STUDIES IN THE SYNTHESIS OF OXYGEN AND SULPHUR HETEROCYCLICS

A THESIS

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BY

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C O N T E N T S

PART - IA

SYNTHESIS OF CHROMANS AND BENZOPYRYLIUM SALTS INVOLVING HYDRIDE TRANSFER

INTRODUCTION

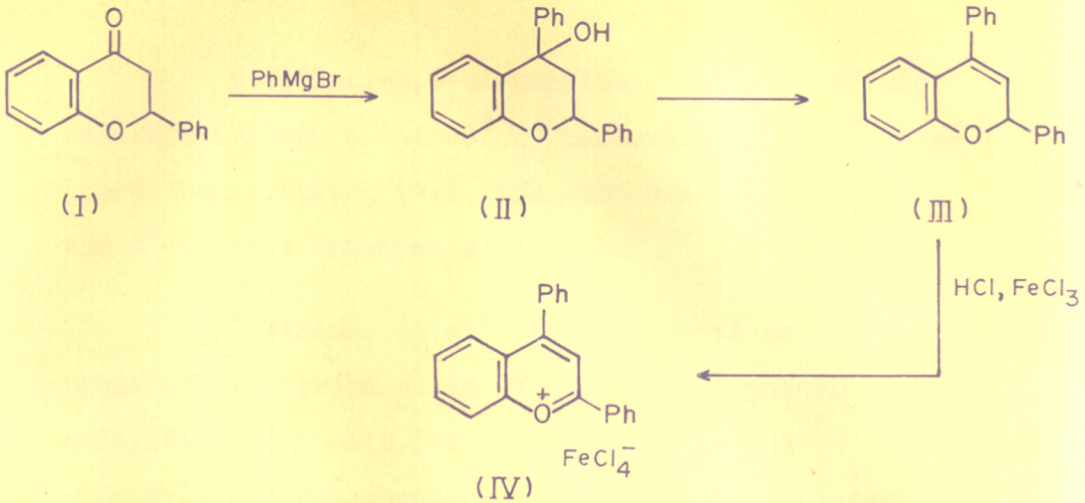
Benzopyrylium salts and chromans are a well known class of compounds. The benzopyrylium salts are important due to their relationship with naturally occurring flavylium salts namely the anthocyanines and the anthocyanidines. The chroman ring system is found in tocopherol, catechins and leucoanthocyanidines. In view of their importance, the above class of compounds have been studied in detail and several methods are available for their syntheses. The present discussion will be restricted to the pertinent aspects of their preparation directly from chromenes or chromene percursors as this has a bearing on the subject of the present thesis.

The conversion of a Δ^2- or Δ^3-chromene to benzopyrylium salts has always been achieved by the use of an oxidising agent, $FeCl_3$ being one of the most widely used reagents. There are numerous examples of such conversions in literature of which the following are a few (charts 1 and 2).

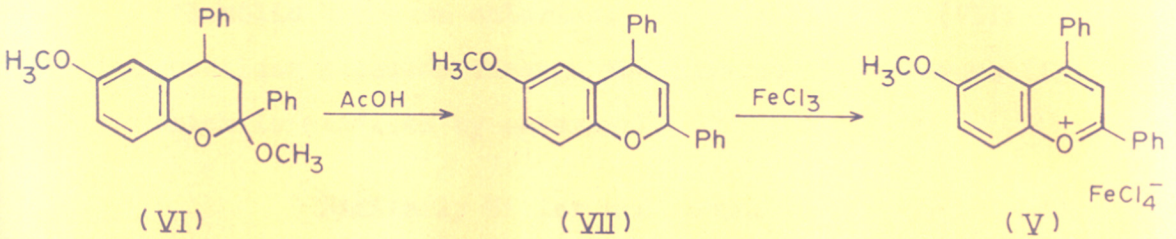
Lowenbein[1] found that the isomeric Δ^2- and Δ^3-2, 4-diphenylchromenes can be oxidised by $FeCl_3$ or PCl_5 or I_2 to give the same 4-phenylflavylium salts.

4-Chromanones (I) react with Grignard reagents and the resulting 4-chromanols (II) readily lose H_2O and yield Δ^3-chromenes (III). The latter on oxidation in acid solution give benzopyrylium salts[1] (IV).

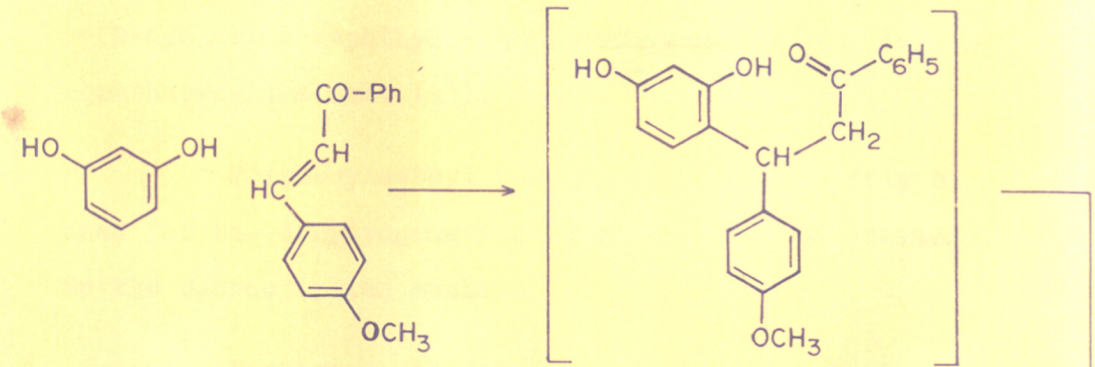
Chart 1

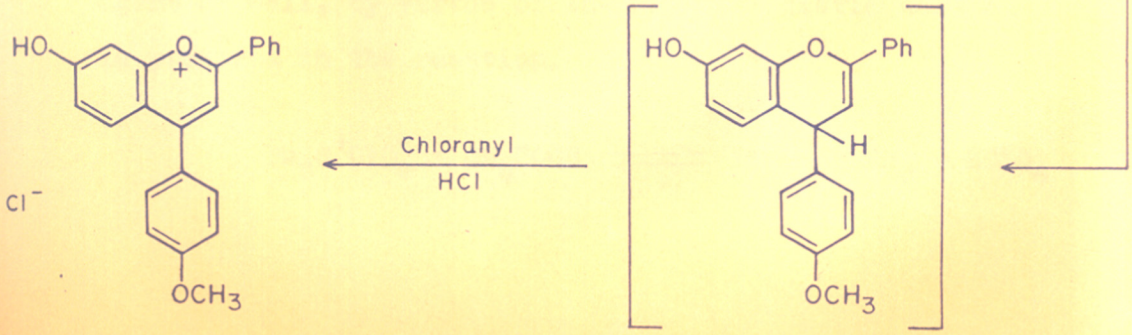


(I) (II) (III) (IV)



(VI) (VII) (V)





(VIII) (IX)

6-Methoxy-2,4-diphenylbenzopyrylium ferric chloride (V) was obtained[2] by refluxing 2,6-dimethoxy-2,4-diphenylchroman (VI) with AcOH and $FeCl_3$, through the Δ^2-flavene intermediate (VII).

Robinson, et al[3] used chloranil as an oxidising agent for the preparation of 7-hydroxy-2-phenyl-4-anisylflavylium salt (VIII). Resorcinol and p-anisylideneacetophenone was treated with chloranil and ethanolic hydrogen chloride. The formation of (VIII) doubtless proceeds through the intermediate flavene (IX) which is oxidised by chloranil.

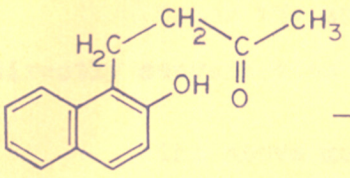
Similarly Miller and Robinson[4] used chloranil in conjunction with $POCl_3$ for the conversion of β-(2-hydroxy-1-naphthyl)-ethyl methyl ketone (X) to the naphthopyrylium salt (XI).

Triphenylmethyl perchlorate[5] has recently been used for the dehydrogenation of chromanols and chromenes to the benzopyrylium nucleus.

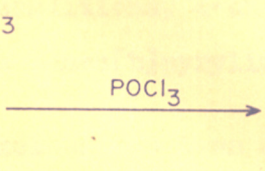
Bonthrone and Reid[5] used triphenylmethyl perchlorate in AcOH, where it functions as a dehydrating agent as well, by virtue of the free perchloric acid which is produced in the reaction.

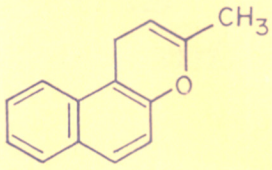
$$Ph_3C^+ClO_4^- + CH_3COOH \rightleftharpoons Ph_3CO.COCH_3 + HClO_4$$

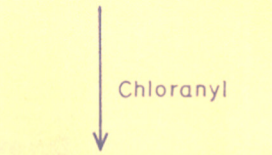
Chart-2

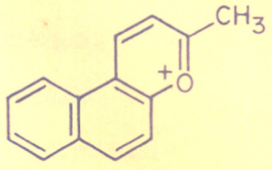


(X)



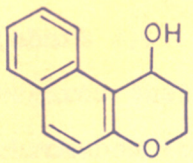




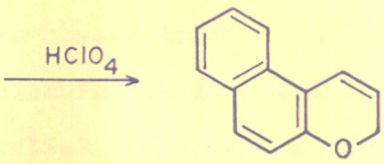


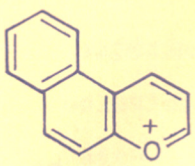
Cl^-

(XI)



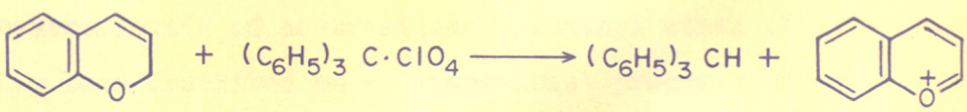
(XII)





ClO_4^-

(XIII)



ClO_4^-

(XIV)

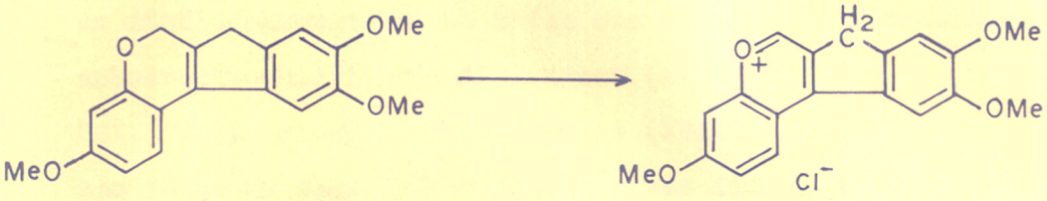
Under the conditions, 4-chromanol (XII) was directly converted to benzo[b]pyrylium perchlorate (XIII).

The above method has been applied by Degani, et al[6] to obtain the unstable benzopyrylium perchlorate (XIV) from Δ^3-chromene.

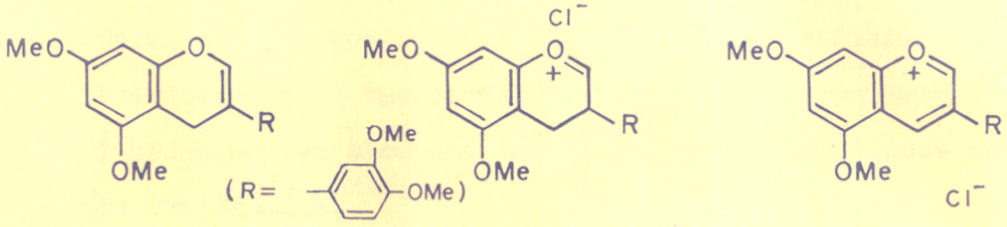
It is thus seen that although several workers have obtained benzopyrylium salts from chromenes, they have invariably used an oxidising agent in their preparation. There are some instances in literature where workers have observed the formation of such salts from chromenes in the absence of oxidising agents (chart 3). These observations have led to speculation as regards their mechanism of formation. The conversion of chromenes to pyrylium salts in absence of oxidising agents has been generally attributed to air oxidation.

Perkin and Ray[7] during their work on the synthesis of brazilin, described the following experiment:- When a stream of dry HCl was passed through a solution of deoxytrimethyl brazilone (XV) in cold $CHCl_3$ with ordinary precautions to exclude air, an orange crystalline substance was gradually deposited consisting of hydrochloride of isobrazilein trimethyl ether (XVI). This has been described as a 'remarkable' property of substance (XV).

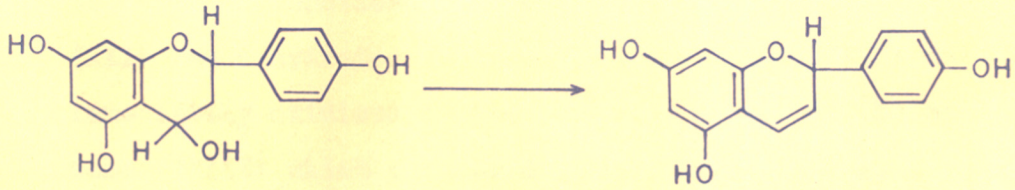
Chart-3



(XV) (XVI)

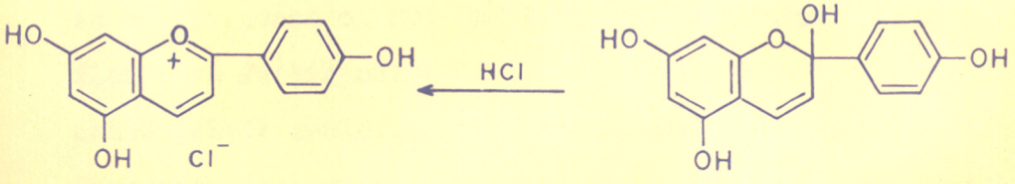


(XVII) (XVIII) (XIX)



(XXI) (XXII)

air oxidation



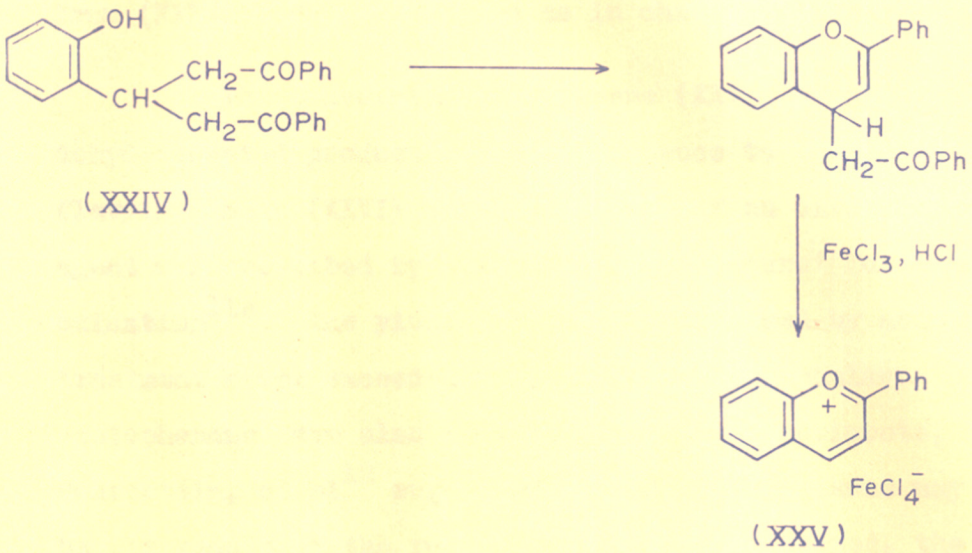
(XX) (XXIII)

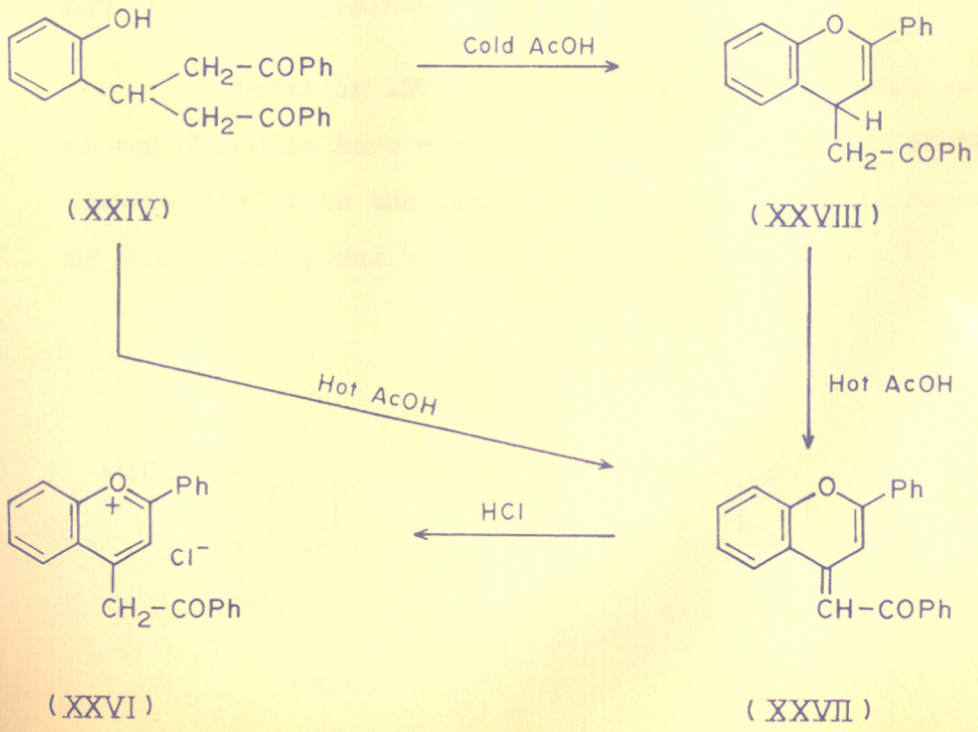
Similarly Freundenberg[8], et al have described an isoflavylium chloride which was obtained by treating anhydrocatechin tetramethyl ether (XVII) with ethereal HCl. They formulated the salt as (XVIII). Later it was shown by Baker[9] that the salt was identical with the true isoflavylium salt (XIX) obtained by them by the oxidation of (XVII) with $KMnO_4$. The formation of (XIX) from (XVII) without the use of an oxidising agent was explained by Baker as being due to aerial oxidation. His observation that the formation of (XIX) in an atmosphere of hydrogen was slow and the yield poor lent support to his explanation.

Y. Asahina, et al[10] who obtained the flavylium salt (XX) from the chromanol (XXXI) suggested the following sequence of reactions for this conversion:- The chromanol (XXI) was dehydrated to give the leuco base (XXII) which immediately oxidises in the presence of air to the carbinol base (XXIII) which with acid gives the salt (XX).

Hill[11] in his work on the synthesis of benzopyrylium salts had made the following observations (chart 4):- o-Hydroxybenzylidenediacetophenone (XXIV) in the presence of HCl and $FeCl_3$ gave the unsubstituted flavylium ferric chloride (XXV). The 4-phenacylflavylium salts (XXVI) could however be obtained by treating 4-phenacylideneflavene (XXVII) with acid.

Chart-4

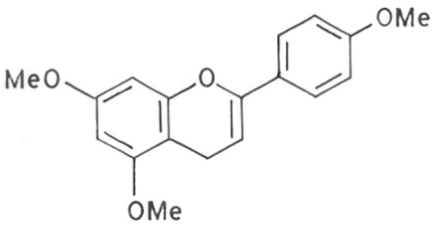

OH
CH2–COPh
CH
CH2–COPh
(XXIV)
O
Ph
H
CH2–COPh
FeCl3, HCl
O
+
Ph
FeCl4−
(XXV)


OH
CH2–COPh
CH
CH2–COPh
(XXIV)
Cold AcOH
O
Ph
H
CH2–COPh
(XXVIII)
Hot AcOH
Hot AcOH
HCl
O
+
Ph
Cl−
CH2–COPh
(XXVI)
O
Ph
CH–COPh
(XXVII)

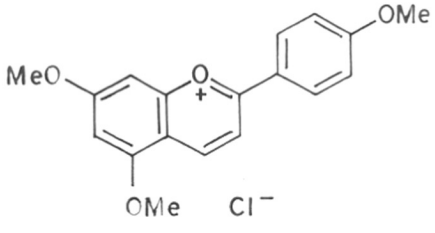
The formation of 4-phenacylideneflavene (XXVII) from (XXIV) was explained as in chart 4.

The conversion of chromene (XXVIII) to the dehydrogenated product (XXVII) and hence to the flavylium salt (XXVI) without the use of an oxidising agent was described by Hill to be an 'obscure' form of oxidation[11a]. The yields of (XXVII) obtained by acid treatment never exceeded 50%. Since dihydrochalkone and acetophenone were also isolated in these experiments, Feurestein, et al[12] suggested that dihydrochalkone may be the result of the reduction of chalkone formed, the chromene (XXVIII) being dehydrogenated in the process. However, the formation of a chalkone in these reactions has not been explained.

Later in 1955, King, et al[13] during their work on epiafelechin have also reported the conversion of the flavene (XXIX) to the flavylium chloride (XXX) in presence of HCl as being due to atmospheric oxidation.

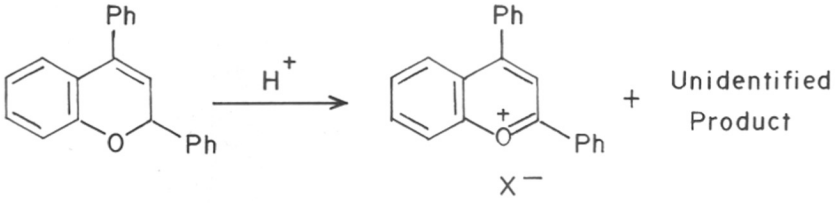


(XXIX)



(XXX)

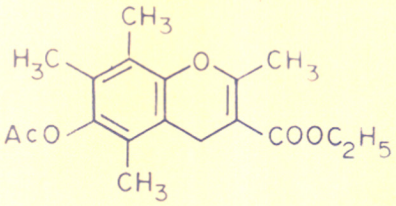
Since no reduction products have been identified in any of these transformations, it has been assumed that aerial oxidation is involved. In 1959, a by-product was isolated in such experiments but was not identified. Thus Krohnke, et al[14] treated 4-phenylflavene (XXXI) in glacial AcOH with 63.5% HBF_4 and obtained 4-phenylflavylium fluoborate (XXXII). The filtrate on work up gave a crystalline solid m.p. 141-42° which was not identified by them. On treating (XXXI) with 70% $HClO_4$ they isolated the 4-phenylflavylium perchlorate and the same unidentified by-product as in the previous case.



