 130.4



Mass spectrum of LXXXII

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