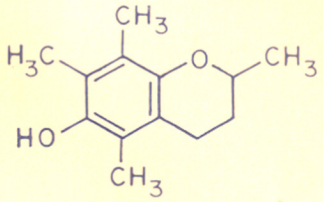
(XXXI) (XXXII)

The only instance where an attempt has been made to rationalise the above type of observations was by Smith, et al[15] (chart 5). The authors observed that when the chromene (XXXIII) was refluxed with 60% H_2SO_4 a white solid appeared in the condenser. This solid proved to be the known 2,5,7,8-tetramethyl-6-hydroxy-chroman (XXXIV). Two mechanisms have been proposed by

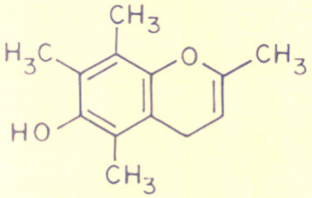
Chart-5



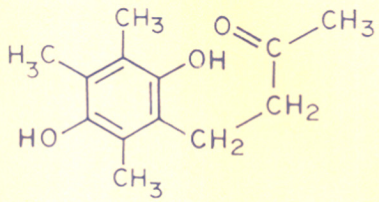
(XXXIII)



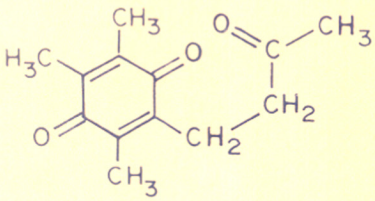
(XXXIV)



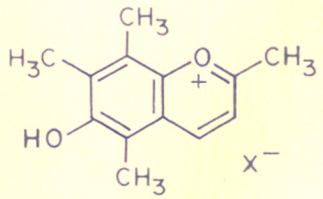
(XXXV)



(XXXVI)



(XXXVII)

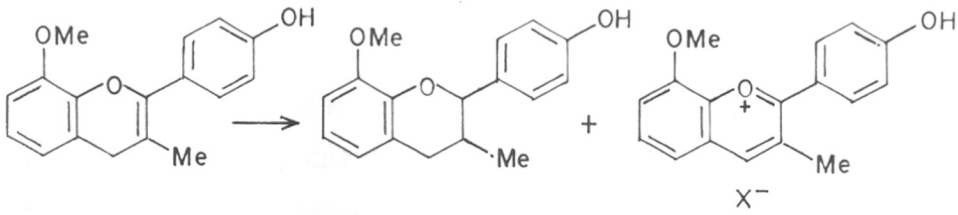


(XXXVIII)

the authors for the conversion of (XXXIII) to (XXXIV). The first mechanism visualises the hydrolysis and loss of CO_2 from (XXXIII) to form 2,5,7,8-tetramethyl-6-hydroxychromene (XXXV) which later suffers ring fission by the action of H_2SO_4 to give the hydroquinone (XXXVI). The latter then disproportionates into the corresponding quinone (XXXVII) or its decomposition products while reducing the chromene (XXXV) to chroman (XXXIV). The authors indicate that the maximum yield of chroman by such a mechanism would be 50%. Alternatively it was also suggested that the chromene (XXXV) would disproportionate directly into the chroman (XXXIV) and a benzopyrylium salt such as (XXXVIII). The authors suggest that since only one atom of hydrogen is transferred, two molecules of the chromene (XXXV) would be necessary to reduce one of its molecules to the chroman (XXXIV) and so the maximum yield that can be expected is 33%. The above authors supported the first mechanism to explain their results. Although they could not isolate the benzopyrylium salt, the deep color which developed in the reaction favoured the second mechanism. The authors while suggesting disproportionation of the chromene to the chroman, explained their results as due to radicals which may be formed. However, it appears from the present work that the above intermolecular reaction is an ionic process involving hydride transfer.

Tilak[16] in 1963 has shown conclusively that Δ^3-thiachromenes disproportionate under acid conditions to thiachroman and thianaphthalenium salts and they also recorded that the corresponding oxygen and nitrogen heterocyclic derivatives also behaved similarly.

This report has been overlooked by Jurd[17] who has shown in 1967 that the flav-2-ene (XXXIX) disproportionates to give the flavan (XL) and the flavylium salt (XLI) in the presence of acid and states



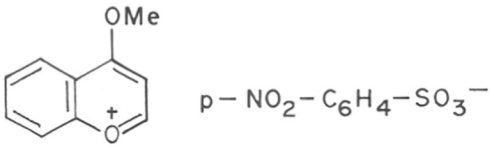
(XXXIX) (XL) (XLI)

that no reduction product has ever been identified in such reactions before.

Although a large number of benzopyrylium salts have been prepared, these mostly have a substituent in the 2-position (except the isoflavylium salts). About the only other salts reported in literature without a 2-substituent are:-

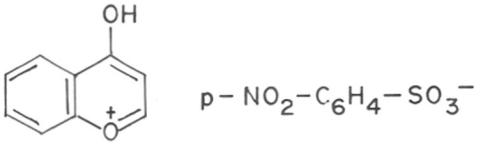
(1) benzopyrylium perchlorate (XIV) already mentioned

(2) 4-methoxybenzopyrylium salt[18] (XLII)



(XLII)

(3) 4-hydroxy benzopyrylium salt (XLIII)[19]



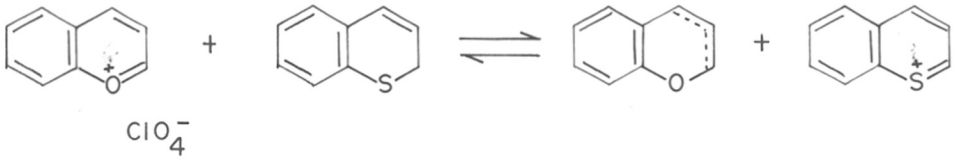
(XLIII)

The paucity of literature on the above pyrylium salts is probably due to the extreme reactivity of the 2-position which makes the salt highly susceptible to nucleophylic attack.

Compound (XIV) has been reported to be very unstable. The stability of (XLII) and (XLIII) is probably due to the fact that the positive charge can resonate between the two oxygen atoms.

Degani, et al[6] have shown that thianaphthalenium salts are more stable than the benzopyrylium salts by

studying the equilibrium:-



(XIV) (XLIV) (XLV)

When benzopyrylium perchlorate (XIV) and Δ^3-thiachromene (XLIV) were dissolved in acetonitrile, UV spectrum of the product showed the characteristics of thianaphthalenium perchlorate (XLV).

PRESENT WORK AND DISCUSSION

The present work deals with the study of the dehydration of 4-methyl-4-chromanols in the presence of perchloric acid which leads to the simultaneous formation of a chroman and a benzopyrylium salt instead of the expected Δ^3-chromene.

The 4-methyl-4-chromanols were prepared as shown in chart 6.

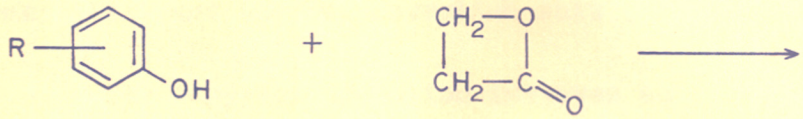
Interaction of phenol and substituted phenols with propiolactone in aq. alkaline solution gave β-phenoxypropionic acids (I)[20] which on cyclisation with PPA gave 4-chromanones (II)[21]. The latter on interaction with MeMgI gave 4-methyl-4-chromanols[21] (III) - (VI).

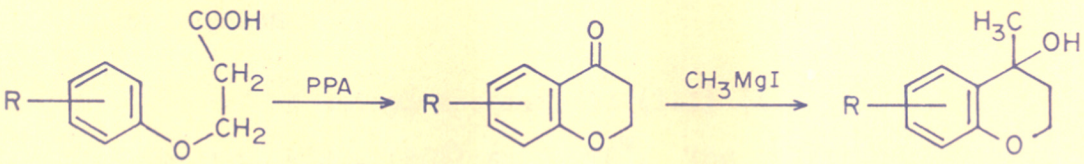
Dehydration of 4-methyl-4-chromanol (III) with $HClO_4$ (60%) gave a mixture of 4-methylchroman (VII) and 4-methylbenzopyrylium perchlorate (VIII).

4-Methyl-Δ^3-chromene (IX)[21] was obtained by the dehydration of (III) with a mild dehydrating agent like $CuSO_4$. (IX), on treatment with $HClO_4$, also yielded (VII) and (VIII).

An authentic sample of chroman (VII) was prepared by the catalytic hydrogenation of (IX) for comparison with the product obtained above. The above

Chart 6





(I) (II) (III)-(VI)

(Ia) ; R = H

(Ib) ; R = p-OCH_3

(Ic) ; R = p-CH_3

(Id) ; R = m-OCH_3

(IIa) ; R = H

(IIb) ; R = 6-OCH_3

(IIc) ; R = 6-CH_3

(IId) ; R = 7-OCH_3

(III) ; R = H

(IV) ; R = 6-OCH_3

(V) ; R = 6-CH_3

(VI) ; R = 7-OCH_3

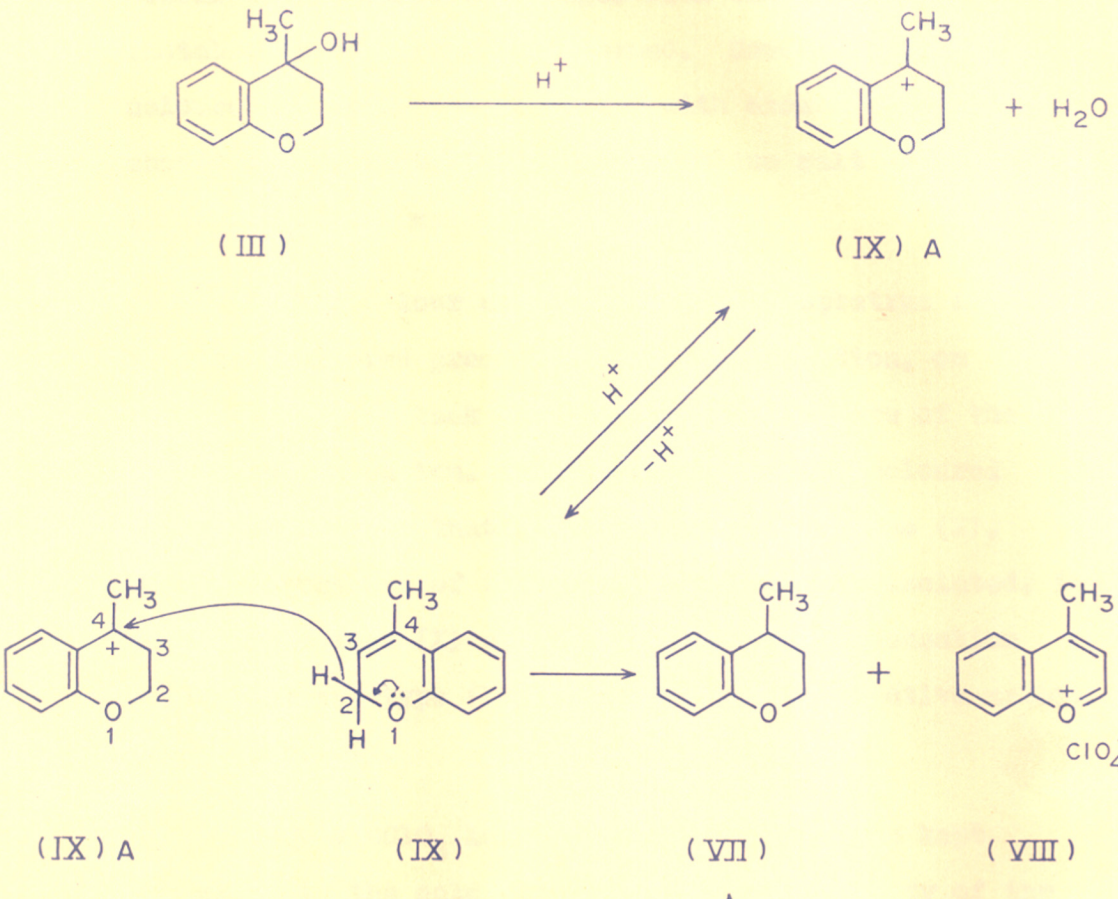
reactions are explained on the basis of formation of 4-methyl-Δ^3-chromene (IX) as an unstable intermediate which disproportionates in the acidic medium to give the chroman (VII) and the benzopyrylium salt (VIII) (chart 7).

The disproportionation involves an intermolecular transfer of a C_2 hydrogen as hydride from (IX) to the 4 position of its protonated form (IXA). The yield of the chroman and benzopyrylium salt can thus not exceed 50%.

4-Methyl-4-chromanol (III) (1 g) was treated with 6 ml $HClO_4$ (60%) at 60-70°. The reaction mixture extracted with pet. ether (60-80°) and solvent evaporated to yield a liquid which was identified as 4-methylchroman (VII) by its analysis and UV spectrum. The compound was found to be identical with authentic 4-methylchroman prepared by hydrogenation of (IX).

The $HClO_4$ layer from the reaction after removal of 4-methylchroman was yellow in colour and showed max. absorption at 320 mμ and 240 mμ. This is in agreement with the UV spectrum of (VIII) (isolated in later experiments). On addition of ether, the $HClO_4$ solution showed max. absorption at 530 and 424 mμ and a shoulder at 500 mμ. If the $HClO_4$ solution was diluted with excess EtOH instead of ether the following visible spectrum was

Chart 7

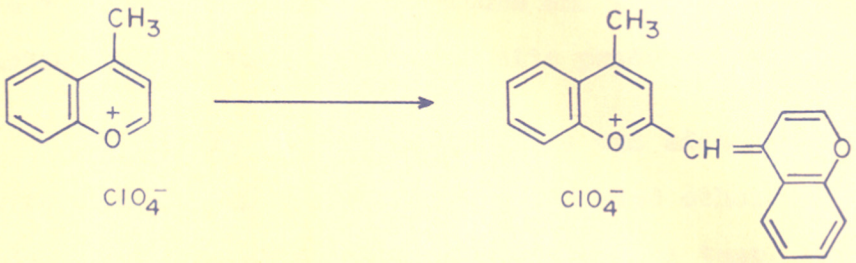

H3C
OH
H+
CH3
+ H2O
(III)
(IX) A
H+
-H+
CH3
4
3
2
1
O
+
H
(IX) A
(IX)
(VII)
(VIII)
ClO4−
CuSO4
Pd/C, H2
(III)
(IX)

obtained:- λmax. at 642, 625, 529, 495 mμ but the colour of the solution changes with time showing the instability of the product formed. However, when the coloured solution was acidified with excess $HClO_4$ it showed the characteristic benzopyrylium salt spectrum (λ max. 320, 240 mμ).

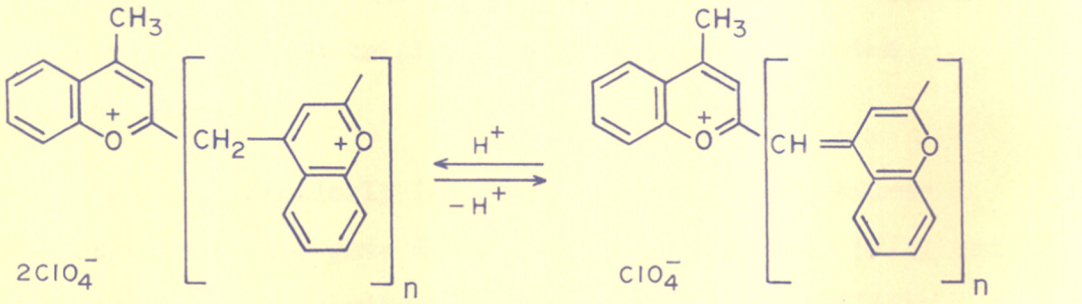
The colour changes and the UV spectrum indicate that the coloured products, formed in solution, on protonation give back the original chromophore of the benzopyrylium cation. The structure of the coloured products could be that of a cyanine dye such as (X). Since no pure dye of this structure could be isolated, it is possible that (X) gives a polynuclear condensation product of the type (XI) by virtue of its reactive methyl group (chart 8).

The $HClO_4$ layer saturated with ether kept overnight in the cold gave a negligible quantity of the coloured product. In order to improve the yield of the latter, 2 g of (III) was treated with 7 ml of $HClO_4$ 60% at 70° using trityl chloride as an external hydride abstractor. On diluting with ether and allowing to stand overnight in the cold, 210 mg of a coloured product was obtained to which it was not possible to assign any definite structure.

Chart 8



(VIII) (X)



n = 1, 2, 3 etc.

(XI)

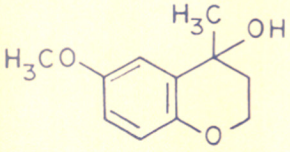
Further attempts were made to get the coloured product in a purer form by treating the chromanol (III) with 70% $HClO_4$ at room temperature and at 10°, but the reaction failed to give any definite products.

Finally the chromanol (III) was added portionwise to 70% $HClO_4$ at -15°. Chilled ether was added to saturation at such a rate that the temp. did not rise above -10°. Under these conditions a crystalline yellow precipitate of 4-methylbenzopyrylium perchlorate (VIII) was obtained. The compound was extremely unstable and turned red within a few seconds. Filtered in an atmosphere of dry N_2 and taken up immediately for analysis it gave the correct chlorine content. Its NMR spectrum in the trifluroacetic acid confirmed the structure.

Similarly (chart 9) 6-methoxy-4-methyl-4-chromanol (IV) gave 6-methoxy-4-methylchroman (XII) and 6-methoxy-4-methylbenzopyrylium perchlorate (XIII). (XIII) could be isolated by carrying out the reaction at room temperature and saturating the $HClO_4$ solution with ether without allowing the temperature to rise above -10°. (XIII) was also very unstable and had to be taken immediately on filtration for analysis and NMR spectrum determination.

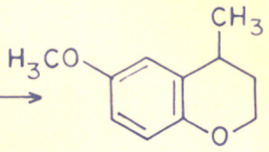
4,6-Dimethyl-4-chromanol (V) on treatment with

Chart 9



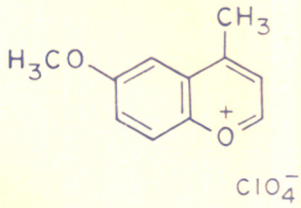
(IV)

$HClO_4$

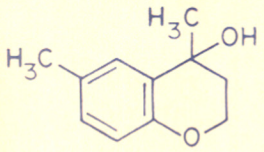


(XII)

+

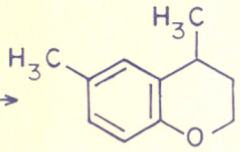


(XIII)



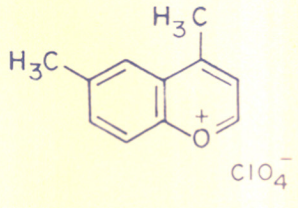
(V)

$HClO_4$



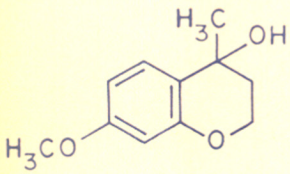
(XIV)

+



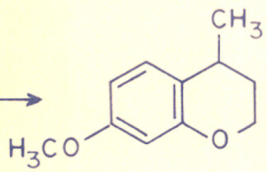
(XV)

(in solution)



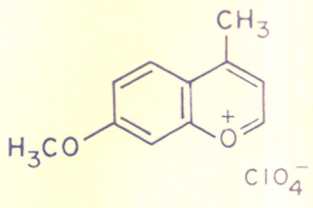
(VI)

$HClO_4$



(XVI)

+

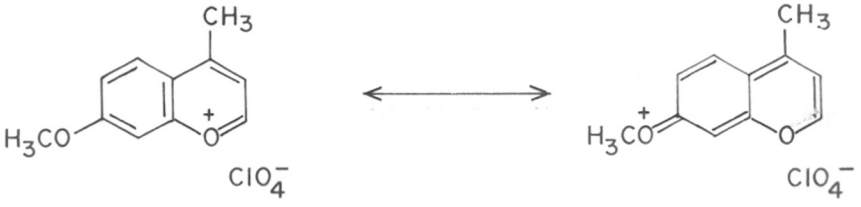


(XVII)

$HClO_4$ gave 4,6-dimethylchroman (XIV) but it was not possible to isolate the salt (XV) although its formation was shown by UV spectrum of the reaction mixture.

7-Methoxy-4-methyl-4-chromanol (VI) was treated with 70% $HClO_4$ at room temperature to give 7-methoxy-4-methylchroman (XVI) and 7-methoxy-4-methylbenzopyrylium perchlorate (XVII).

The perchlorate (XVII) was much more stable as compared with (VIII) and (XIII). Obviously the two resonating structures that are possible by charge distribution between the oxygen atoms contribute to the stability of the salt.



(XVII)

Since the salt (XVII) was quite stable, attempts were made to convert it to a cyanine type of dye, by adopting the following procedures but no pure dye was obtained.

(1) The chromanol (VI) was heated with 60% $HClO_4$ at 100° in the presence of trityl chloride.

(2) The salt (VI) was refluxed in gl. AcOH with

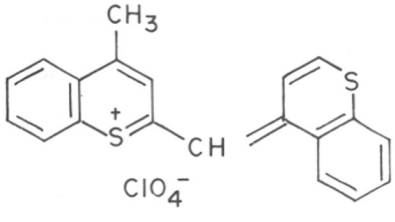
trityl chloride.

(3) One equivalent of the salt (VI) was treated with 1/2 equivalent of sodium methoxide. The colour was totally discharged.

(4) Acetonitrile was used as a mild base and the salt (VI) was refluxed with it.

Attempts were also made to obtain a dye from (III) by dissolving it in gl. AcOH and passing dry HCl in the presence of anhy. $FeCl_3$. Only tarry coloured products were isolated.

In this respect the benzopyrylium salts behave quite differently from their sulphur analogues[22] where it was possible to isolate a thiacyanine dye (XVIII) from thianaphthalenium perchlorate obtained from similar disproportionation reactions.

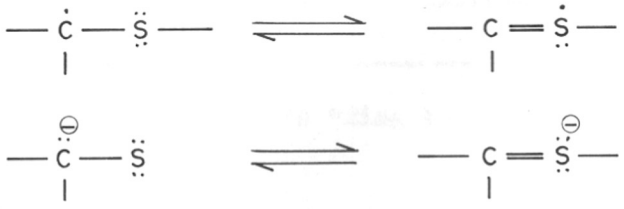


(XVIII)

The oxygen and sulphur atoms, because of their

unshared electrons, are capable of releasing electrons in conjugative interaction with electron deficient groups or with electron withdrawing unsaturated groups through their mesomeric ability. In the case of sulphides such electron release involves contribution from a 2p-3p bond between C and S whereas in the case of ethers a 2p-2p π bond between C and O is involved. Experimental facts as well as theoretical considerations support the concept that a π bond involving two 2 p orbitals contributes more to the stability of a molecule than a bond formed between 2p and 3p orbitals. However, when O and S form part of a conjugated ring system there is a fundamental difference in the nature of their conjugation. In these cases the sulphur atom not only displays electron releasing but also electron accepting conjugation effects as well, because of the vacant 3d orbitals on sulfur.

For similar reasons unlike ether oxygen atom, sulfide sulfur can participate in the resonance stabilisation of free radical centres and of electron rich centres.



In structures contributing to such stabilisation the sulfur atom has expanded the number of electron in the outer valence shell from 8 to 9 and 10 respectively.

Sulfide sulfur thus differs from ether oxygen, since in oxygen the 2nd valence shell has no d orbitals to accommodate electrons in excess of 8.

This fundamental difference between the electronic structures of oxygen and sulfur are probably responsible for the large difference in stability of thiacyanine dye of the type (XVIII) as compared to its oxygen analogue.

The disproportionation reaction has been extended to 4-methyl-5,6-benzo-4-chromanols (XIX-XXI) which contain two one or no hydrogen in the 2 position (chart 10).

The chromanols were prepared from the corresponding 5,6-benzo-4-chromanones (XXII-XXIV)[23,24,25] by the action of CH_3MgI.

Treatment of (XIX) with perchloric acid (60%) at 60-70° gave 4-methyl-5,6-benzochroman[26] (XXV) and 1-methylnaphtho(2,1-b)pyrylium perchlorate (XXVI)*.

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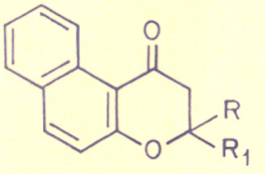
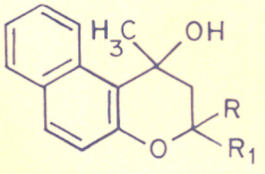
*Numbering as in Patterson's "Ring Index" (1959) and Chemical Abstracts.

Chart 10



CH_3MgI →



(XXII) ; R, R′= H

(XXIII) ; R = H, R′= CH_3

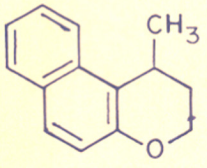
(XXIV) ; R, R′= CH_3

(XIX) ; R, R′= H

(XX) ; R = H, R′= CH_3

(XXI) ; R, R′= CH_3

(XIX) $\xrightarrow{HClO_4}$



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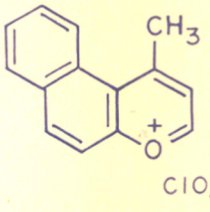
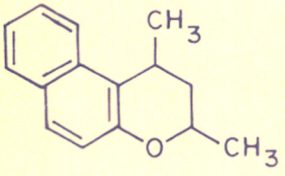


(XXV) (XXVI)

(XX) $\xrightarrow{HClO_4}$



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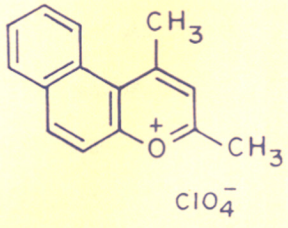
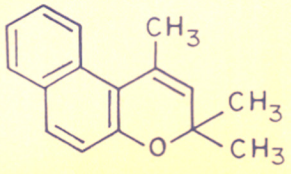


(XXVII) (XXVIII)

(XXI) $\xrightarrow{HClO_4}$



(XXIX)

Compound (XX) on treatment with $HClO_4$ similarly gave 2,4-dimethyl,5,6-benzochroman (XXVII) and 1,3-dimethylnaphtho(2,1-b)pyrylium perchlorate (XXVIII)*.

When (XXI) was treated with $HClO_4$ 1,3,3-trimethylnaphtho(2,1-b)pyran (XXIX)* was the only product formed there being no possibility of hydride transfer from the 2 position.

The structure of (XXIX) was confirmed by UV analysis and NMR.

The naphthopyrylium salts were quite stable and could be isolated without difficulty. The naphthalene ring system contributes to the stability of the salts as the +ve charge can be delocalised over an extended conjugated system.

Stereochemistry of hydride transfer

Since the hydride transfer takes place at a planar carbonium ion which is capable of accepting the hydride from either side of the molecule, it was of interest to study the stereochemistry of a chroman formed by disproportionation where stereo isomers were possible.

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*Numbering as in Patterson's "Ring Index" (1959) and Chemical Abstracts.

With this end in view, disproportionation of 3,4-dimethyl-4-chromanol (XXX) and 3,4-dimethyl-Δ^3-chromene (XXXI) was studied (chart 11).

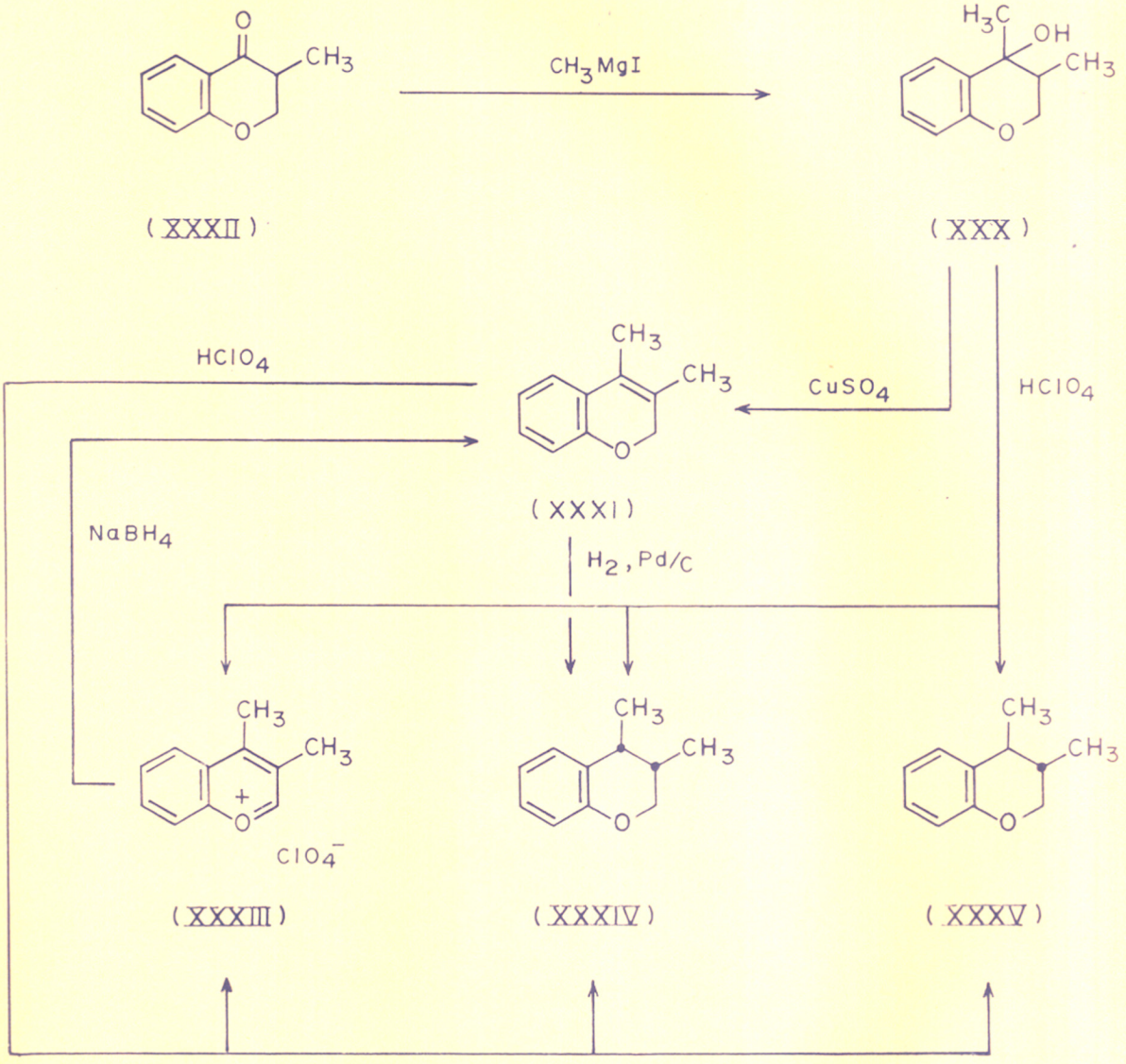
3-Methyl-4-chromanone (XXXII) was prepared[27] by the action of formaldehyde on the sodium salt of o-hydroxypropiophenone. The chromanol (XXX) was obtained by reacting (XXXII) with CH_3MgI.

The action of $HClO_4$ on (XXX) yielded 3,4-dimethylbenzopyrylium perchlorate (XXXIII) and 3,4-dimethylchroman (shown to be a 50:50 mixture of cis (XXXIV) and trans (XXXV) isomers).

Dehydration of (XXX) with anhydrous $CuSO_4$ gave 3,4-dimethyl-Δ^3-chromene (XXXI) which was also obtained by sodium borohydride reduction of (XXXIII). The UV and NMR spectra of (XXXI) confirmed that it was pure Δ^3-chromene with no impurity of the Δ^2-isomer. Catalytic reduction of (XXXI) gave the pure cis 3,4-dimethyl chroman (XXXIV). When (XXXI) was treated with $HClO_4$ it likewise gave (XXXIII) and a 50:50 mixture of cis-3,4-dimethylchroman (XXXIV) and trans-3,4-dimethylchroman (XXXV).

That the 3,4-dimethylchroman obtained by disproportionation was a 50:50 mixture of cis and trans isomers was shown by the study of its NMR and VPC.

Chart 11


O
CH3
CH3MgI
H3C
OH
CH3
(XXXII)
(XXX)
HClO4
CH3
CH3
CuSO4
HClO4
(XXXI)
NaBH4
H2, Pd/C
CH3
CH3
+
ClO4−
CH3
CH3
CH3
CH3
(XXXIII)
(XXXIV)
(XXXV)

Similar studies with (XXXIV) obtained by catalytic reduction confirmed it to be a pure cis compound.

NMR (Fig. 1) spectrum of cis-3,4-dimethylchroman (XXXIV) obtained by catalytic hydrogenation of (XXXI) was as follows (the position of the protons are indicated in ppm and J values in cps.):-

(a) two methyl doublets at 0.97 and 1.17 (J = 7).

(b) two pairs of overlapping quartets for the benzylic methine proton at C_4 centred at 2.9 ($JH_{4,3}$ = 6). The coupling constant 6 for C_4 and C_3 protons confirmed their cis orientation.

(c) a complex band for C_3-H centred at 2.15.

(d) a band for O-CH_2-protons centred at 3.9.

(e) a multiplet for four aromatic protons centred at 6.9.

NMR spectrum (Fig. 2) of the mixture of cis- and trans-dimethylchromans obtained by treatment of (XXX) and (XXXI) with perchloric acid showed the following characteristics:-

(a) four pairs of methyl doublets at 0.97, 1.17, 0.91 and 1.27. Of these, the two pairs at 0.97 and 1.17 belong to the cis-isomer (XXXIV) as seen from the NMR spectrum of (XXXIV), obtained by catalytic hydrogenation

of (XXXI). The other pair at 0.91 and 1.27 (a small amount of which is also discernible in the catalytic reduction product (XXXIV) is due to the trans isomer (XXXV).

Integration showed the ratio of the two isomers to be 50:50.

(b) The band for C_4 proton in this mixture was too complex for analysis. The C_3 and C_4 protons show as a complex band from 2-3.

(c) a complex band for O-CH_2 protons centred at 3.85.

(d) a multiplet for four aromatic protons centred at 6.8.

The NMR data agreed with the following VPC analysis (Fig. 3).

Using a 50 ft SE-30 (Golay) column (col. temp. 125°, H_2 flow rate 375 ml/min), (XXXIV), obtained by catalytic hydrogenation of (XXXI), gave a peak with retention time of 9 min. 36' showing 90% of cis isomer and 10% of trans isomer with a retention time 8 min. 15'. The product obtained by acid catalysed disproportionation of (XXXI) on the other hand under similar conditions gave two peaks with retention time 9 min. 36' and 8 min. 15'

corresponding to 50% of each of the isomers (XXXIV) and (XXXV) respectively.

EXPERIMENTAL

The ultraviolet spectra were recorded in 95% ethanol, unless otherwise stated (DK_2 Ratio Recording Spectrophotometer, Beckman and Perkin Elmer 350 Spectrophotometer). λ max values are given in mμ and log ϵ values in parenthesis. NMR spectra were taken in carbon tetrachloride unless otherwise stated (Varian A-60). Values are reported in ppm and J values in cps. IR spectra were taken as indicated using Perkin Elmer Infracord 137. M.Ps. are uncorrected and boiling points refer to bath temperatures unless mentioned (liquids being distilled in bulb tubes).

(1) <u>β-Phenoxypropionic acids (Ia - Id)</u>

The acids were prepared as reported in the literature[20].

(i) β-Phenoxypropionic acid (Ia)

Propiolactone 72 g and phenol (94 g) gave Ia (28 g) m.p. 90-92° (lit.[20] 94-95°).

(ii) β-(p-Methoxyphenoxy)-propionic acid (Ib)

Propiolactone (18 g) and p-methoxyphenol (31.04 g) gave Ib (5.5 g), m.p. 106-108° (lit.[20] 106-7°).

(iii) β-(p-Methylphenoxy)-propionic acid (Ic)

Propiolactone (18 g) and p-cresol (27.03 g) gave

Ic (6.08 g), m.p. 143-5° (lit.[20] 144-5°).

(iv) β-(m-Methoxyphenoxy)-propionic acid (Id).

Propiolactone (12 g) and m-methoxyphenol (20.6 g) gave Id (8.7 g), m.p. 80-82° (lit.[20] 81-82°).

(2) Chromanones (IIa - IId)

The acids (Ia - Id) were cyclised with PPA at 60-70° for 1 1/2 to 2 hrs. The reaction mixture was poured over ice and extracted with ether. The ether extract was washed with $NaHCO_3$ solution and water, and evaporated. The residue distilled to give the corresponding chromanones (IIa - IId).

(i) 4-Chromanone (IIa).

Ia (9.7 g) with PPA [P_2O_5 (45 g) and H_3PO_4 (28 ml)] gave IIa (7.682 g) b.p. 100°/1 mm.

(ii) 6-Methoxy-4-chromanone(IIb).

Ib (3 g) with PPA [P_2O_5 (12 g) and H_3PO_4 (7.5 ml)] gave (IIb) (2.036 g), b.p. 148-51°/7 mm (lit.[21] 178-80°/23 mm).

(iii) 6-Methyl-4-chromanone (IIc).

Ic (6 g) with PPA [P_2O_5 (34 g) and H_3PO_4 (18 ml)] gave (IIc), b.p. 117-118°/3.5 mm (lit.[21]

160-62°/28 mm).

(iv) 7-Methoxy-4-chromanone (IId).

Id (4 g) with PPA [(P_2O_5 (25 g) and H_3PO_4 (16 ml)] gave (IId) (3.48 g), b.p. 138-40°/1.5 mm; m.p. 55° (lit.[21] 55°).

(3) 4-Methyl-4-chromanols[21] (III-VI)

The chromanones (IIa - IId) were treated with two equivalents of CH_3MgI at 0°. The temperature was gradually allowed to come to room temperature and the complex decomposed with NH_4Cl solution to give the chromanols (III - VI).

(i) 4-Methyl-4-chromanol (III).

(IIa) (5 g) gave (III) (3.9 g), m.p. 105-6° (pet. ether, b.p. 60-80°) (lit.[21] 107°).

(ii) 6-Methoxy-4-methyl-4-chromanol (IV).

(IIb) (2.03 g) gave (IV) (1.2 g), m.p. 72-73° (pet. ether, b.p. 60-80°) (lit.[21] 71°).

(iii) 4,6-Dimethyl-4-chromanol (V).

(IIc) (2 g) gave (V) (1.5 g), m.p. 114-115° (pet. ether b.p. 60-80°) (lit.[21] 116°).

(iv) 7-Methoxy-4-methyl-4-chromanol (VI).

(IId) (8.6 g) gave (VI) (8.92 g). The product was obtained as a viscous oil. It was used without further purification as IR taken as a thin film showed strong OH absorption and no carbonyl impurity (lit.[21] m.p. 61°).

(4) 5,6-Benzo-4-chromanone (XXII)[23].

(i) β-2-Naphthoxypropionitrile.

β-Naphthol (80 g) was refluxed with acrylonitrile (138 ml) for 20 hours using triethylamine (7.5 ml) as catalyst instead of triton B as reported to give 49 g of the product m.p. 105-107° (lit.[23] 105-106°).

(ii) Cyclisation of β-2-naphthoxypropionitrile to give (XXII).

β-2-Naphthoxypropionitrile (2 g) with 85% sulphuric acid (20 ml) gave (XXII) (1.315 g) b.p. 125-129°/0.015 mm.

(5) 2-Methyl-5,6-benzo-4-chromanone (XXIII)[24].

(i) Preparation of β-naphthylcrotonate[28].

β-Naphthylcrotonate (27.4 g), m.p. 54-55° was obtained by condensing β-naphthol (20.16 g) with crotonyl

chloride (14.720 g) in dry benzene (100 ml) in the presence of magnesium turnings (0.2 g).

(ii) Cyclisation of β-naphthylcrotonate to give (XXIII).

The ester (22 g) was treated with 60 ml HF for 3 hours at room temperature. The crude product (20 g) was not distilled as reported, but purified by chromatography over alumina eluting with pet. ether (60-80°) to give pure (XXIII) (6.8 g), m.p. 72-73° (lit. 73-74°).

(6) 2,2-Dimethyl-5,6-benzo-4-chromanone (XXIV)

(XXIV) could not be prepared as reported[25]. It was obtained by the following procedure:-

(i) Preparation of β-naphthyl-2,2-dimethyl-acrylate.

2,2-Dimethylacrylic acid chloride (8.6 g) was refluxed with β-naphthol (10.5 g) in dry benzene (50 ml) with magnesium turnings (200 mg) for 2 hrs. to give the ester (15.7 g) (yield, 96%), m.p. 54-56°.

(ii) Cyclisation of β-naphthyl-2,2-dimethyl acrylate to give (XXIV).

The ester (22.3 g) was treated with HF

(60-70 ml) at room temperature for 2 hours. HF was removed by passing a stream of N_2. The reaction mixture was dissolved in ether and the ether extract washed five times with 1.5% alkali solution and then with brine till free of alkali. The crude chromanone (18.6 g) was chromatographed over neutral alumina (400 g) using pet. ether (b.p. 60-80°). The product (11.3 g) on further purification by three crystallisations from pet. ether (b.p. 40-60°) gave pure chromanone (XXIV), m.p. 79-81° (lit.[25] m.p. 81°).

(7) 4-Methyl-5,6-benzo-4-chromanol[21] (XIX)

The chromanone (XXII) (1.3 g) with 2 equivalents of CH_3MgI gave (XIX) (0.98) m.p. 123-4° (pet. ether, benzene) (lit.[21] 124°).

(8) 2,4-Dimethyl-5,6-benzo-4-chromanol (XX)

A solution of chromanone (XXIII) (5.89 g) in ether was added dropwise at 0° to two equivalents of CH_3MgI in ether. The reaction was allowed to come to room temperature very gradually and then refluxed for one hour. The Grignard complex was decomposed with 20% aqueous ammonium chloride and the ether layer washed with 2% aqueous $Na_2S_2O_3$ solution and saturated brine. Removal of ether gave (XX) as a white solid (5.56 g) (yield, 88%). On crystallisation from ethanol it gave white needles,

m.p. 134-35° (Found: C, 78.7; H, 6.8; $C_{15}H_{16}O$ requires: C, 78.9; H, 7.1%).

(9) 2,2,4-Trimethyl-5,6-benzo-4-chromanol (XXI)

The chromanone (XXIV) (5.65 g) with CH_3MgI as above gave crude (XXI) (4.42 g). The latter on several crystallisations from ethanol gave white needles m.p. 161-63° (2.6 g; yield, 43%) (Found: C, 79.2; H, 7.8. $C_{16}H_{18}O$ requires: C, 79.3; H, 7.4%).

(10) 3-Methyl-4-chromanone (XXXII) was prepared by treating the sodium salt of o-hydroxypropiophenone with formaldehyde as reported[27]. However, the experimental details have not been described. By adopting the following procedure, (XXXII) was obtained in yields varying from 27-50%. o-Hydroxypropiophenone (6 g) was dissolved in the required quantity of sodium hydroxide in water (40 ml) at 50°. Aqueous (37-41%) formaldehyde (5 ml) was added and the mixture heated at 50° for 75 min. After keeping at room temperature for 2 hours the mixture was extracted with ether. The ether extract washed free of alkali gave a liquid which was distilled. The fraction distilling between 112-126°/ 3 mm was collected. On redistillation (XXXII) was obtained (b.p. 113-15°/3 mm) (Found: C, 74.2; H, 6.5. $C_{10}H_{10}O_2$ requires: C, 74.1; H, 6.2%).

(11) 3,4-Dimethyl-4-chromanol (XXX) was prepared as

described above. The chromanone (XXXII) (8.23 g) gave (XXX) as a colourless viscous oil (8.79 g). The latter showed a strong OH absorption and absence of carbonyl band in IR and was used as such in subsequent reactions.

(12) 4-Methyl-Δ^3-chromene[21] (IX)

(III) (5.1 g) was refluxed in dry C_6H_6 with anhydrous $CuSO_4$ to give (IX) (3.8 g).

(13) 4-Methylchroman

A solution of (IX) (0.25 g) in ethyl acetate and 30% palladised carbon (10 mg) was treated with hydrogen till absorption ceased. Removal of solvent and distillation of the residue gave 4-methylchroman as a colourless liquid (0.16 g), b.p. 80-90°/5 mm. (Found: C, 80.6; H, 8.1. $C_{10}H_{12}O$ requires: C, 81.0; H, 8.1%).

UV spectrum:- 274 (3.35), 283 (3.32).

(14) 3,4-Dimethyl-Δ^3-chromene (XXXI)

A solution of the chromanol (XXX) (6 g) in dry benzene (250 ml) was refluxed with anhydrous $CuSO_4$ (3 g). Water formed in the reaction was removed azeotropically. The benzene solution was filtered and evaporated. The residue distilled to give (XXXI) (4.98 g; yield, 92%), b.p. 102-7°/3-4 mm. (Found: C, 82.8; H, 7.7. $C_{11}H_{12}O$

requires: C, 82.5; H, 7.6%).

UV spectrum:- 307-8 (3.65), 266 (3.74).

NMR (Fig. 4):-

(a) a peak at 1.75 of 3 proton intensity for C_3-Methyl

(b) a peak at 1.95 of 3 proton intensity for C_4-Methyl

(c) a signal at 4.54 of 2 proton intensity for C_2 methylene protons

(d) a complex band at 6.88 for 4 aromatic protons

(15) Cis-3,4-Dimethyl chroman (XXXIV)

A solution of (XXXI) (0.3 g) in ethyl acetate (10 ml) and 10% palladised carbon (100 mg) was treated under stirring with hydrogen at atmospheric pressure till hydrogen absorption ceased. Removal of solvent and distillation of the residue gave (XXXIV) (0.20 g; yield, 66%) as a colourless oil, b.p. 106°/5 mm. (Found: C, 81.7; H, 8.7. $C_{11}H_{14}O$ requires: C, 81.4; H, 8.7%).

UV spectrum:- 275 (3.39), 283 (3.37).

(16) General procedure for treatment of 4-methylchromanols, benzochromanols, or Δ^3-chromenes with 60% perchloric acid

The chromanols and benzochromanols were treated with 60% aqueous perchloric acid (5-10 ml per gm of the compound) at 60-70° for 2 hours, except in the case of chromanol (IV) which was treated with 70% aqueous perchloric acid at room temperature for 2 hours. The reaction mixture was extracted with petroleum ether (b.p. 60-80°). The solvent extract was washed with aqueous sodium bicarbonate solution, and water. After drying (Na_2SO_4), the solvent was removed and the residual liquid distilled in vacuum whereby the chromans were obtained as colourless liquids. The perchloric acid solution left after extraction with petroleum ether was cooled in an ice bath and ether gradually added under agitation until the mixture was saturated with ether. The reaction mixture gave the relevant perchlorates which separated out in a few cases as crystalline solids. In the case of chromanols (III), (IV) and (V), the above perchloric acid treatment gave dark violet solutions from which very small quantities of coloured compounds were isolated which, however, have not been examined fully so far. The benzopyrylium salt from (III) and (IV) were isolated in experiments described separately.

The physical constants, properties, yields and elementary analysis of 4-methylchromans obtained by the disproportionation of 4-methyl-4-chromanols are described in Table I.

The physical constants, properties and elementary analysis of 4-methyl benzopyrylium perchlorates obtained by the disproportionation of 4-methyl-4-chromanols are described in Table II.

(17) Disproportionation of 4-methyl-Δ^3-chromene (IX)

(IX) (1.08 g) was treated with 60% $HClO_4$ (10 ml) as described above to give (VII) (0.27 g, yield 27%) identified by its UV spectrum (λ mas. 274, 284). The $HClO_4$ layer, after removal of (VII) showed the UV characteristics of (VIII) (λ max. 319, 240). On the addition of ether to the $HClO_4$ layer, the usual dark coloured solutions were obtained.

(18) Disproportionation of 3,4-dimethyl-Δ^3-chromene (XXXI)

(XXXI) (3 g) was treated with 60% $HClO_4$ (12 ml) as described above to give a 50:50 mixture of cis-3,4-dimethyl chroman (XXXIV) and trans-3,4-dimethyl chroman (XXXV) (1.39 g; yield, 46%), b.p. 81-83°/2.75-3.25 mm. (Found: C, 81.7; H, 8.3. $C_{11}H_{14}O$ requires: C, 81.4; H, 8.7%).

UV spectrum:- 278 (3.42), 285 (3.38).

(19) 4-Methylbenzopyrylium perchlorate (VIII)

The chromanol (III) (0.50 g) was gradually added to aqueous 70% perchloric acid (2.5 ml) at -15°. The reaction mixture was kept for 1 hour at -13 to -15° with occasional stirring. Chilled ether was added very gradually keeping the temperature below -10°. After adding ether to saturation point, the mixture was allowed to stand for a few minutes and then filtered in an atmosphere of nitrogen and washed with dry ether. The crystalline perchlorate (VIII) was immediately analysed and its NMR spectrum in trifluoroacetic acid also immediately taken. The perchlorate (yield 16 mg) had no sharp m.p. It shrinks at 95° and melts at 105-110°.

NMR (Fig. 5):-

(a) a three proton peak for the C_4-methyl group at 3.36

(b) a multiplet for the four aromatic protons and C_3 proton between 8.16 and 8.8

(c) a one proton doublet (J=4.5) for the C_2 proton at 9.59

(20) 6-Methoxy-4-methylbenzopyrylium perchlorate (XIII)

Chromanol (IV) (0.5 g) was gradually added to 70% aqueous perchloric acid (2.5 ml) cooled in an ice-salt bath. The reaction mixture was then kept at room temperature for one hour, after which it was again cooled in an ice-salt bath and ether added to saturation point. The yellow precipitate obtained was immediately filtered and washed with ether. The crystalline perchlorate (XIII) (0.15 g) was immediately analysed and its NMR spectrum recorded in trifluoroacetic acid.

NMR (Fig. 6):-

(a) a three proton peak for the 4-methyl group at 3.26

(b) a peak for the 6-OCH_3 group at 4.16

(c) a multiplet for the three aromatic protons and the C_3 proton between 7.67 and 8.26

(d) a one proton doublet (J=4.5) for the C_2 proton at 9.36.

(21) 7-Methoxy-4-methylbenzopyrylium perchlorate (XVII)

The chromanol (VI) (4.6 g) on treatment with 70% aqueous perchloric acid (12 ml) at room temperature for two hours gave on saturation with ether (XVII)(1.72 g).

NMR (trifluoroacetic acid):-

(a) a three proton peak for the 4-methyl group at 3.2

(b) a peak for the 7-OCH_3 group at 4.27

(c) a multiplet for the three aromatic protons and the C_3 proton between 7.67 and 8.7

(d) a one proton doublet (J=5) for the C_2 proton at 9.2

(22) 1,3,3-Trimethylnaphtho[2,1-b]pyran (XXIX)

A solution of compound (XXI) (0.6 g) in benzene (7 ml) was stirred with 60% perchloric acid (1 ml) for 15 minutes at room temperature. The benzene layer was washed with aqueous sodium bicarbonate. Removal of benzene and distillation of the product gave a pale yellow liquid (0.53 g), b.p. 120-40°/0.2 mm. On redistillation, a white solid was obtained which after three crystallizations from petroleum ether (b.p. 40-60°) gave (XXIX) as colourless cubes, m.p. 81-82° (lit.[25] 74-76°) (Found: C, 86.2; H, 7.4. $C_{16}H_{16}O$ requires: C, 85.7, H, 7.1%).

UV spectrum:- 347 (3.64), 313 (3.60), 301 (3.64), 244 (4.74).

NMR:-

(a) a six proton peak for the 3,3-dimethyl group at 1.4

(b) a three proton peak for the C_1-methyl group at 2.36

(c) a one proton peak for the C_2 proton at 5.37

(d) a multiplet for the six aromatic protons between 6.67 and 8.15

TABLE 1

Synthesis of 4-Methylchromans from Chromanols, by treatment with perchloric acid

Starting compd.	Chroman	% yield	m.p./b.p.	Appearance	Analysis				UV spectrum λ max (log ε)
					Found		Required		
					C	H	C	H	
III	VII	25	75-85/4 mm	Colourless liquid	81.5	8.0	81.0	8.1	275 (3.40); 283 (3.37)
IV	XII	28	100-25°/2 mm	Colourless liquid	74.3	7.9	74.1	7.9	229 (4.02); 294 (3.54)
V	XIV	34.4	105-15°/5 mm	Colourless liquid	81.3	8.9	81.5	8.6	281 (3.49); 289 (3.27)
VI	XVI	35	90-95°/7 mm	Colourless liquid	73.7	8.0	74.1	7.9	282 (3.50); 288 (3.46)
XIX	XXV	30	135-50°/2.5 mm m.p. 61-62°	White solid	84.8	6.8	84.8	7.1	233 (4.86); 257 (3.45) 266 (3.62); 277 (3.70) 288 (3.58); 319 (3.31) 333.5 (3.40)
XX	XXVII	36	140-60°/0.5 mm m.p. 76°	White solid	85.2	7.8	84.9	7.8	232 (4.88); 288 (3.56) 276 (3.68); 267 (3.60) 318 (3.28); 332 (3.33)
XXX	XXXIV + XXXV	36	81-82°/3 mm	Colourless liquid	81.2	8.5	81.4	8.7	278 (3.40); 285 (3.33)

TABLE 2

Synthesis of benzopyrylium and naphthopyrylium perchlorates by treating chromanols with $HClO_4$

Starting compd.	Chroman	% yield	m.p.	Appearance	Analysis						UV spectrum (solvent) λ max (in mμ) (log ε)
					Found			Required			
					C	H	Cl	C	H	Cl	
III	VIII	2	105-110°	Yellow microneedles	-	-	15.0	-	-	14.5	(70% $HClO_4$) 317 (4.10); 240 (4.51)
IV	XIII	21	156-7°	Yellow microneedles	-	-	12.9	-	-	13.1	(70% $HClO_4$) 245 (4.27); 258 (4.13); 325 (4.05); 269-70 (3.54)
VI	XVIII	28	182-83°	Buff-colored needles	48.6	4.4	12.3	48.0	4.0	12.9	(70% $HClO_4$) 248 (4.27); 372 (3.94)
XIX	XXVI	29	235°	Golden yellow needles	57.2	3.4	12.8	57.1	3.7	12.1	(AcOH + 1% $HClO_4$) 282 (4.25); 399 (4.08)
XX	XXVIII	31	231°	Golden yellow flakes	58.4	4.1	11.3	58.3	4.2	11.5	(AcOH + 1% $HClO_4$) 286.5 (4.67); 396 (4.54)
XXX	XXXIII	17	160-2°	Pale yellow needles	51.2	4.7	14.0	51.0	4.2	13.7	(70% $HClO_4$) 243 (4.37); 328 (4.10)

CONCLUSION

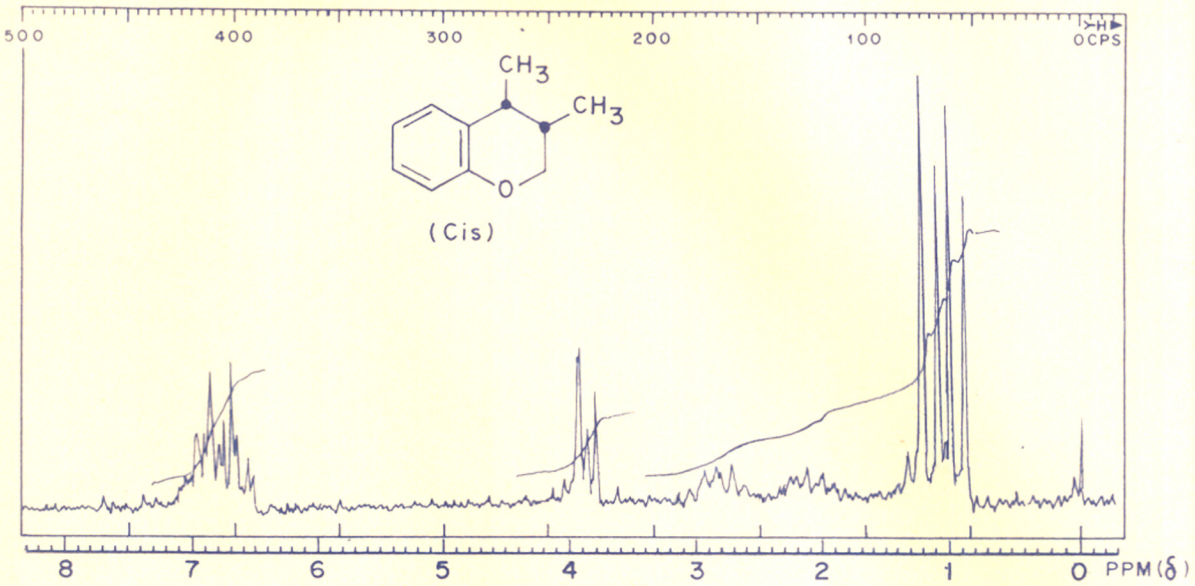
The reactions described above show that Δ^3-chromenes, disproportionate in acid media to give chromans and benzopyrylium salts as a result of intermolecular transfer of the C_2 hydrogen from Δ^3-chromene to the C_4 position of its protonated species.

The method has been used for the preparation of some unstable benzopyrylium salts without a substituent in the 2 position and the corresponding chromans. Benzochromans and naphthopyrylium salts have also been prepared.

For the bicyclic Δ^3-chromenes studied, it has been established that the hydride transfer reaction is nonstereospecific and that the hydride can attack with equal ease from either side of the planar molecule to give 50:50 mixture of cis and trans products.

The disproportionation reaction can explain the observations made by previous workers (c.f. introduction). The observed formation of benzopyrylium salts from chromene in the absence of oxidising agent or air is most probably the result of disproportionation rather than aerial oxidation as has been usually assumed. Where the oxidation has been attributed to the presence of substances like chalkones or hydroquinones the direct disproportionation of the chromenes involved offers a more rational explanation.

ILLUSTRATIONS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200
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7
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5
4
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2
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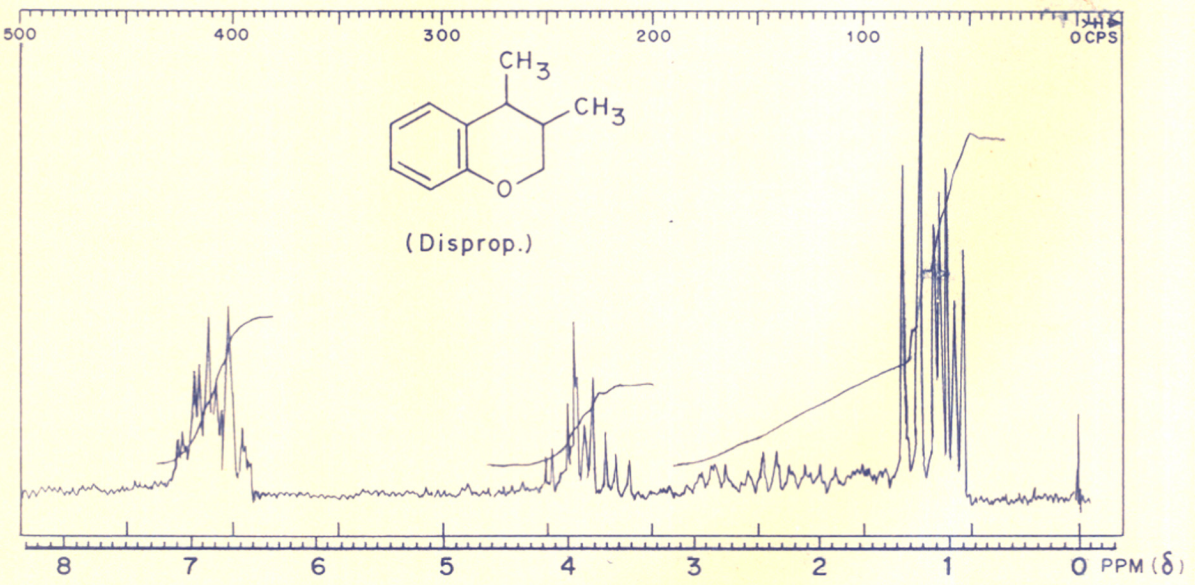
0
PPM (δ)

FIG. 1.


500
400
300
200
100
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CH3
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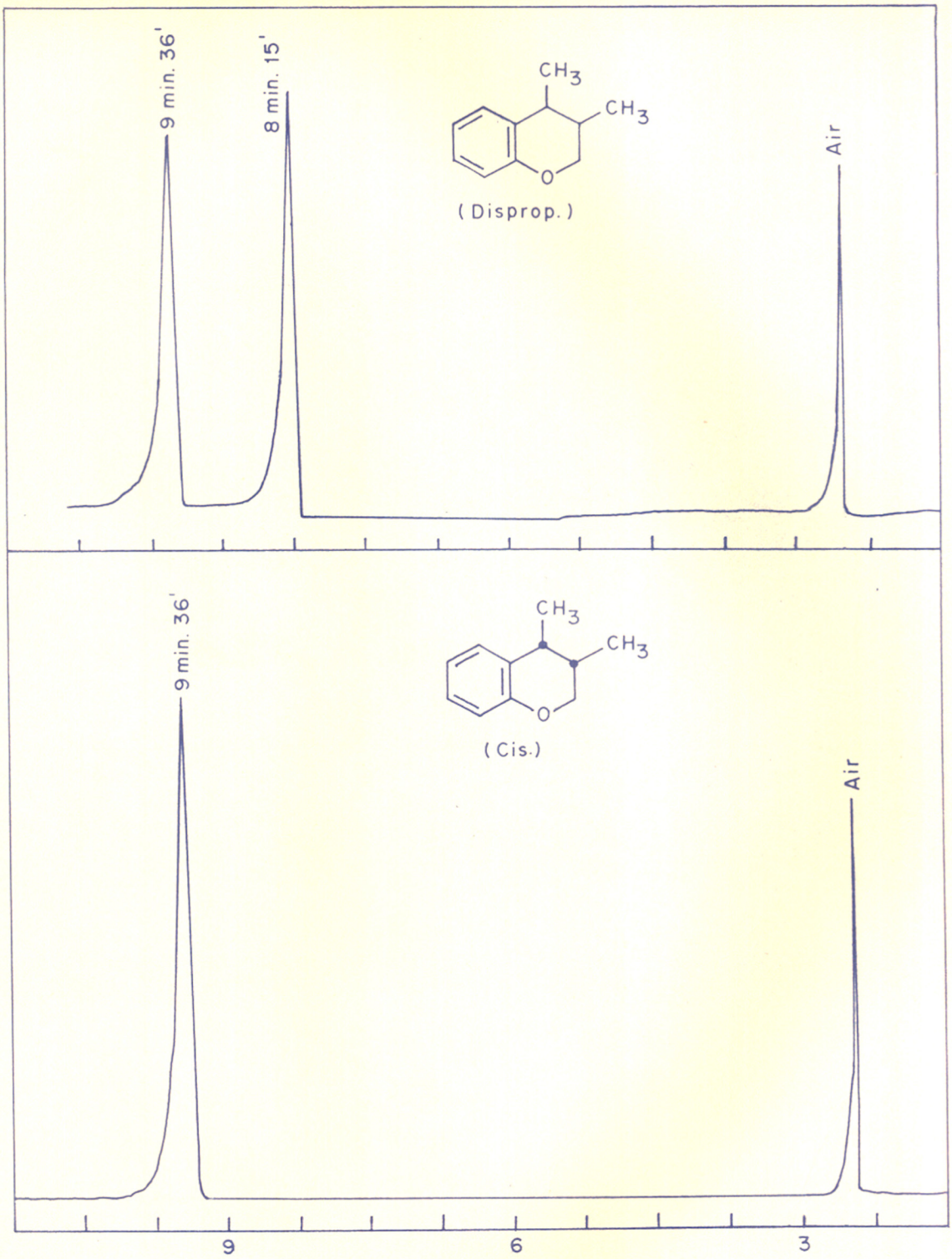
O
(Disprop.)
8
7
6
5
4
3
2
1
0
PPM (δ)

FIG. 2.



COLUMN: SE-30 (GOLAY). COLUMN TEMP.: 125 °C. FLOW RATE: 375 ml./min.
CARRIER GAS: H_2. CHART SPEED: 40"/hr.

FIG. 3.

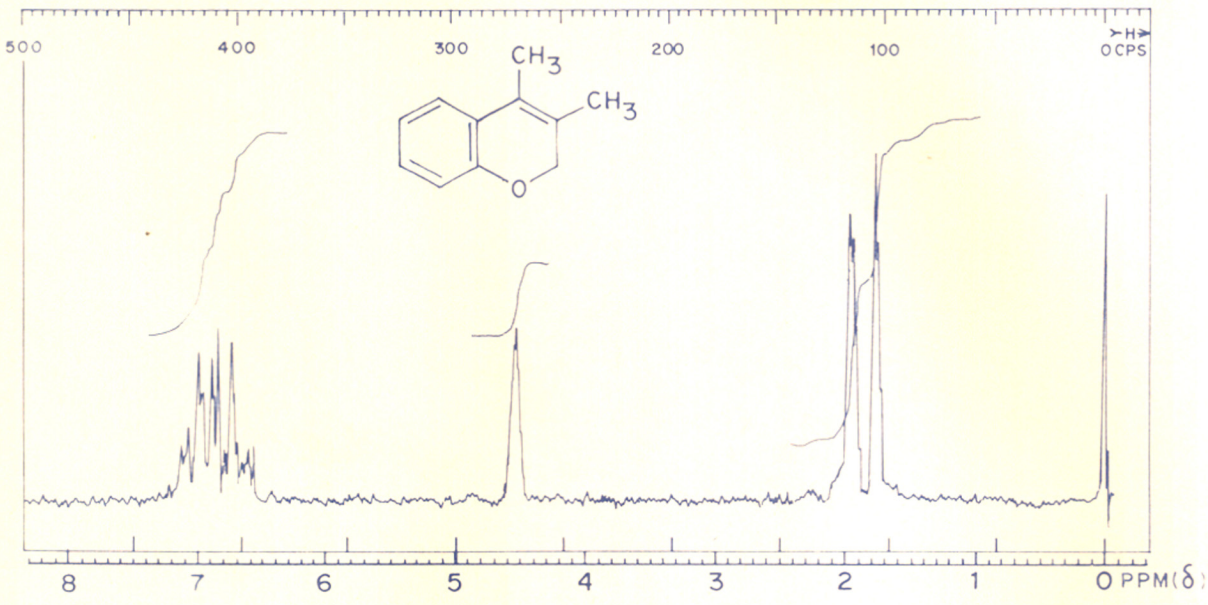
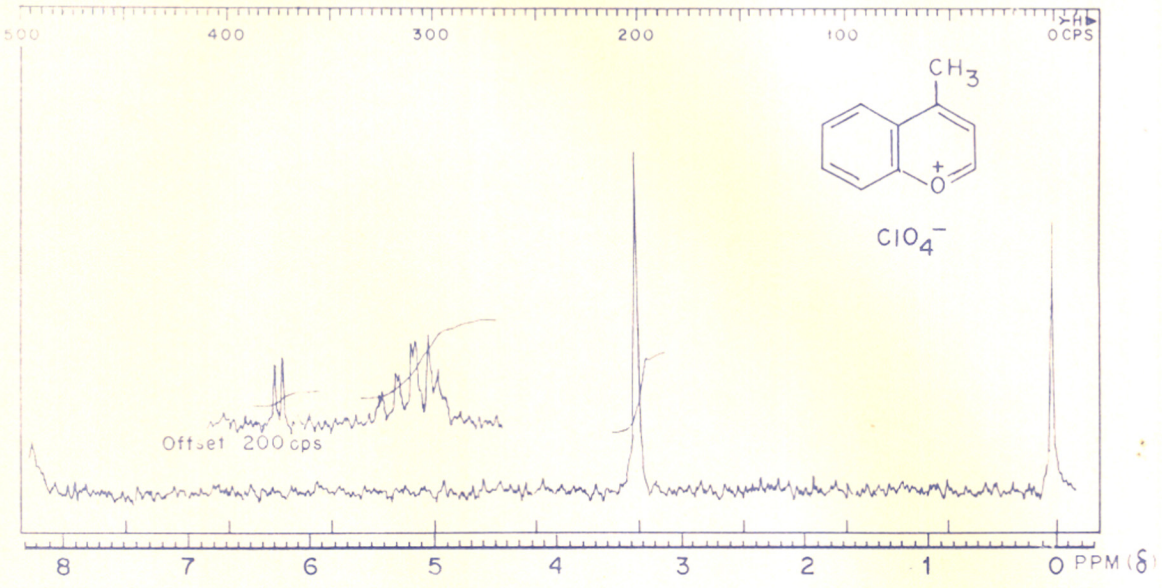


FIG. 4.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ClO4−
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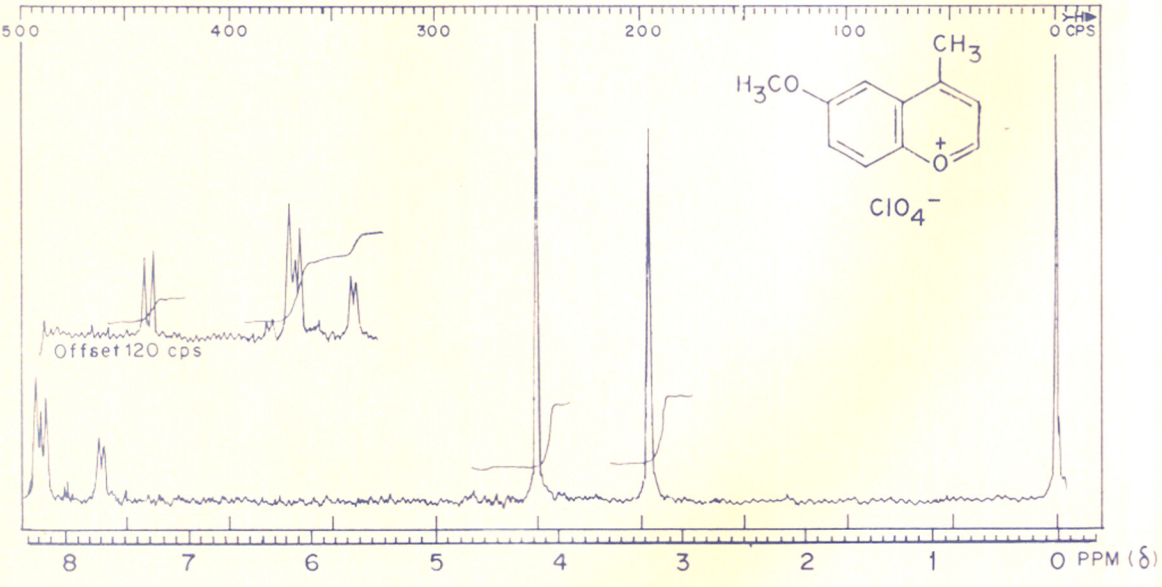
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 5.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O
ClO4−
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7
6
5
4
3
2
1
0 PPM (δ)

FIG. 6.

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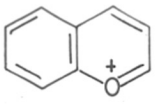
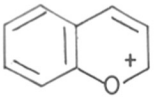
PART - IB

SODIUM BOROHYDRIDE RUDUCTION OF NAPHTHO (2-1, b) PYRYLIUM PERCHLORATES

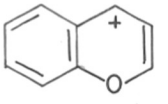
The benzopyrylium nucleus is highly susceptible to nucleophilic attack by virtue of the fact that the positive charge of the pyrylium cation stabilised by aromatization does not reside solely on the oxygen atom but is distributed in the ring (I - III).



(I)



(II)

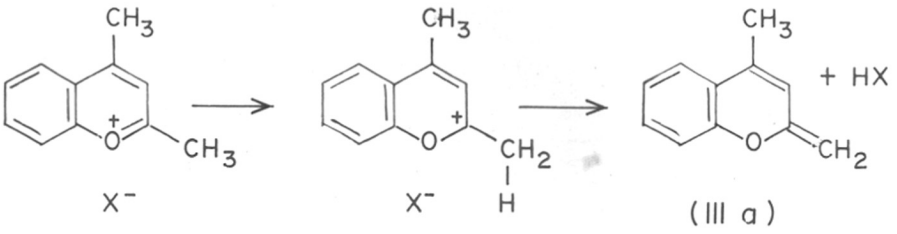


(III)

Although a systematic study of the relative electrophilicity of the C_2 and C_4 position has not been done it is generally observed that any nucleophilic attack takes place preferentially at the C_2 position[1,2]. Although the positive charge on oxygen can get delocalised to the 2 or 4 carbon atom with equal facility by mesomerism, the electronegativity of the hetero atom makes the carbon atom next to it more electrophilic.

It is also seen[3] that the reactivity of the 2-methyl substituents is more than that of a 4-methyl substituent for condensation reaction involving these methyl groups for e.g. preparation of oxacyanines. This is because the 2-carbon atom is more electron deficient than the 4-carbon atom making the 2-CH_3 protons more acidic to give the methylene bases (IIIa) which are the

reactive intermediates in the above reaction.



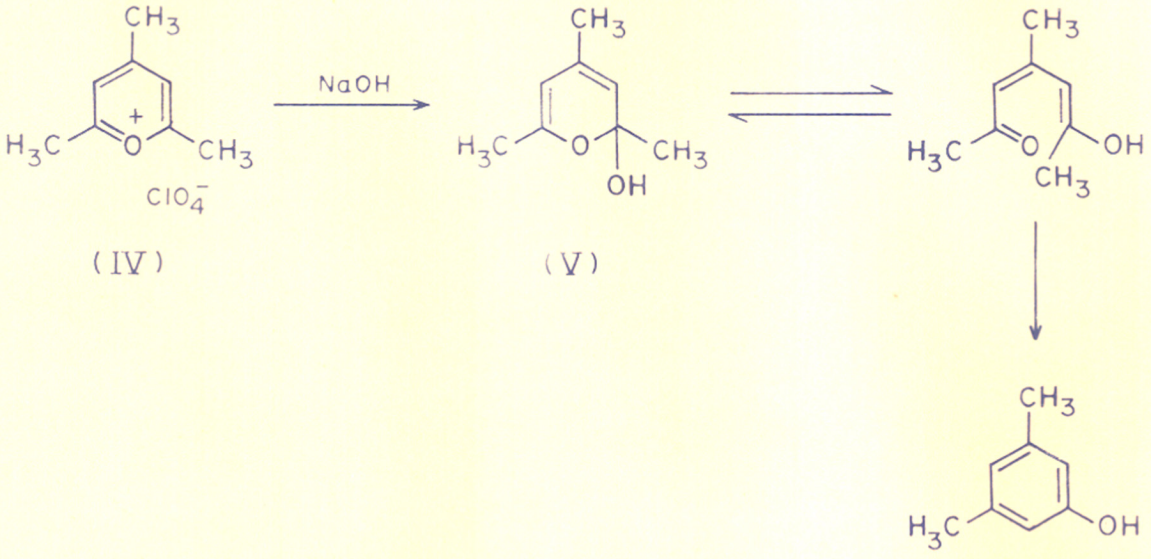
Calculations of electron density[4] in the pyrylium salts also show that the position C_2 and C_6 are the favoured ones for nucleophilic attack, although no definite conclusions can be drawn from experimental evidence. It is however[5], known with certainty that bulky substituents decisively direct the attack at the C_2 or C_4 positions (chart 12).

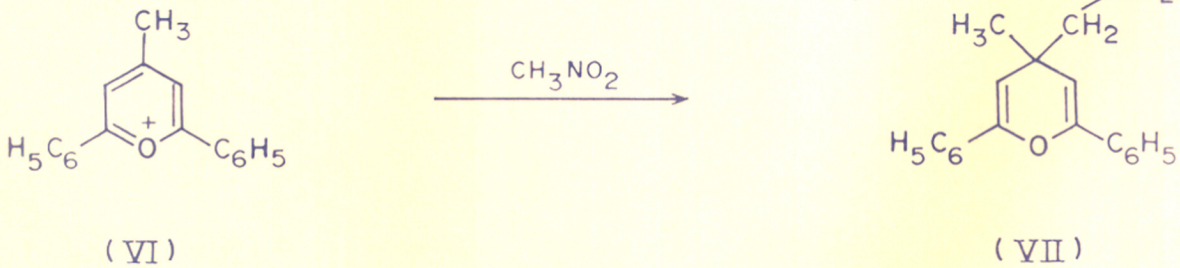
Symmetrically substituted pyrylium salts (IV) are converted into benzene derivatives[6] by boiling with 10% NaOH by the initial attack of OH^- at C_2 to give the intermediate (V).

The condensation of nitromethane[7] with 2,6-diphenyl-4-methylpyrylium salt (VI) gives exclusively the 4-H pyran (VII). It seems probable that the influence of the less bulky methyl group favours addition at C_4 atom so strongly that no addition at C_2-carbon atoms takes place.

Similar trends in nucleophilic attack are observed

Chart 12


CH3
H3C
O
CH3
ClO4−
NaOH
OH
(IV)
(V)


CH3
H5C6
O
C6H5
CH3NO2
NO2
CH2
(VI)
(VII)

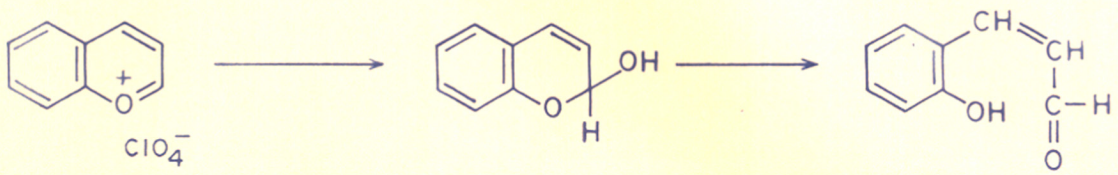
in the benzopyrylium[1,2] series (chart 13). The benzopyrylium perchlorate (VIII) is cleaved by alkali by initial reaction at the C_2 position to give (IX).

Also 2,3,4-triphenylbenzopyrylium salt[2] (X) gives the 2,2,3,4-tetraphenyl-Δ^3-chromene (XI) by the attack of Ph^- at the 2 position.

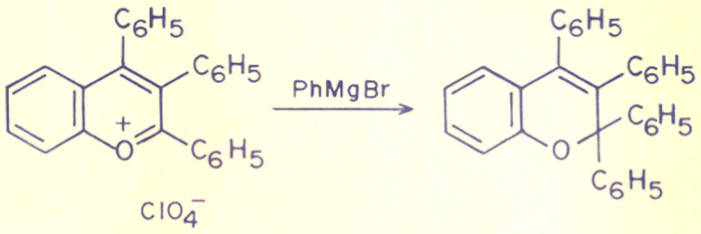
In the case of the 2,3-diphenyl benzopyrylium salt[2] (XII) the attack is on the unsubstituted 4-position giving 2,3-diphenyl-4-(α-naphthyl)-Δ^2-chromene (XIII).

It appears from the above discussion that the C_2 position in the benzopyrylium salt is more reactive. In both the unsubstituted and 2,4-disubstituted salts the nucleophylic attack occurs at the 2-position, whereas in the case of 2,3-disubstituted compounds the attack is at the unsubstituted and therefore the unhindered 4-position. In the present work nucleophylic substitution in naphthopyrylium salts has been studied.

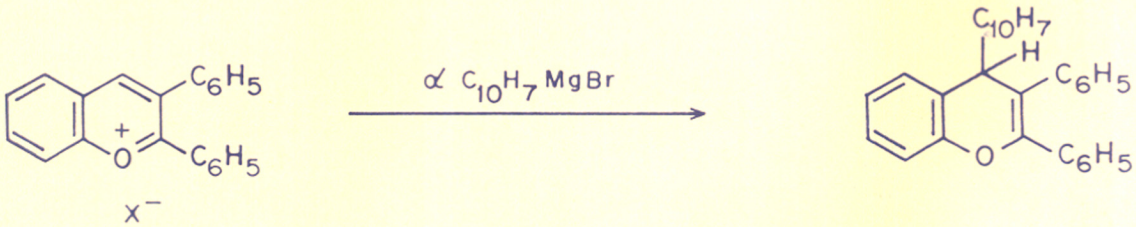
Chart 13



(VIII) (IX)



(X) (XI)



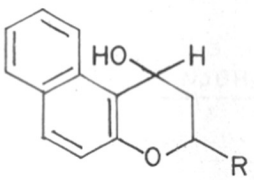
(XII) (XIII)

PRESENT WORK AND DISCUSSION

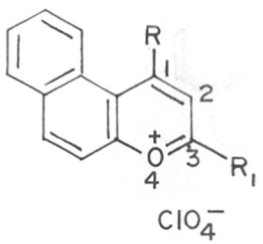
It has been shown that both electronic and steric factors affect the products formed by the attack of a nucleophilic reagent on the pyrylium nucleus. No such studies have been reported on the naphthopyrylium salts.

The present work deals with a study of the nucleophilic attack on the naphthopyrylium salts I* and its derivatives (II-IV) (chart 14).

The perchlorates (II) and (IV) were prepared as described in Part IA. The perchlorates (I)[8] and (III) were prepared from 5,6-benzochromanols (V[9] and VI) which were obtained by the LAH reduction of the corresponding ketones (cf. Part IA).



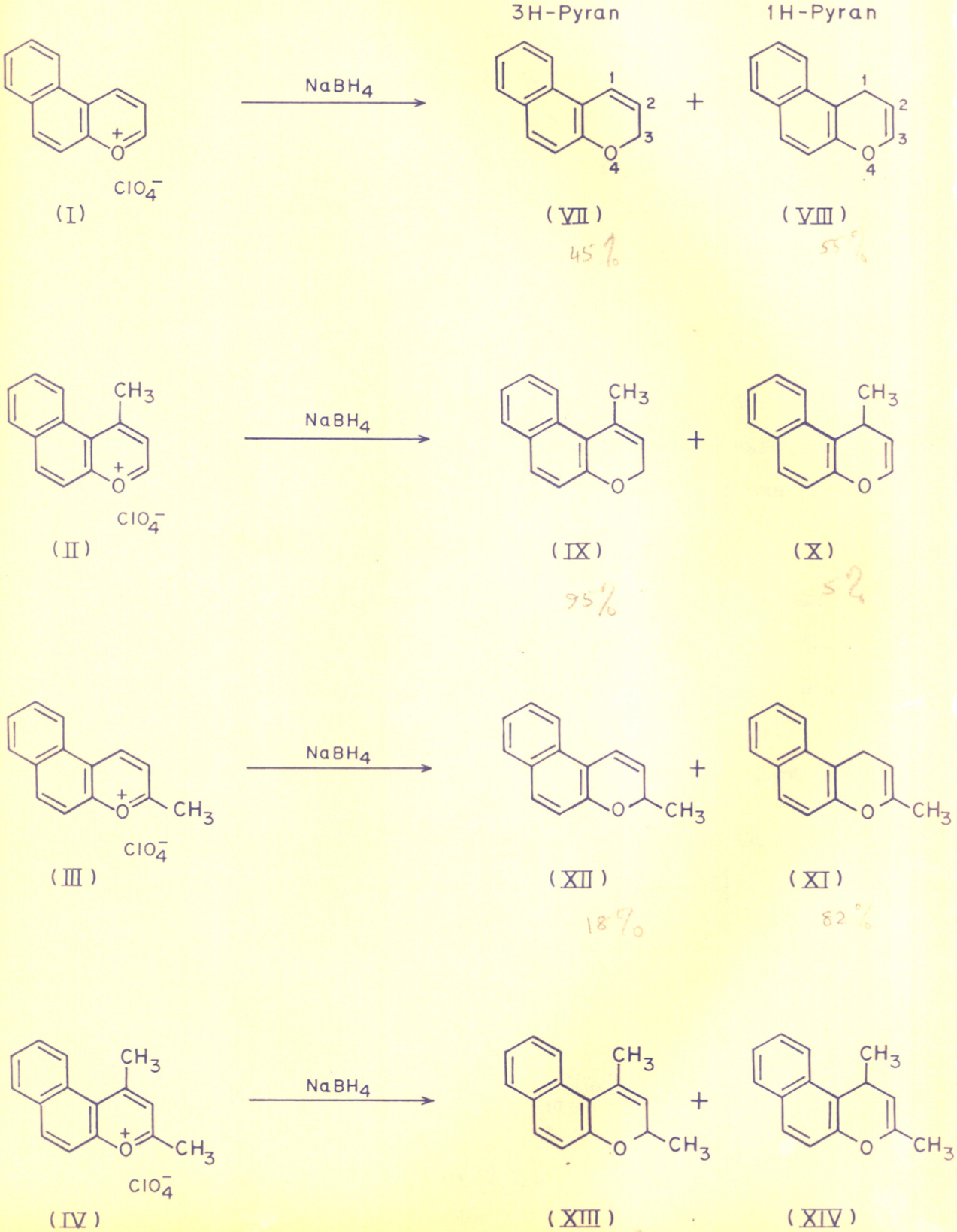
(V); R=H
(VI); R=CH_3



(I); R,R' = H
(II); R=CH_3, R'=H
(III); R=H, R'=CH_3
(IV); R,R'=CH_3

*Numbering as in Patterson's Ring Index and Chemical Abstracts.

Chart 14

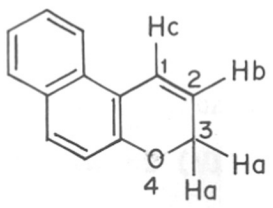

3H-Pyran
1H-Pyran
NaBH4
ClO4−
(I)
(VII)
45 %
(VIII)
55 %
CH3
(II)
(IX)
95 %
(X)
5 %
(III)
(XII)
18 %
(XI)
82 %
(IV)
(XIII)
80 %
(XIV)
20

Sodium borohydride reduction was chosen as a typical reaction where BH_4^- is the attacking nucleophile for the above perchlorates. Depending on whether the attack is at C_3 or C_1 position 3H-pyran or 1H-pyran would be the resulting product. A measure of the ratio of the two isomeric pyrans formed would thus indicate the relative reactivity of the two carbonium ions at C_1 and C_3.

The ratio of the isomeric pyran was determined by the NMR of the reaction products. The NMR were taken in carbon tetrachloride (Varian A 60). Values are given in ppm and J values in cps.

(I) was treated with $NaBH_4$ and the reaction worked up (as described in experimental section). The distilled liquid (yield, 75%) of analytical purity was found to consist of 45% naphtho(2,1-b)-3H-pyran (VII) and (55% naphtho(2,1-b)-1H-pyran (VIII) from NMR evidence.

The NMR of the above mixture showed the following characteristics for (VII) and (VIII) (Fig. 7):-



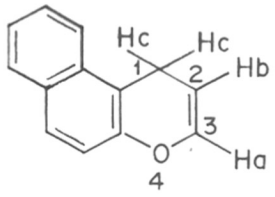
(VII)

(a) a quartet for the C_3 methylene protons at 4.76 (J_{Ha-Hb} = 3.5); (J_{Ha-Hc} = 1.75)

(b) a pair of triplets for the C_2 methine proton at 5.02 (J_{Hb-Hc} = 6.5); (J_{Hb-Ha} = 3.5)

(c) a pair of triplets for the C_1 methine proton at 6.54 (J_{Hc-Hb} = 6.5); (J_{Hc-Ha} = 1.75)

(d) the aromatic protons are shown between 6.82 and 7.82



(VIII)

(a) a band for the C_1 methylene protons at 3.6

(b) a pair of triplets for C_2 methine proton at 5.77 (J_{Hb-Ha} = 10); (J_{Hb-Hc} = 4)

The C_3 methine proton is merged with the aromatic region as seen from integration.

The ratio of the C_1 methylene protons of (VIII) to the C_3 methylene protons of (VII) was 56:45.

The perchlorate (II) with a methyl substituent

in the C_1 position was similarly reduced to give an analytically pure liquid in 75% yield. The NMR showed it to consist of more than 95% of naphtho(2,1-b)-1-methyl-3H-pyran (IX), the other isomer (X) being present to the extent of only 5%.

The NMR spectrum (Fig. 8) showed the following characteristics for (IX):-

(a) a peak for the C_1 methyl group at 2.3

(b) a band for the C_3 methylene protons at 4.43

(c) a band for the C_2 methine proton at 5.54

(d) the aromatic protons are shown from 6.95 - 8.18

The isomer (X) was indicated in the NMR by a doublet for C_1-methyl at 1.3 (J = 7).

The ratio of the C_1 methyl in (IX) to the C_1 methyl in (X) works out to be 95:5.

The perchlorate (III) with a CH_3 in the 3 position was next reduced when it gave 76% of analytically pure material consisting of 82% of naphtho(2,1-b)-3-methyl-1H-pyran (XI) and 18% of naphtho(2,1-b)-3-methyl-3H-pyran (XII).

The NMR (Fig. 9) showed the following characteristics for (XI):-

(a) a fine doublet due to allylic coupling for C_3 methyl at 1.86 (J = 1)

(b) a band for the C_1 methylene protons at 3.55

(c) a band for the C_2 vinyl proton at 4.71

(d) the aromatic protons are shown from 6.81 to 7.8

The presence of (XII) was shown by the following characteristics of NMR spectrum:-

(a) a doublet for the C_3 methyl group at 1.41 (J = 6.5)

(b) a doublet of doublet centered at 5.6 for the C_2 vinyl proton.

The ratio of C_3 methyl in (XI) to the C_3 methyl in (XII) is 82.18.

1,3-Dimethylnaphtho(2,1-b)-pyrylium perchlorate (IV) was reduced by $NaBH_4$ to give 93% of analytically pure liquid which consisted of 80% 1,3-dimethylnaphtho(2, 1-b)-3H-pyran (XIII) and 20% of 1,3-dimethylnaphtho(2, 1-b)-1H-pyran (XIV).

NMR (Fig. 10) showed the following characteristics for (XIII):-

(a) a doublet for C_3 methyl at 1.5 (J = 6.5)

(b) a signal with fine splitting for C_1 methyl protons at 2.3

(c) a band for C_3 methine proton at 4.6

(d) a multiplet for C_2 vinyl proton at 5.37

(e) the aromatic protons are shown from 7-8.1

The presence of the 1H-pyran isomer (XIV) was seen by (a) a doublet for C_1 methyl at 1.44 (J = 6) [one of the peaks is merged with the adjacent peak for the C_3-methyl of (XIII)]; (b) a peak showing a fine splitting due to allylic coupling for the C_3 methyl group at 1.9.

The ratio of the C_3 methyl peak for (XIII) to the C_3 methyl peak of (XIV) is 80:20.

The results of the above reactions are summarised in the following table:-

Compound	1H-pyran	% yield	3H-pyran	% yield
(I)	(VII)	56	(VIII)	44
(II)	(X)	5	(IX)	95
(III)	(XI)	82	(XII)	18
(IV)	(XIV)	20	(XIII)	80

The almost equal formation of 1H- and 3H-pyrans in the reduction of the unsubstituted salt (I) shows an equal distribution of the positive charge at C_1 and C_3 positions of the naphthopyrylium cation. The slightly higher reactivity of the C_1 position is probably due to the fact that the charge at C_1 can be more effectively stabilised by the naphthalene ring than in the benzopyrylium series. It appears that carbonium ion structure with the charge on C_1 contributes more effectively to the cationic structure of a naphthopyrylium salt.

In the perchlorate (II) with a methyl substitutent in the C_1 position, the attack is entirely at the C_3-position. Since (as we have seen above) electronically C_1 and C_3 are almost equally reactive and the presence of a methyl group on C_1 would only enhance the stability of the carbonium ion at C_1 through hyperconjugation, it is apparent that the attack by BH_4^-

is directed to the C_3 position because of steric factors. The C_1-position is sterically hindered because of the presence of the methyl group and the reduction thus takes place preferentially at C_3-position. Similar results were observed with C_3 substituted perchlorate (III) where the presence of a methyl group at C_3-position causes steric hindrance and the attack is preferentially at the C_1-carbonium ion. It should be noted, however, that the yield of 3H-pyran (XII) (by attack at the hindered carbonium ion) in this case is more than the yield of 1H-pyran (X) formed (by the attack at the hindered carbonium ion) during the reduction of (II). This indicates that C_1-position carrying a methyl group is far more hindered that C_3-position carrying the same group. This is further borne out by the fact that when both C_1- and C_3-positions are substituted by a CH_3 group as in the case of (IV) the attack is preferentially on the C_3 carbon atom giving 80% of 3H-pyran (XIII). This difference in the steric hindrance offered by a CH_3 group in C_1 and C_3 positions may be due to the presence of the peri hydrogen of the naphthalene moety which could cause more resistance to the incoming nucleophile.

EXPERIMENTAL

The ultraviolet spectra were recorded in 95% ethanol using Perkin Elmer 350 Spectrophotometer. λ max values are given in mμ.

Melting points are uncorrected and boiling points refer to bath temperatures (liquids distilled in bulb tubes).

5,6-Benzo-4-chromanol (V)

5,6-Benzo-4-chromanone (3.45 g) in dry ether was added dropwise to LAH (100 mg) in ether with stirring. After addition was complete the reaction mixture was refluxed for two hours. Excess LAH was decomposed with water and the ether layer dried (Na_2SO_4) and evaporated to give (V) (3.478 g), m.p. 107-108° (lit.[9], m.p. 109-109.5°).

2-Methyl-5,6-Benzo-4-chromanol (VI)

2-Methyl-5,6-benzo-4-chromanone (1.05 g) was reduced as above to give the chromanol (VI) (1.06 g) m.p. 91-93°C (Found: C, 78.7; H, 6.4; $C_{14}H_{14}O_2$. requires: C, 78.5; H, 6.5%).

Naphtho[2,1-b]pyrylium perchlorate (I)

Trityl chloride (2.085 g) with 70% $HClO_4$ (1 ml) was heated on a boiling water bath for 15 min. AcOH (5 ml) was added and the reaction brought to room temperature.

Chromanol (V) (1.5 g) was added to the above mixture and stirred for one hour. It was then cooled in an ice-salt bath and diluted with ether. The yellow precipitate was filtered and washed with ether to give the perchlorate (I) (118 mg), m.p. 196° (lit.[8], m.p. 200°).

3-Methylnaphtho[2,1-b]pyrylium perchlorate (III)

(III) was prepared as above from the chromanol (VI) (107 mg) trityl chloride (139 mg), AcOH (1 ml) and 70% $HClO_4$ (0.3 ml).

(III) (75 mg) was obtained as a yellow powder m.p. 181-83°.

$NaBH_4$ reduction of (I)

(I) (118 mg) was dissolved in methylene chloride (10 ml). It was stirred with $NaBH_4$ (100 mg) at room temp. till the initial green colour of the solution disappeared (2 hours). The CH_2Cl_2 solution was washed with water till free of alkali, dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained is immediately distilled to give a colourless liquid (57 mg; yield 75%), b.p. 100-110°/0.01 mm (Found: C, 86.2; H, 5.7. $C_{13}H_{10}O$ requires: C, 85.7; H, 5.5%).

UV:- 350(S), 333, 311, 298, 281, 240.

$NaBH_4$ reduction of (II)

The perchlorate (II) (0.368 g) was dissolved in CH_2Cl_2 (25 ml) and a saturated solution of $NaBH_4$ in ethanol was added dropwise till the original yellow colour became colourless. The reaction was worked up as above to give a pale yellow liquid (184 mg; yield 75%), b.p. 120-140°/0.4 mm (Found: C, 85.7; H, 6.4. $C_{14}H_{12}O$ requires: C, 85.7; H, 6.2%).

UV:- 243, 299, 312, 345.

$NaBH_4$ reduction of (III)

Perchlorate (III)(110 mg) was reduced as above to give a colourless liquid (62 mg; yield 76%), b.p. 100-110°/0.01 mm (Found: C, 86.1; H, 6.7. $C_{14}H_{12}O$ requires: C, 85.7; H, 6.2%).

UV:- 330, 313, 280(S), 240.

$NaBH_4$ reduction of (IV)

Perchlorate (IV) (0.308 g) was reduced as above to give a colourless liquid (0.195 mg; yield, 92.8%), b.p. 105°/0.05 mm (Found: C, 85.8; H, 6.8. $C_{15}H_{14}O$ requires: C, 85.7; H, 6.7%).

CONCLUSION

The $NaBH_4$ reductions carried out on naphtho(2,1-b)pyrylium perchlorate and substituted naphtho(2,1-b) pyrylium perchlorates indicate that in the unsubstituted salt the charge in the pyrylium nucleus is almost equally distributed at the C_1 and C_3 positions. The presence of a methyl substituent in the C_1 or C_3 position directs the attack preferentially to the unsubstituted position, but a methyl substituent at the C_1 position offers greater steric hindrance to an incoming nuclephile than a methyl substituent in the C_3 position with the result that a C_1 substituted position in the above salts is less vulnerable to nucleophilic attack than a similarly substituted C_3-position.

ILLUSTRATIONS

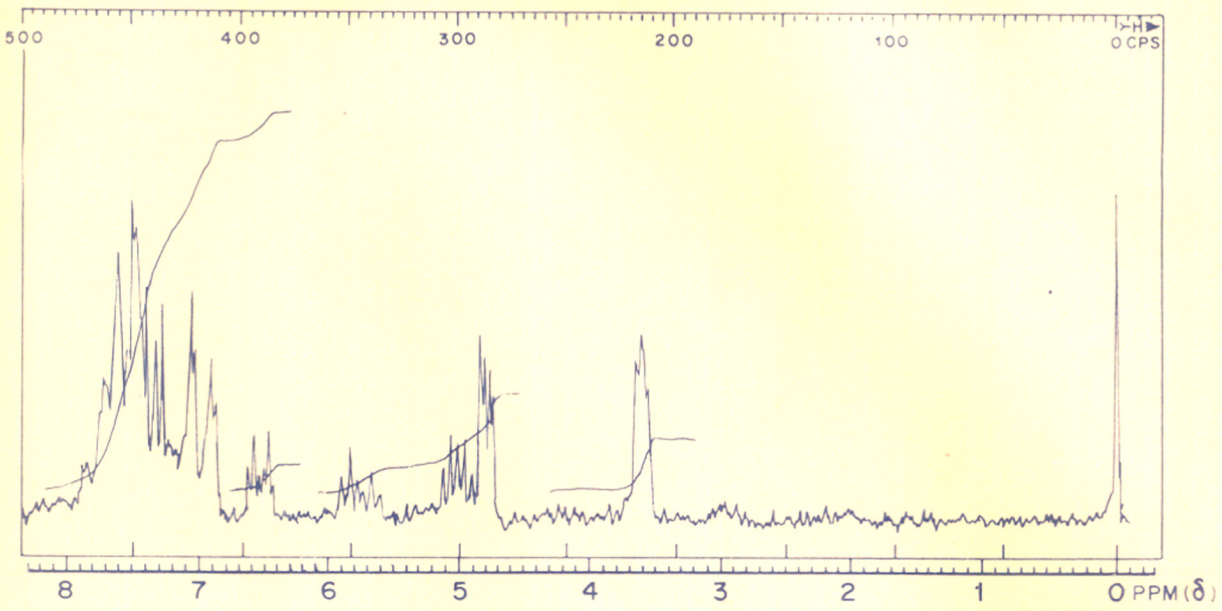

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 7.

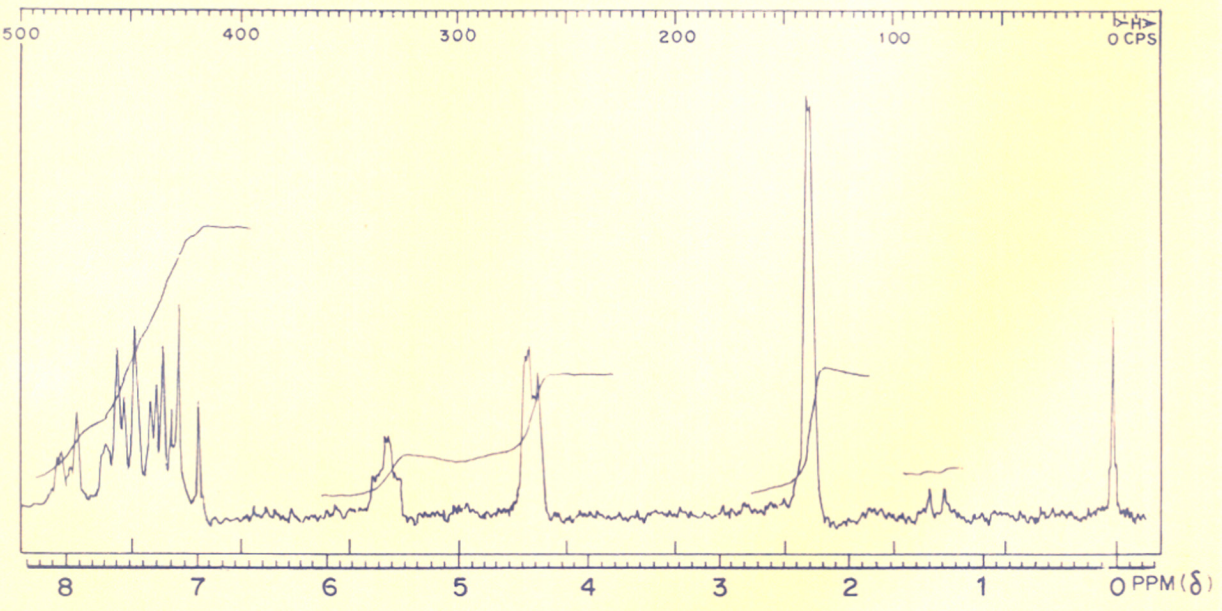

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 8.

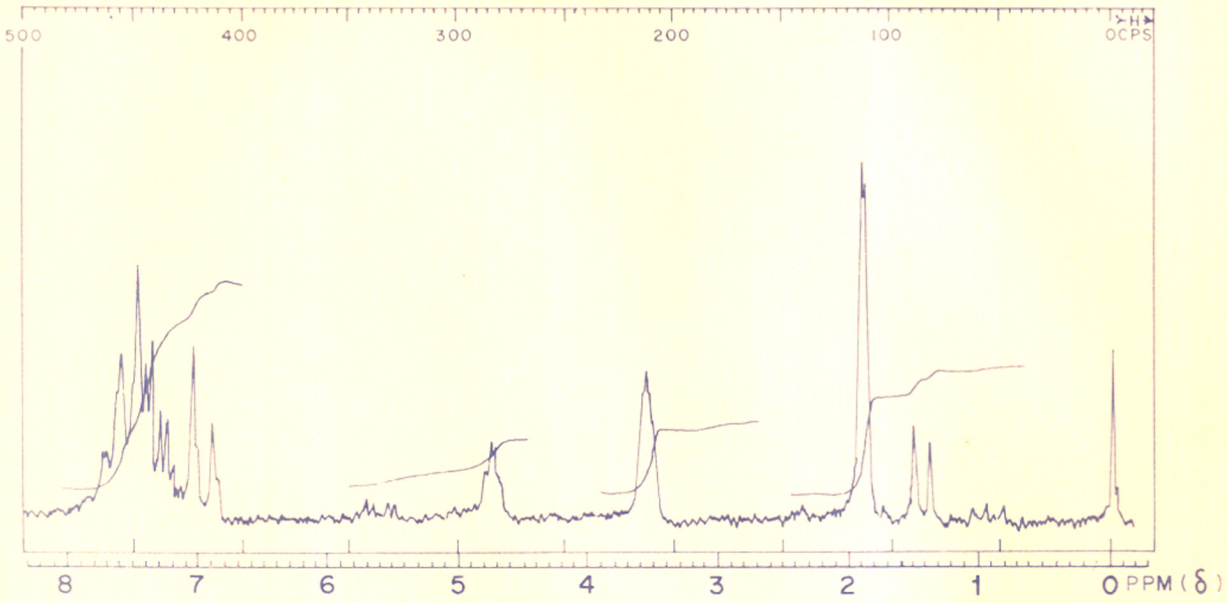

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 9.

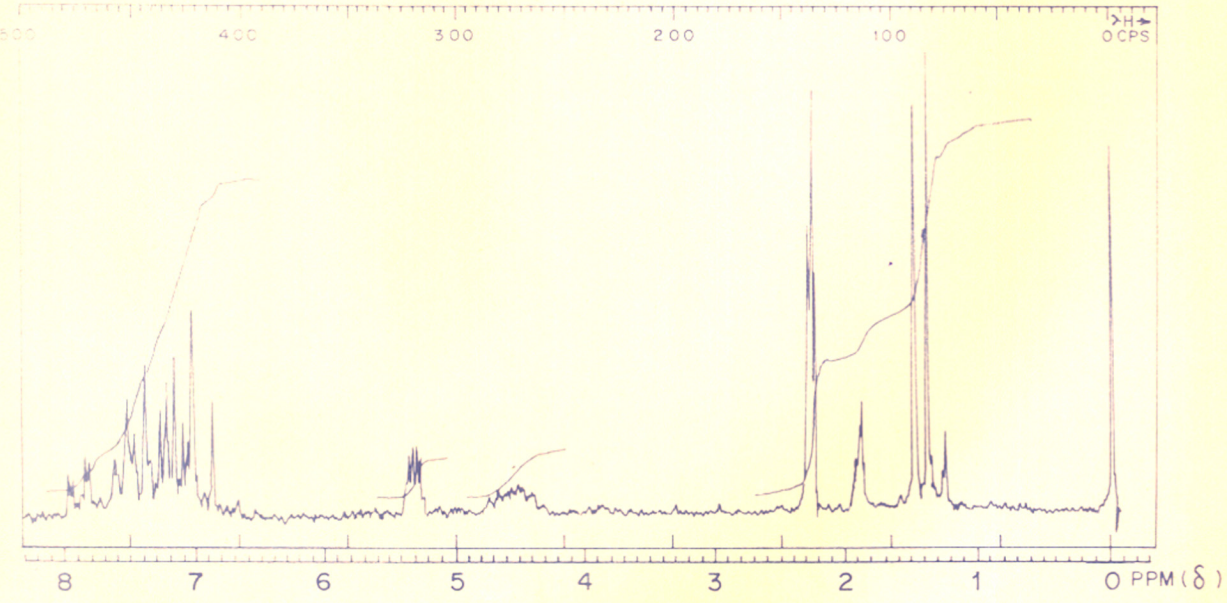

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 10.

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PART - II

STEREOCHEMISTRY OF HYDRIDE TRANSFER IN OXYGEN AND SULPHUR HETEROCYCLICS

INTRODUCTION

Very scant work appears in literature regarding the stereochemical aspects of intermolecular hydride transfer in acid media.

Kramer[1] has studied the energetics of the hydride transfer reaction with particular reference to t-butyl carbonium ion with hydride transfer agents in concentrated sulphuric acid and found that the reaction which appears to predominate at the interface is first order in ion and donor concentration, and is subject to large steric requirements. He observed a large difference in the activation energy of hydride transfer from methylcyclohexane as compared with methylcyclopentane (11 K.cal/mole) to the t-butylcarbonium ion in conc. sulphuric acid.

This difference in the activation energy is understandable if reaction proceeds through a bimolecular transition state with large steric requirements. The 4 K.cal/mole difference in activation energies is attributed to the comparative ease of forming the methylcyclopentyl ion compared to the methylcyclohexyl ion. The remaining difference may be attributed to the high degree of steric crowding in the transition state. Dreiding models prepared by him indicated that the attack of a t-butyl ion on equatorial methylcyclohexane i.e. on the axial hydrogen leads to considerable interaction between a methyl group of the ion and the 3,5 axial hydrogens of

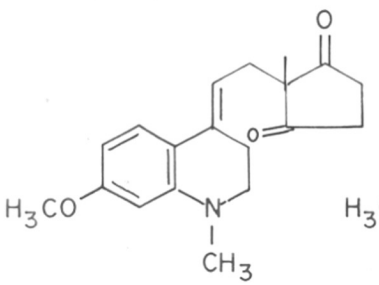
methylcyclohexane. In this configuration the interacting groups are nearly twice as close as in the corresponding attack on methylcyclopentane.

Deno, et al[2] studied the kinetics of hydride transfer from xanthene to a series of triarylmethyl cations and estimated the steric effect of replacing one of the aryl groups on a triarylmethyl cation by first methyl and then hydrogen. They found that for a constant ΔpK_R^+ (difference in pK_R^+ between cation reacting and cation forming) replacing aryl by methyl increases the rate of hydride transfer four fold and replacing aryl by hydrogen increases the rate 3600 fold.

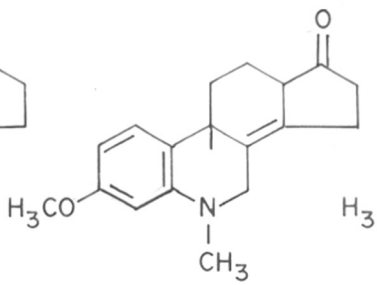
In the transition state of intermolecular hydride transfers, the $C^+ - H^- - C^+$ system must be linear. Molecular model show that much deviation from linearity, particularly in the transfer of hydride between triaryl methyl cations, leads to interpenetration of atomic radii. Also for 1,5-transannular hydride shifts, models indicate that a linear arrangement is most probable, while for 1,2-intramolecular hydride shifts, the C-H-C system must form a triangle.

The cyclisation of the 1,4-diketone (I) to give the steroidal intermediate (II) has been reported[3]. This cyclisation involves a reduction step during

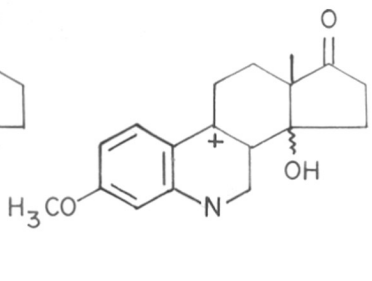
disproportionation of the intermediate (III) formed during cyclisation. (II) is thus obtained by the abstraction of a hydride by (III) from another such molecule.



(I)



(II)

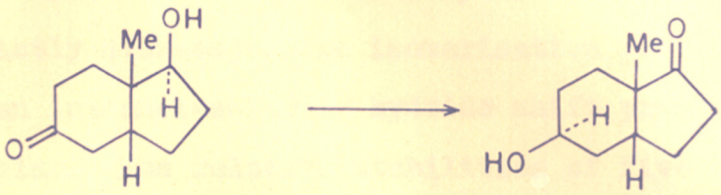


(III)

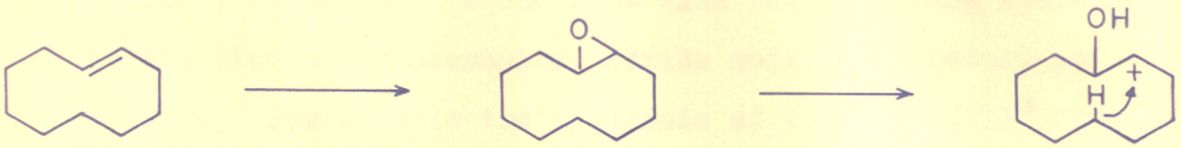
Since the bulk of the hydride donor can make its approach preferentially from one side of the sterioid plane, this mechanism of formation of (II) involves stereochemical implications. The authors have suggested α-configuration for the C_9-H in (II) since in this case the hydride donor can make its approach from that side.

Several interesting observations (chart 15) have been made in connection with intramolecular hydride transfer reactions.

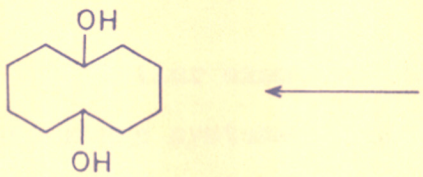
In certain suitably constituted bicyclic systems a 1:5 hydride shift[4] sometimes takes place with surprising ease. Chromatography on alumina causes a complete isomerisation of 1-hydroxy-8-methyl-cis-5-hydrindanone (IV)



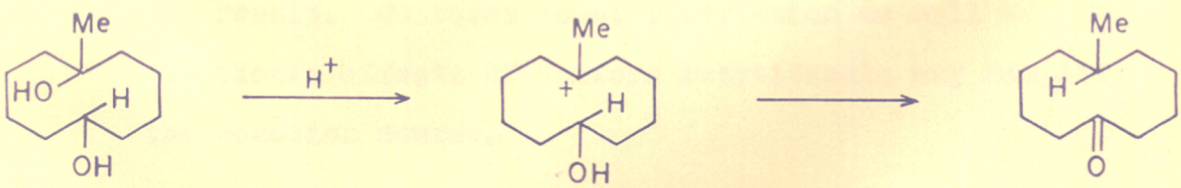
(IV) (V)



(VII)



(VI)



(VIII) (IX)

to 5-hydroxy-8-methyl-cis-1-hydrindanone (V). This strictly stereospecific isomerisation probably proceeds by an intramolecular 1,5 hydride shift promoted by alumina. The relative stabilities of five and six membered cycloalkanones and cycloalkanols provide the driving force for rearrangement[5].

In the transannular reactions of medium sized rings it has been found that with the same ring system, the kind of transannular hydride shift that occurs may vary. For example the synthesis of 1,6-diol (VI)[6] from cyclodecene (VII) by the action of peroxyformic acid, clearly indicates that a 1,5 shift must have occurred, whereas acid catalysed rearrangement of 6-methyl-6-cyclodecanediol (VIII) to 6-methylcyclodecanone[7] (IX) occurs through a 1,6 hydride shift.

Similar examples can be drawn from the chemistry of other rings systems. These differences may arise from electronic control and conformational restrictions by the different substituents. The unsubstituted rings can utilise more conformational possibilities than substituted rings and mixtures of compounds by possible hydride shifts can result. Conformational restriction as well as electronic effects of various substituents may simplify the reaction course.

Also the stereospecificity encountered in some of

the transannular hydride shifts is noteworthy. Cis-1,4-diol is formed from cis-cyclooctane and trans-1,4 diol from trans-cyclooctene[8,9,10]. Similar stereospecificity is found with cis- and trans-cyclodecenes[6]. In these ring systems, the ring geometry is essentially unchanged in passing from epoxide to carbonium ion to rearranged carbonium ion[11]. One lobe of the p orbital of the carbonium ion protrudes into the ring in proximity to intraannular hydrogen where it is protected from attack by the nucleophilic reagent, thus the transannular reaction is stereospecific[12].

The above considerations emphasise the fact that in both inter- and intra-molecular hydride transfer reactions, stereochemical factors play an important role.

PRESENT WORK AND DISCUSSION

It has been seen (cf. Part IA) that in the disproportionation of 3,4-Δ^3-chromene, hydride transfer takes place with equal facility on either side of the planar carbonium ion leading to the formation of 50:50 cis- and trans-3,4-dimethylchroman.

The present work deals with the study of the stereochemistry in tricyclic systems (with both sulphur and oxygen as the heteroatom) where hydride transfer takes place in a more rigid system at a ring junction.

Chart (16) describes the scheme of synthesis followed in the thia-series.

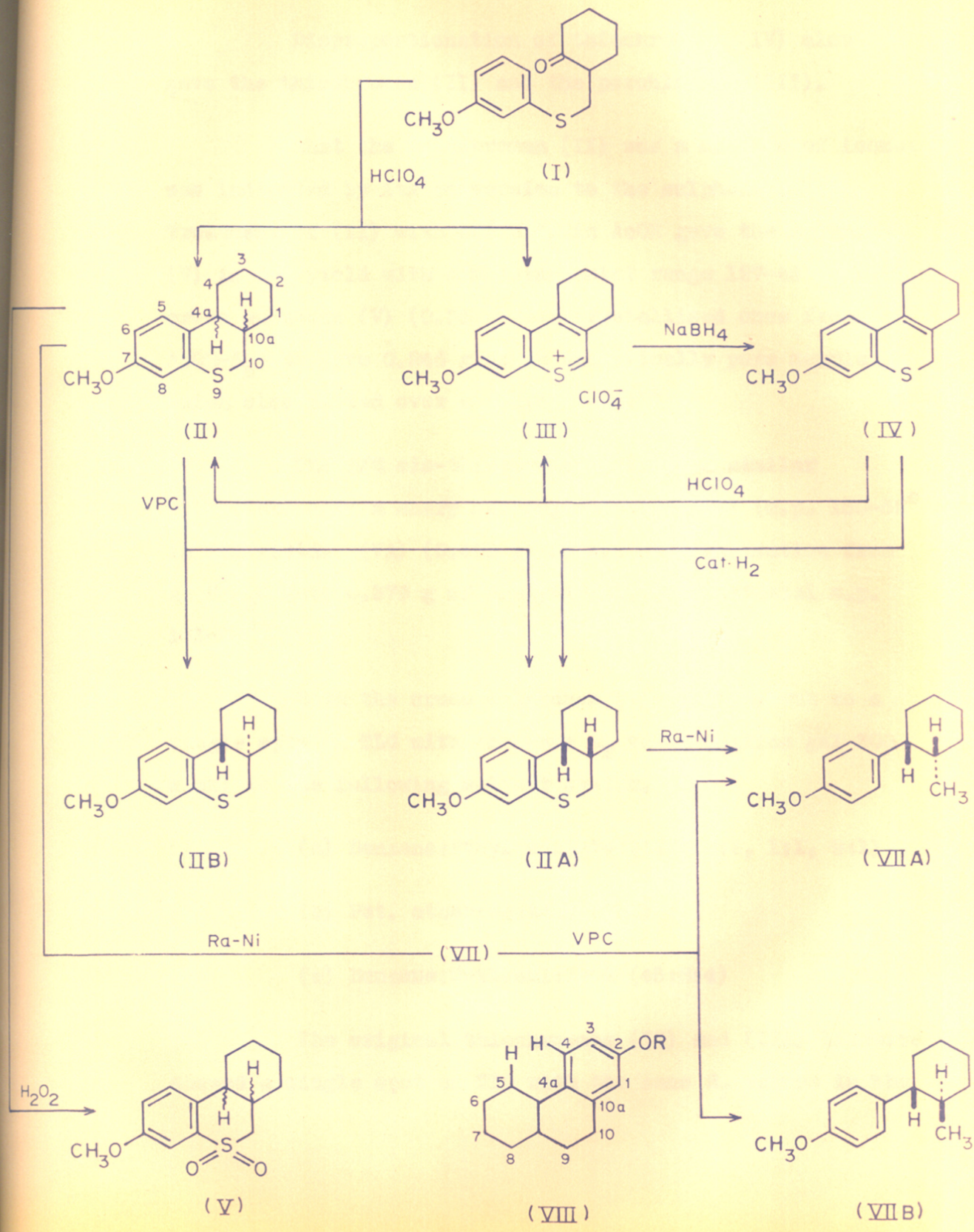
Reaction of m-methoxythiophenol with the mannich base 2-dimethylaminomethylcyclohexanone[13] gave 2-(m-methoxyphenyl-mercaptomethyl)-cyclohexanone (I).

Cyclodehydration of (I) with 60% $HClO_4$ gave by disproportionation[14] 9-thia-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (II) and 9-thia-1,2,3,4-tetrahydrophenanthrylium perchlorate (III).

Reduction of the perchlorate (III) with $NaBH_4$ furnished the 9-thia-1,2,3,4,9,10-hexahydrophenanthrene (IV). Its structure was confirmed by UV and NMR spectrum.

Catalytic hydrogenation of (IV) gave the B/C cis thiachroman (IIA).

Chart 16


HClO4
(I)
(II)
(III)
NaBH4
(IV)
VPC
HClO4
Cat·H2
(IIB)
(IIA)
Ra-Ni
(VIIA)
Ra-Ni
(VII)
VPC
H2O2
(V)
(VIII)
(VIIB)
(VA) Cis; (VB) Trans

Disproportionation of thiachromene (IV) also gave the thiachroman (II) and the perchlorate (III).

That the thiachroman (II) was a mixture of isomers was indicated by its conversion to the sulphone (V). Treatment of (II) with 30% H_2O_2 in AcOH gave the sulphone (V) in 93% yield with a melting point range 127-45°. The crude sulphone (V) (0.38 g) was crystallised once from AcOH-H_2O to give 0.246 g of an analytically pure sample which also melted over a range (127-41°).

The B/C cis-thiachroman (IIA), on similar oxidation, gave a sharp melting sulphone (VA) (m.p. 150-52°) in 92% yield. (VA) (0.485 g) on one crystallisation from AcOH-H_2O gave 0.379 g of analytically pure material m.p. 151-52°.

Both the crude sulphones (V) and (VA) ran as a single spot on TLC with the same R_F value (silica gel 300 mesh) in the following solvent system.

(a) Benzene:Ethyl acetate (1:3, 2:3, 1:1, 9:1)

(b) Pet. ether:acetone (3:1)

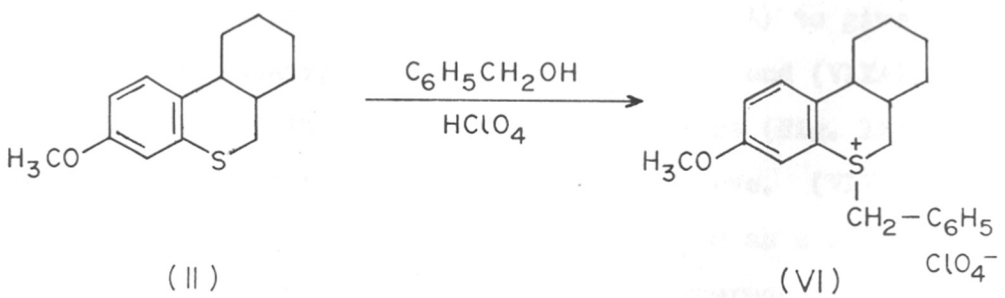
(c) Benzene:Methanol:AcOH (45:8:4)

The original thiachromans (II) and (IIA) likewise showed a single spot on TLC with the same R_F values in the

following solvent systems:- Benzene:Petroleum ether (1:3, 1:1, 3:1). The TLC studies thus precluded the presence of any other impurity apart from the sulphones (VA) and (VB).

NMR spectrum of thiachroman (II) and (IIA) did not reveal any significant difference at first sight. It was not possible to distinguish between the C_{10a} and C_{4a} methine and the C_{10} methylene protons because of the close chemical shifts of these protons.

An attempt was made to get a clearer picture of C_{4a} and C_{10a} protons by preparing a sulphonium salt (VI) from (II), which would cause the C_{10} methylene protons to be shifted downfield. However the NMR spectrum of (VI) did not help towards the desired end.



(II) (VI)

The NMR spectrum of sulphone (V) and (VA) were likewise identical and an attempt to clear the signals for C_{4a} and C_{10a} protons by deuterating the C_{10} methylene

protons was also not successful as there seemed to be indiscriminate deuteration.

The content of cis- and trans-isomers in (II) was finally determined by VPC. (Fig. 11) using a 16 ft. 1/4 in. dia. column of 0.25% Me_2SiCl_2 and 20% Apeizon L on 60-80 mesh of chromosorb. Pure cis thiachroman (IIA) appeared as a single peak with retention time of 67.3 mts. (column temp. 285°; flow rate (helium) 60 ml/min.). Under the same conditions (II) showed 2 peaks:- one (77%) identical with the cis-isomer with a retention time of 67 mins. and another peak (23%) with a retention time of 74 min. for the trans-isomer (IIB). That the peak at 67 min. was identical with the cis-isomer at 67.3 min. was shown by the gas chromatography of a mixture of (II) and (IIA).

The above VPC results were further confirmed by Raney nickel desulphurisation of (II) and (IIA) to give 1-methyl-2-p-methoxyphenylcyclohexanes (VII) and (VIIA). The VPC study of the desulphurization product (Fig. 12) was carried out under the same conditions as above. (VIIA) prepared from pure cis-thiachroman, appeared as a single peak with a retention time of 16.2 min., whereas (VII) prepared from thiachroman (II) was shown to be a mixture of 72% cis-isomer (VIIA) with retention time 16.2 min. and 28% of the trans-isomer (VIIB) with retention time 13 mins. The identity of the desulphurized products was confirmed by

NMR spectrum of the mixture which showed the following characteristics (Fig. 13 and 14):- a CH_3 doublet at 0.67 (J = 7 cps); a 9-proton band for the methylene protons at 1.62; benzylic proton centered at 2.76; $-OCH_3$ at 3.73; 4 aromatic protons centered at 6.87. These protons exhibited clearly the typical AB type quartet (J = 9) for a p-disubstituted phenyl group. In the NMR of (VII), besides the above characteristics the methyl doublet was accompanied by a slight hump which may be due to the trans isomer and which was absent in (VIIA).

That (II) was a mixture of cis-trans isomers was also revealed by a careful comparison of the NMR spectra of (II) and the pure cis-isomer (IIA) taken at both 60 MC and 100 MC. The spectra of the two compounds were almost identical except in the aromatic region. In the spectrum of the pure cis-compound (IIA) (Fig. 15) the C_5 aromatic proton meta to $-OCH_3$ group appeared as a doublet as 6.93 (J = 9.5). No other peaks were discernible near this doublet. In the spectrum of (II) (Fig. 16), however, apart from the above mentioned doublet, another doublet of weaker intensity (ratio ca. 80:20 by integration) was visible slightly downfield at 7.15 (J = 9.5) and was due to the aromatic C_5 proton for the trans isomer (IIB) present in (II). This doublet was even more clearly visible in the 100 MC spectrum reproduced in Fig. 17. The assignment of

this lower field doublet to C_5 proton of trans-isomer (IIB) was based on the recent work by Nagata et al[15] who reported that in the parent octahydrophenanthrene (VIII) the chemical shift of the aromatic C_4 proton is dependent on the B/C cis-trans configuration. This proton is strongly deshielded owing to the steric effect of an equatorial C-5 proton, the degree of deshielding depending upon the distance between the C_4 and C_5 protons expressed as a van der Waals compression factor. This factor varies with both B/C ring junction and conformations, but, in general, the trans isomer exhibits the highest compression and therefore the largest deshielding of the C_4-proton. This proton appears up to 0.2 ppm downfield compared to the same proton in the cis isomer.

The above results show that the disproportionation of thiachromene (IV) proceeds stereoselectively leading predominantly to the cis isomer (77%).

The bicyclic 3,4-dimethylthiachroman[15a] (IX) prepared by similar disproportionation was subjected to VPC studies and was found to consist of 85% of the cis isomer and 15% of the trans isomer. Using a 6 ft. 1/4 in. diameter column of 20% polyester on firebrick (column temp. 200°, H_2 flow rate 60 ml/min.), pure cis 3,4-dimethyl-thiachroman[15a] (Fig. 18) showed a single peak with retention time 4.4 mins. Under the same conditions 3,4-dimethyl-

thiachroman, obtained by disproportionation, showed two peaks, one (85%) identical with the cis isomer and another (15%) with a retention time of 3.3 mins. for the trans isomer.

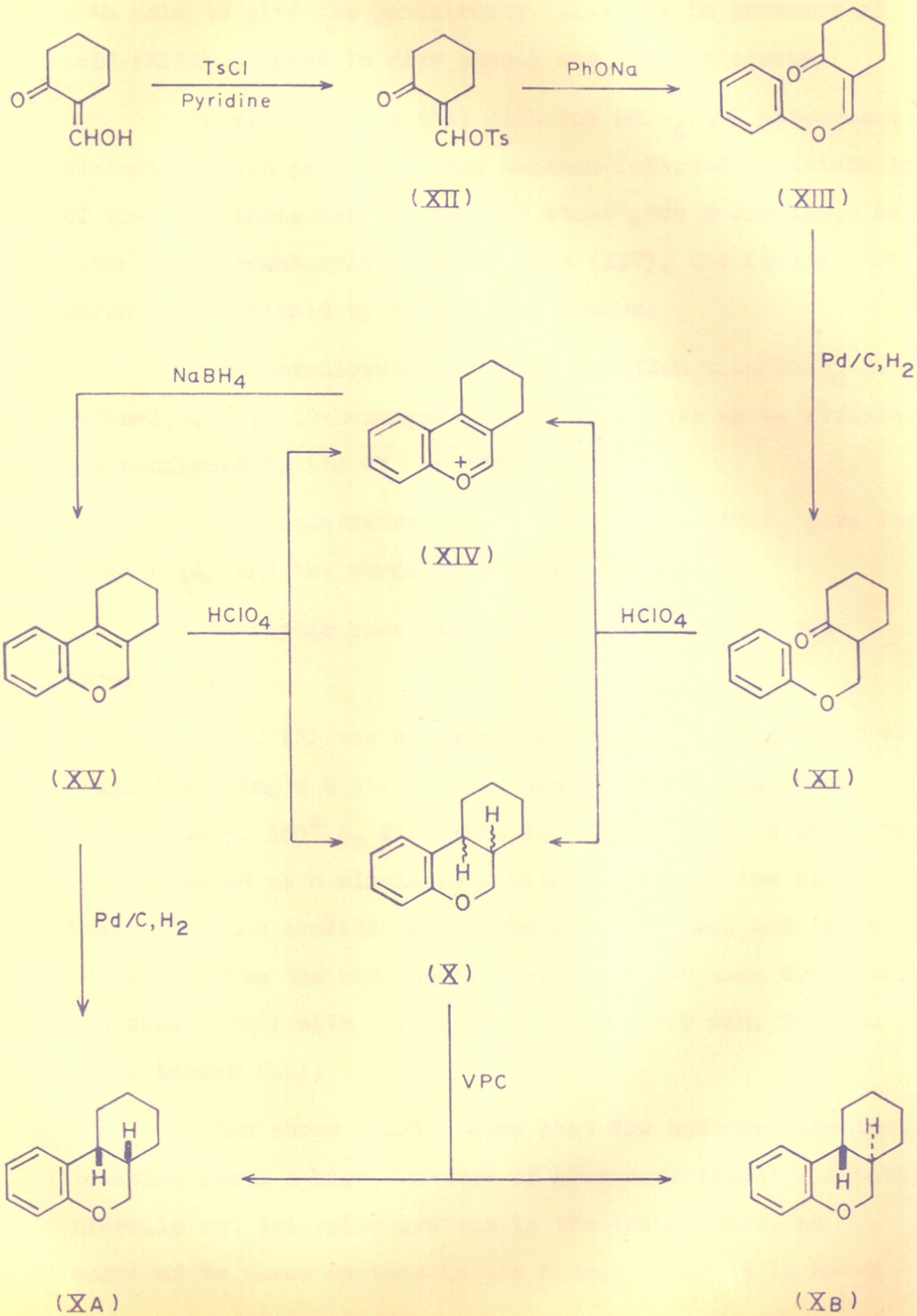
In the oxa series the tricyclic chroman 9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (X) and its pure cis isomer (XA) were synthesised according to the scheme outlined in Chart (17).

Since it is not possible to condense phenols with mannich base to get the phenoxy ketones, as in the case of thiols, a method had to be developed for the preparation of 2-(phenoxymethyl)-cyclohexanone (XI). This was achieved by reacting the sodium salt of phenol with 2-tosyloxymethylene-cyclohexanone (XII). The tosyl group being a good leaving group could be easily displaced by the nucleophilic attack of the phenolate anion to give almost quantitative yield of 2-(phenoxymethylene)-cyclohexanone (XIII) which on catalytic reduction afforded the desired product (XI).

The tosylate (XII) was obtained by the tosylation of 2-hydroxymethylenecyclohexanone[16] in methylene chloride, in the presence of pyridine. (XII) was stable in solution in the cold, but decomposed rapidly when isolated. Its identity was confirmed by IR.

An attempt was made to cyclise (XIII) directly

Chart 17


TsCl
Pyridine
PhONa
CHOH
CHOTs
(XII)
(XIII)
Pd/C, H2
NaBH4
(XIV)
HClO4
HClO4
(XV)
(XI)
(X)
Pd/C, H2
VPC
(XA)
(XB)

with acid to give the perchlorate (XIV) but in presence of acid (XIII) cleaved to give phenol and tarry products.

Cyclisation of (XI) with 70% $HClO_4$ and subsequent extraction with pet. ether and benzene followed by saturation of the perchloric acid layer with ether gave 9-oxa-1,2,3,4-tetrahydrophenanthrylium perchlorate (XIV), the identity of which was confirmed by UV and NMR spectra.

The perchlorate (XIV) on reduction with $NaBH_4$ gave 9-oxa-1,2,3,4,9,10-hexahydrophenanthrene (XV) whose structure was confirmed by its UV and NMR spectra.

Disproportionation of (XV) with 70% $HClO_4$ gave the chroman (X) and the perchlorate (XIV).

Catalytic reduction of (XV) gave the B/C cis chroman (XA).

That (X) was a mixture of isomers was shown by VPC (Fig. 19) using a 2 ft. 1/4 in. diameter tung oil column (column temp. 185° H_2 flow rate 100 ml/min.), pure cis chroman (XA) appeared as a single peak with retention time of 6.4 mins. Under the same conditions (X) showed two peaks, one (65%) identical with the cis isomer with retention time 6.4 mins. and the other (35%) with a retention time of 7.5 min. for the trans isomer (XB).

The above results show that the hydride transfer reaction shows a higher degree of stereospecificity in both bicyclic and tricyclic systems in the thia-series, as compared to these systems in the oxa-series. It is known

that in the parent octahydrophenanthrene series of compounds, the ring B/C cis and trans-configurations are thermodynamically about equally stable. This is due to a flattening effect of the aromatic ring A over the rest of the molecule, which reduces the difference in the energy levels of the cis- and trans-isomers. Assuming then that the 9-thiaoctahydrophenanthrene and 9-oxa-octahydrophenanthrene derivatives described here are subject to similar considerations, the cis- and trans-isomers would be expected to have similar thermodynamic stabilities, and if the course of hydride transfer was governed only by the thermodynamic stability of the end-product, one could expect approximately equal quantities of cis- and trans-isomers showing lack of stereoselectivity. Since in the thia-series both the bicyclic and tricyclic compounds gave predominantly the cis-isomer thermodynamic control in such hydride transfers alone cannot explain the results. Rather, steric factors play a major role and the stereochemistry of the ion and the transition state appear to control the hydride transfer. This could perhaps also explain the slight preponderance of the cis-isomer in the tricyclic oxa series as compared to the bicyclic system (cf. Part IA).

The question then arises as to the nature of steric control operating in the above thia series.

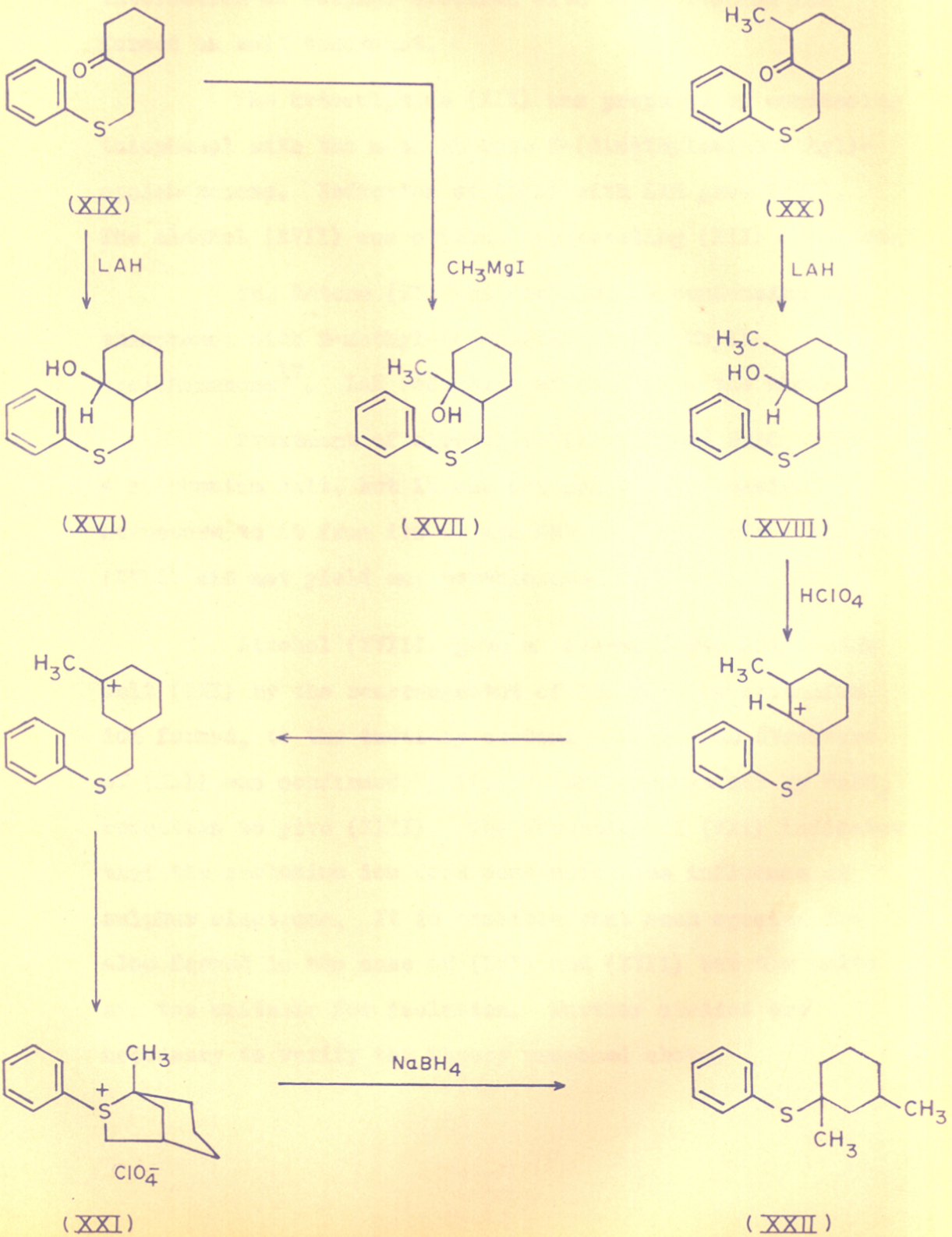
In view of the fact that in the oxa-series the bicyclic

3,4-dimethylchroman (cf. Part IA) is formed as only a 50:50 mixture of cis-trans isomers with lack of stereospecificity, whereas the 3,4-dimethylthiachroman similarly obtained consists of 85% of the cis isomer and the greater degree of stereospecificity (77%) achieved in the formation of 9-thia-1,2,3,4,9,10,4a,10a-octahydrophenanthrene as compared to its oxygen analogue (65%), it appears that the substituents in the 3- and 4-positions are not the only stereochemically controlling factors for hydride transfer. Rather some other mechanism seems to be operating in the thia-series. One possibility that appears attractive is the participation by the sulphur atom in the carbonium ion formed by protonation of thiachromenes. Such participation would essentially block one face, resulting in stereoselectivity during hydride attack.

This reasoning is well in line with the explanation offered by Prelog[12] to explain the stereospecific hydroxylation of cyclooctenes and cyclodecenes (cf. introduction).

An attempt has been made to substantiate this theory of sulphur participation (chart 18). The alcohols (XVI), (XVII) and (XVIII) were treated with 60% $HClO_4$ to see if it were possible to isolate a 4-membered sulphonium salt. The formation of such a salt would result by the

Chart 18



interaction of sulphur electron with the carbonium ion formed on acid treatment.

The ketosulphide (XIX) was prepared by condensing thiophenol with the mannich base 2-(dimethylaminomethyl)-cyclohexanone. Reduction of (XIX) with LAH gave (XVI). The alcohol (XVII) was obtained by reacting (XIX) with MeMgI.

The ketone (XX) was prepared by condensing thiophenol with 2-methyl-(6-dimethylaminomethyl)-cyclohexanone[17]. LAH reduction of (XX) gave the alcohol (XVIII).

Treatment of alcohol (XVI) with 60% $HClO_4$ gave a sulphonium salt, but it was not possible to assign any structure to it from its UV and NMR analysis data. Alcohol (XVII) did not yield any perchlorate.

Alcohol (XVIII) gave a five-membered sulphonium salt (XXI) by the rearrangement of the primary carbonium ion formed, to the tertiary carbonium ion. The structure of (XXI) was confirmed by its UV, NMR spectra and by $NaBH_4$ reduction to give (XXII). The formation of (XXI) indicates that the carbonium ion does come under the influence of sulphur electrons. It is possible that such species are also formed in the case of (XVI) and (XVII) but the salts are too unstable for isolation. Further studies are necessary to verify the theory proposed above.

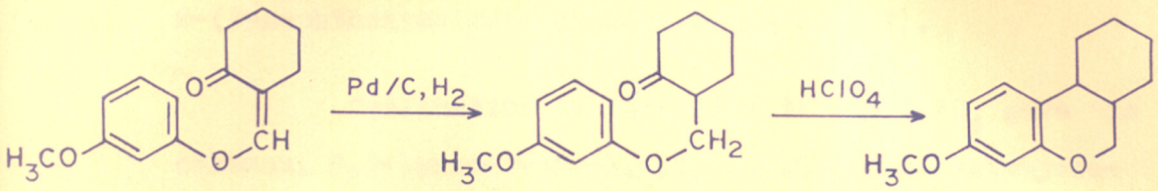
The condensation of tosylate (XII) with phenol described above was extended to m-methoxyphenol and β-naphthol (chart 19) to examine the general applicability of the method for the preparation of 2(aryloxymethylene)-cyclohexanones of the type (XIII).

Condensation of the sodium salt of m-methoxyphenol with the tosylate (XII) gave 2(m-methoxyphenoxymethylene)-cyclohexanone (XXIII). Catalytic reduction of (XXIII) gave 2-(m-methoxyphenoxymethyl)-cyclohexanone (XXIV). Cyclodehydration of the latter with 70% perchloric acid gave 7-methoxy-9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (XXV) and the methoxy derivative of (XIV) which however could not be isolated.

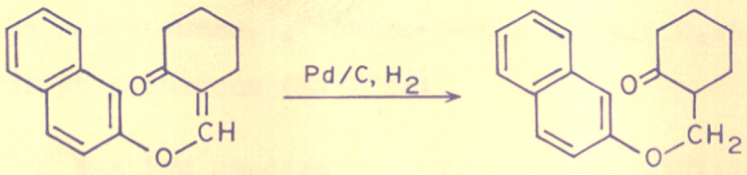
VPC of (XXV) using a 6 ft. 1/4 in. diameter polyester column (column temp. 206° H_2 flow rate 100 ml/min.) showed 2 peaks, one (65%) with retention time 14.3 mins. and another (35%) with retention time 16.7 mins. showing (by analogy) that (XXV) also consists of 65% cis- and 35% trans-isomers.

Similar series of reactions were carried out starting from β-naphthol.

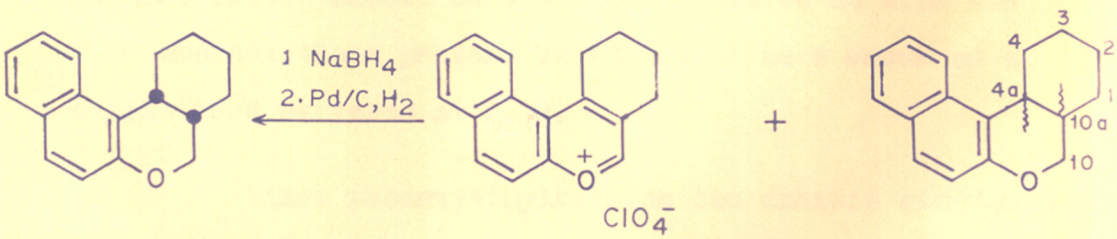
Condensation of sodium salt of β-naphthol with (XII) gave 2-(β-naphthoxymethylene)-cyclohexanone (XXVI) in quantitative yields which on catalytic reduction gave



(XXIII) (XXIV) (XXV)



(XXVI) (XXVII)



(XXVIII A) (XXIX) (XXVIII)

2-(β-naphthoxymethyl)-cyclohexanone (XXVII).

Cyclisation of (XXVII) with 70% $HClO_4$ gave the chroman, 5,6-benzo-9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (XXVIII) and 5,6-benzo-9-oxa-1,2,3,4-tetrahydrophenanthrylium perchlorate (XXIX). The structure of the latter was confirmed by its NMR spectrum.

The perchlorate (XXIX) was reduced with $NaBH_4$ and the product (liquid) obtained, was hydrogenated to give the cis-chroman,5,6-benzo-9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (XXVIIIA).

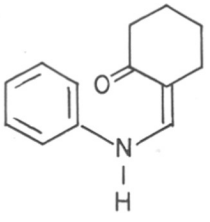
The VPC studies on (XXVIII) and (XXVIIIA) are in progress.

The NMR spectra of the two products (XXVIII) and (XXVIIIA) were the same except for the fact that in (XXVIII) one of the C_4 methylene protons and the C_{10a} methine proton showed as two bands centered at 2.15 and 2.35 whereas these protons in (XXVIIIA) were shown as a single band centered at 2.35.

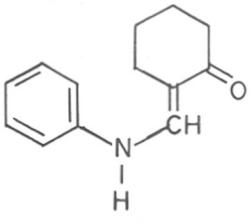
Since phenoxyvinylketones can exhibit cis-trans isomerism, it was of interest to study the stereochemistry of the phenoxyketones obtained in the course of the above

work. Their stereochemistry was indirectly determined by studying the anilino-ketones prepared by the condensation of amines with tosylate (XII).

Aniline was condensed with tosylate (XII) to give 2-anilinomethylenecyclohexanone (XXX).



(XXX)



(XXXI)

Aniline was also condensed with hydroxymethylene-cyclohexanone to give 2-(anilinomethylene)-cyclohexanone (XXXI)*

The IR of (XXX) and (XXXI) were superimposable, but there were significant differences in the NMR of (XXX) and (XXXI) whereby it was possible to assign the cis structure to (XXX) and the trans structure to (XXXI).

NMR of (XXX) in CCl_4 (Fig. 20):-

(a) a 4 proton band for C_4 and C_5 methylene protons centered at 1.74

(b) a 4 proton band for C_3 and C_6 methylene protons centered at 2.41

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*Prepared by T. Ravindranathan of this laboratory.

(c) a 6 proton multiplet centered at 7.13 for the 5 aromatic protons and the vinyl proton

(d) a one proton band for the N-H proton at 12.24 (exchangeable with D_2O)

The significant differences noticed in the NMR of (XXX) and (XXXI) were as follows:-

(i) the position of the vinyl proton and

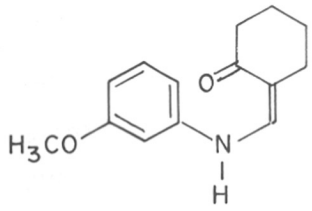
(ii) the position of the N-H proton.

Whereas in the NMR spectrum of (XXX) the vinyl proton is merged with the aromatic region as seen from integration, in the spectrum of (XXXI) this proton appears as low as 8.12 ($J_{CH - NH} = 14$) due to deshielding effect of the carbonyl group, thus indicating that the carbonyl group in (XXXI) is on the same side as the vinyl hydrogen and trans to the amine function.

Similarly the NH proton in the NMR of (XXX) is shown way down at 12.24 as a result of the deshielding effect of the carbonyl group due to hydrogen bonding thus showing that the carbonyl group in (XXX) is on the same side as the amine function. In the NMR of (XXXI), no signal is seen below 8.12. The signal for the N-H proton is merged with other signals at higher field.

m-Anisidine was condensed with the tosylate (XII)

to give cis 2-(m-anisidinomethylene)-cyclohexanone (XXXII) which was identified by its IR and NMR spectra.



(XXXII)

NMR ($CDCl_3$) (Fig. 21)

(a) a 4 proton band for C_4 and C_5 methylene protons centered at 1.74

(b) a 4 proton band for C_3 and C_6 methylene protons centered at 2.32

(c) a 3 proton peak for the methoxyl group at 3.73

(d) a 5 proton multiplet for the 4 aromatic protons and the vinyl proton centered at 6.78

(e) a one proton band for the N-H proton centered at 12.24 (exchangeable with D_2O)

From the chemical shifts of the N-H and vinyl proton which are the same as in the case of (XXX), Compound

(XXXII) was also assigned the cis structure.

It is seen that the condensation of tosylate (XII) with amines leads to the formation of cis-aminovinyl ketones. Since the condensation would take place by an addition elimination mechanism, the tosylate (XII) must have trans configuration. The condensation of this tosylate (XII) with phenols or amines thus constitutes a stereospecific method for preparing the corresponding cis 2-aryloxymethylenecyclohexanones and cis 2-arylaminomethylenecyclohexanones.

EXPERIMENTAL

Melting points and boiling points are uncorrected. The b.ps. refer to both temperatures unless mentioned (liquids being distilled in bulb tubes).

UV spectra were recorded (Beckmann and Perkin Elmer 350 spectrophotometer) in 95% ethanol unless otherwise stated. λ max values are given in mμ and log ϵ in parenthesis.

IR spectra were recorded (Perkin Elmer Infracord 137) as thin films, unless otherwise indicated. Values are given in cm^{-1}.

NMR spectra were taken in carbon tetrachloride unless otherwise mentioned using a Varian A 60 spectrometer. Values are given in ppm and J values in cps.

(1) 2-Diethylaminomethylcyclohexanone

It was prepared as reported[13].

(2) 2-(m-Methoxyphenylmercaptomethyl)-cyclohexanone (I)

A mixture of m-methoxythiophenol (3.6 g) and 2-(dimethylaminomethyl)-cyclohexanone (3.875 g) was heated at 130-135° for half an hour under a stream of nitrogen. The reaction mixture was diluted with ether, washed with dil. NaOH and dil. HCl. The ether layer dried over Na_2SO_4 and ether removed when keto sulphide (I) (5.319 g, yield, 83%) b.p. 137-38°/0.009 mm) was obtained (Found: C, 67.2; H, 7.3;

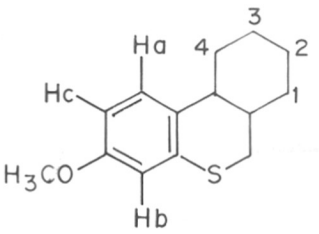
S, 12.8. $C_{14}H_{18}O_2S$ requires: C, 67.3; H, 7.5; S, 13.1%).

(3) Cyclodehydration of (I)

(I) (1.5 g) was stirred with 60% $HClO_4$ for 2 hours at 50-60°. The reaction mixture was extracted with pet. ether (b.p. 60-80°). Pet. ether extract was washed with sodium bicarbonate solution and water, dried (Na_2SO_4) and solvent removed when a thick liquid (0.69 g) was obtained. The latter was chromatographed over alumina (Bockman grade I) using pet. ether (60-80°) as eluent. The major fraction gave a liquid which on distillation gave thiachroman (II) (0.412 g, yield, 29%), b.p. 120-25°/0.001 mm (Found: C, 71.9; H, 7.6; S, 13.2. $C_{14}H_{18}OS$ requires: C, 71.7; H, 7.74; S, 13.6%).

UV spectrum:- 221 (4.45), 257 (3.96), 291 (3.47), 299 (3.40).

NMR



(II)

(a) a complex band for 8 methylene protons (C_1-C_4) centered at 1.62

(b) signals for the C_{10} methylene protons, C_{10a} and C_{4a} methine protons from 2.03 to 3.42

(c) a 3 proton methoxy peak at 3.73

(d) a quartet for Hc proton at 6.53 (J_{Hc-Ha} = 9.5; J_{Hc-Hb} = 3)

(e) a doublet for H_b proton at 6.55 (J_{Hb-Hc} = 3)

(f) a doublet for H_a proton at 6.93 (J_{Ha-Hc} = 9.5)

(g) a low intensity doublet at 7.15 (J_{Ha-Hc} = 9.5)

The $HClO_4$ layer from the above reaction, after removal of thiachroman (I) was cooled in an ice bath and saturated with ether when it gave the perchlorate (III) as yellow needles, m.p. 172-3° (0.78 g; yield 39%) (Found: S, 9.9; Cl, 10.6. $C_{14}H_{15}ClO_5S$ requires: S, 9.6; Cl, 10.7%).

UV spectrum (AcOH + $HClO_4$):- 273 (4.60), 340 (3.66), 420 (3.86).

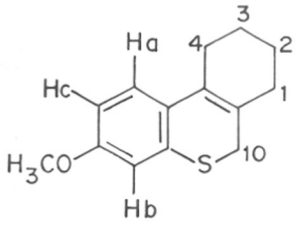
(4) <u>9-Thia-1,2,3,4,9,10-hexahydrophenanthrene (IV)</u>

The perchlorate (III) (3.324 g) was dissolved in methylene chloride (25 ml). A saturated solution of $NaBH_4$ in ethanol was added dropwise till the solution became

colourless. A few drops of acetic acid were added to decompose excess $NaBH_4$. The reaction mixture was diluted with water and washed with $NaHCO_3$ solution. The methylene chloride (dried over Na_2SO_4) was evaporated under reduced pressure and the residual liquid distilled immediately to give the thiachromene (IV) (2.08 g; yield, 89%), b.p. 140-160°/0.01-0.009 mm (Found: C, 72.1; H, 6.8; S, 14.0. $C_{14}H_{16}OS$ requires: C, 72.39; H, 6.94; S, 13.7%).

UV spectrum:- 256 (4.14), 330 (3.05).

NMR (Fig. 22)



(IV)

(a) a 4-proton band for the C_2 and C_3 methylene protons centred at 1.70

(b) a 4-proton band for the C_1 and C_4 methylene protons centred at 2.25

(c) a single 2-proton peak for the C_{10} methylene proton at 3.07

(d) a 3 proton methoxyl peak at 3.70

(e) a one proton doublet of doublets for Hc centred at 6.50 (J_{Hc-Ha} = 8.5; J_{Hc-Hb} = 2.5)

(f) a one proton doublet for the H_b proton at 6.72 (J_{Hb-Hc} = 2.5)

(g) a one proton doublet for Ha proton at 7.06 (J_{Ha-Hc} = 8.5)

(h) a very low intensity signal at 5.62 which may be due to the other isomer (7-methoxy-9-thia-1,2,3,4, 9,4a-hexahydrophenanthrene)

(5) Disproportionation of (IV)

Thiochromene (IV) (3.38 g) was stirred with 60% $HClO_4$ (20 ml) for 2 hours at 60°. Reaction mixture was worked up as in Experiment 3, to give the thiachroman (II) (yield, 38%) and perchlorate (III) (yield, 34%).

(6) Cis-9-thia-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (IIA)

The perchlorate (III) (2.67 g) was reduced with $NaBH_4$ as in Experiment 4, the residual liquid after removal of methylene chloride was dissolved in ethyl acetate and hydrogenated with 10% palladised carbon (0.8 g) at 45 lb/sq.in. for 23 hours. After removal of solvent the residue (oil) was distilled when it gave thiachroman (IIA)

(1.7 g; yield, 90%), b.p. 130-35°/0.001 mm (Found: C, 71.5; H, 7.9; S, 13.5. $C_{14}H_{18}OS$ requires: C, 71.7; H, 7.74; S, 13.6%).

UV spectrum:- 220 (4.45), 259 (3.93), 295 (3.47), 303 (3.41).

NMR: Identical as for (II) except for the low intensity doublet at 7.15.

(7) 9-Thia-1,2,3,4,9,10,4a,10a-octahydrophenanthrene-9,9-dioxide (V)

A mixture of thiachroman (II) (0.380 g), acetic acid (3 ml) and 30% hydrogen peroxide (4 ml) was stirred for half an hour at room temperature and the mixture left overnight. 30% hydrogen peroxide (0.5 ml) was added and the reaction left at room temperature for a further period of 24 hours, after which it was cooled. The white precipitate obtained was filtered and washed with dil. AcOH to give the crude sulphone (V) (0.40 g; yield, 93%), m.p. 127-45°). On crystallisation from dil. acetic acid the sulphone gave colourless needles, m.p. 127-41° (Found: C, 63.1; H, 6.9; S, 12.3. $C_{14}H_{18}O_3$ requires: C, 63.1; H, 6.8; S, 12.1%).

NMR

(a) a complex band for 8 methylene protons

(C_1-C_4) centered at 1.63

(b) signals for 4 protons for the C_{10} methylene, C_{4a} and C_{10a} methine protons between 2.1 and 3.6

(c) a 3 proton peak for the methoxyl group at 3.83

(d) a multiplet for 3 aromatic protons centered at 7.05

(8) Cis-9-thia-1,2,3,4,9,10,4a,10a-octahydrophenanthrene-9,9-dioxide (VA)

Oxidation of the thiachroman (IIa) (0.475 g) as in the above experiment gave the sulphone (VA) (0.485 g; yield, 91%) m.p. 150-52°. The latter on crystallisation from dil. acetic acid gave thick white needles, m.p. 151-52° of the sulphone (VA) (Found: C, 63.2; H, 6.8; S, 11.9. $C_{14}H_{18}O_3S$ requires: C, 63.1; H, 6.8; S, 12.0%).

NMR was identical with (V).

(9) 7-Methoxy-1,2,3,4,9,10,4a,10a-octahydro-9-thiaphenanthrylbenzylsulphonium perchlorate (VI)

A mixture of the thiachroman (II) (0.226 g), 60 ml $HClO_4$ (0.5 ml) and benzyl alcohol (0.5 ml) was stirred at room temperature overnight. Ether was added to the reaction mixture and the pale yellow amorphous solid filtered and washed with ether when it gave (VI) (0.267 g; yield, 65%),

m.p. 143-45° (Found: S, 8.3; Cl, 7.4. $C_{21}H_{25}ClO_5S$ requires: S, 8.4; Cl, 7.5%).

NMR

(a) a 8 proton band centered at 1.65 for the methylene protons

(b) a complex multiplet between 2.3 and 4.2 for the methine and $-S^+-CH_2-$methylene protons

(c) a peak for the methoxyl protons at 3.76

(d) a 2 proton band for S^+-CH_2-Ph methylene proton centered at 4.82

(e) the 8 aromatic protons were seen as a 7 proton multiplet centered at 7.48 and a 1 proton intensity doublet at 6.52

(10) Desulphurization of (II)

Thiachroman (II) (0.105 g) was refluxed in ethanol (15 ml) under stirring with Raney nickel (1.1 g) for half an hour. Reaction mixture was filtered and washed with ethanol. Alcohol was evaporated from the filtrate under reduced pressure and the residual liquid distilled when it gave (VII) as a colourless oil (0.085 g) b.p. 80-100°/0.25 mm.

(11) Desulphurization of (IIA)

Thiachroman (IIA) (0.110 g) treated as above gave (VIIA) (0.086 g), b.p. 80-100°/0.25 mm.

(12) Preparation of 2-hydroxymethylenecyclohexanone

It was prepared as reported[16].

(13) 2-Tosyloxymethylenecyclohexanone (XII)

A solution of hydroxymethylenecyclohexanone (13 g) in methylene chloride (50 ml) and pyridine (10 ml) was cooled to -10°. To the above cooled solution was added during half an hour a solution of p-toluene sulphonyl chloride (20 g) in methylene chloride (50 ml) and pyridine (6 ml). The reaction mixture was stirred for 3 hours maintaining the temperature below 0°. Ice cold water was then added to the reaction mixture and the methylene chloride layer washed thoroughly with water (8-10 times). Removal of methylene chloride under reduced pressure gave (XII) as a white solid (23 g; yield, 80%).

IR spectrum (in CCl_4) Fig. (28):-

Tosylate bands at 1185 and 1378; Carbonyl function at 1680.

(14) 2-(Phenoxymethylene)-cyclohexanone (XIII)

Sodium phenate was prepared by adding phenol (2.35 g) in dry benzene to a suspension of sodium hydride (1.2 g; 50% in oil) in benzene and the mixture stirred at room temperature for 2 hours. To the above suspension of sodium phenate was added a solution of the tosylate (XII) (7 g) in benzene (100 ml) and the reaction mixture stirred for 2 hours and then left overnight. The mixture was filtered and the filtrate washed with water, dried (Na_2SO_4) and benzene removed when (XIII) (4.12 g; yield 82%) was obtained. The product was purified by chromatography over Grade IV neutral alumina using pet. ether (b.p. 60-80°) as eluant. The product from the major fraction on distillation gave (XIII) as a colourless oil, 120-40°/ 0.2 mm (Found: C, 76.9; H, 7.3. $C_{13}H_{14}O_2$ requires: C, 77.2; H, 6.9%).

IR spectrum (Fig. 29): α,β-unsaturated ketone band at 1690 double bond at 1620.

(15) 2-(Phenoxymethyl)-cyclohexanone (XI)

(XIII) (2.786 g) was hydrogenated at atmospheric pressure in ethyl acetate in presence of 5% palladised carbon (0.50 g) till hydrogen absorption ceased (6 hrs.). The reaction mixture was filtered and the solvent removed. The residue was dissolved in ether and the solution washed

with 1% NaOH, water, dried (Na_2SO_4) and ether removed. The residue on distillation gave (XI) (2.42 g; yield 86%) b.p. 120°/0.1 mm (Found: C, 76.0; H, 8.0. $C_{13}H_{16}O_2$ requires: C, 76.4; H, 7.8%).

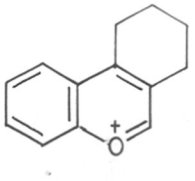
IR spectrum (Fig. 30):- Saturated ketone band at 1710.

(16) 9-Oxa-1,2,3,4-tetrahydrophenanthrylium perchlorate (XIV)

A mixture of the ketone (XI) (1.396 g) and 70% $HClO_4$ (2 ml) was stirred while cooling in an ice bath for 1 hr. and then at room temperature for 1 hr. The reaction mixture was extracted with pet. ether and the $HClO_4$ layer saturated with ether. The pale yellow crystalline solid which separated out was filtered and washed with ether to give (XIV) (0.4 g; yield, 29%), m.p. 200-2°. (Found: Cl, 12.9. $C_{13}H_{13}ClO_5$ requires: Cl, 12.5%).

UV spectrum in 70% $HClO_4$:- 240 (4.33), S262 (3.45), 324 (3.99).

NMR spectrum in trifluoroacetic acid (Fig. 23)



(XIV)

(a) a complex band for 2 pairs of methylene protons (C_2 and C_3 centered at 2.19

(b) a complex band for the axial C_1 and C_4 methylene protons centered at 3.25

(c) a complex band for the equitorial C_1 and C_4 methylene protons centered at 3.76

(d) a multiplet for the 4 benzenoid protons centered at 8.4

(e) a singlet for the C_{10} proton at 9.54

(17) 9-Oxa-1,2,3,4,9,10-hexahydrophenanthrene (XV)

The perchlorate (XIV) (115 mg) was dissolved in methylene chloride (15 ml) and a saturated solution of $NaBH_4$ in ethanol was added dropwise till the solution became colourless. The methylene chloride layer was washed with water till free of alkali, dried (Na_2SO_4) and solvent removed. The liquid obtained was distilled immediately when it gave (XV) (60 mg; yield, 80%), colourless liquid b.p. 100-120°/0.1 mm (Found: C, 83.7; H, 7.3. $C_{13}H_{14}O$ requires: C, 83.9; H, 7.5%).

UV spectrum:- 305 (3.71), 266 (3.78).

NMR (XV) (Fig. 24).

(a) a 8 proton complex signals for the methylene protons centered at 2

(2) a 2 proton band for the C_{10} methylene proton at 4.51

(c) a 4-proton multiplet for the aromatic protons centered at 6.85

(18) Cis-9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (XA)

The perchlorate (XIV) (300 mg) was reduced with $NaBH_4$ as above and the liquid obtained on removal of methylene chloride was dissolved in ethyl acetate (10 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladised carbon (50 mg) for 3 hours. The reaction was filtered, ethyl acetate removed by distillation and the residual liquid distilled to give (XA) (160 mg; yield, 81%) as a colourless liquid, b.p. $100^{\circ}/0.1^{mm}$ (Found: C, 83.2; H, 8.6. $C_{13}H_{16}O$ requires: C, 82.9; H, 8.5%).

UV spectrum:- 227 (3.71), 275 (3.34), 282.5 (3.26).

NMR (Fig. 25)

(a) a 9 proton band for the eight methylene protons and the C_{10a} methine proton centered at 1.82

(b) a one proton band for the benzylic proton centered at 2.82

(c) a two proton band for the O-CH_2 methylene protons centered at 4.04

(d) a multiplet for the four aromatic protons centered at 6.84

(19) Disproportionation of chromene (XV)

The perchlorate (187 mg) was reduced with $NaBH_4$ as above and the liquid obtained treated with 70% $HClO_4$ (1 ml) in the cold. The reaction mixture was kept at room temp. for 1 hr. and worked up as in Experiment 3 to give the chroman (X) (52 mg; yield, 35%), b.p. 100°/0.1 mm (Found: C, 82.9; H, 8.4. $C_{13}H_{16}O$ requires: C, 83.0; H, 8.5%).

UV spectrum:- 227 (3.7), 275 (3.31), 282.5 (3.24).

NMR identical with (XA).

From the $HClO_4$ layer was obtained the perchlorate (XIV) (97 mg; yield, 34%).

(20) 2-(Phenylmercaptomethyl)-cyclohexanone (XIX)

Thiophenol (3.3 g) was condensed with

2- dimethylaminomethylcyclohexanone[13] (4.6 g) as in Experiment 2 to give (XIX) (4.5), b.p. 122-24°/0.06 mm (Found: C, 70.9; H, 7.1; S, 14.1. $C_{13}H_{16}OS$ requires: C, 70.9; H, 7.1; S, 14.5%).

(21) 2-(Phenylmercaptomethyl)-cyclohexanol (XVI)

The ketone (XIX) (5 g) was refluxed with LAH (0.7 g) in ether (100 ml) for 2 hours. Excess LAH decomposed with water and ether removed whereby (XVI) (4.515 g), b.p. 122-25°/0.001 mm was obtained.

IR: Absence of carbonyl band; OH band at 3400.

(22) 2-(Phenylmercaptomethyl)-1-methylcyclohexanol (XVII)

The ketone (XIX) (1 g) was treated with MeMgI 2 equivalent at 0°. The complex was decomposed with NH_4Cl solution and ether evaporated to give (XVII) (1 g).

IR: Absence of carbonyl band; OH band at 3400. The product was used as such for further reaction.

(23) 2-Methyl-(6-dimethylaminomethyl)-cyclohexanone

It was prepared as reported[13].

(24) 2-(Phenylmercaptomethyl)-6-methyl-cyclohexanone (XX)

Interaction of thiophenol (4.4 ml) and 2-methyl-(6-dimethylaminomethyl)-cyclohexanone (8.4 g) as in

Experiment 1 gave (XX) (2.66 g; yield, 27%), b.p. 129-30°/0.2 mm (Found: C, 72.1; H, 8.0; S, 13.9. $C_{14}H_{18}SO$ requires: C, 71.8; H, 7.7; S, 13.7%).

(25) 2-(Phenylmercaptomethyl)-6-methylcyclohexanol (XVIII)

Interaction of the ketone (XX) (2 g) and LAH (0.300 g) as in Experiment (21) gave (XVIII) (1.57 g; yield, 79%), b.p. 120-40°/0.15 mm (Found: C, 71.2; H, 8.6; S, 13.3. $C_{14}H_{20}OS$ requires: C, 71.2; H, 8.5; S, 13.5%).

(26) 1-Methyl-7-thiabicyclo[3.2.1]octane phenyle sulphonium perchlorate (XXI)

A mixture of the alcohol (XVIII) (0.40 g) and 60% $HClO_4$ (4 ml) was stirred at room temperature for 4 hours and then at 60-70 for 4 hrs. The reaction mixture was extracted with benzene and ether added until the $HClO_4$ layer was saturated. The mixture was filtered and cooled when (XXI) separated as colourless cubes, m.p. 181-82° (0.127 g; yield, 24%) (Found: S, 9.7; Cl, 11.2. $C_{14}H_{19}ClO_4S$ requires: S, 10.0; Cl, 11.1%).

UV spectrum: 275 (3.01), 267.5 (3.14), 261 (3.14), 256 (3.12), 229 (4.04).

NMR (trifluoroacetic acid) (Fig. 26)

(a) a 3 proton peak for the methyl group at 1.25

(b) a 8 proton complex band for the methylene

protons between 1.73 and 2.6

(c) a one proton band for the methine proton centered at 3.5

(d) a 5 proton peak for the aromatic protons at 7.85

(27) $NaBH_4$ reduction of (XXI)

To (XXI) (0.21 g) in methylene chloride (25 ml) was added a suspension of $NaBH_4$ (0.10 g) in 95% alcohol (2 ml). The reaction mixture was stirred for 3 1/2 hours. A drop of AcOH was added to decompose excess $NaBH_4$, the methylene chloride layer washed with sodium bicarbonate solution and water. Removal of solvent gave an oil which on distillation gave (XXII) (0.065 g; yield, 45%) as a colourless liquid (Found: C, 76.5; H, 9.1; S, 14.6. $C_{14}H_{20}S$ requires: C, 76.4; H, 9.1; S, 14.5%).

NMR

(a) a 3 proton doublet for the methyl on the secondary carbon at 0.82 ($J = 4$).

(b) a 3 proton peak for the methyl on the tertiary carbon atom at 1.21

(c) a 8 proton band for the methylene protons centered at 1.56

(d) a one proton complex band for the methine proton at 2.8

(e) a 5 proton multiplet for the aromatic protons centered at 7.27

(28) 2-(m-Methoxyphenoxymethylene)-cyclohexanone (XXIII)

m-Methoxyphenol, sodium hydride (1.68 g; 50% in oil) and tosylate (XII) (9.8 g) were reacted as in Experiment 14 to give (XXIII) (7.5 g; yield, 99%), b.p. 140-160°/0.1 mm (Found: C, 72.8; H, 7.2. $C_{14}H_{16}O_2$ requires: C, 72.4; H, 6.9%).

IR: α,β-unsaturated ketone band at 1690; double bond at 1610.

(29) 2-(m-Methoxyphenoxymethyl)-cyclohexanone (XXIV)

(XXIII) was hydrogenated as in the preparation in Experiment 15 to give (XXIV) (2.22 g; yield, 61%), b.p. 120-40°/0.05 mm (Found: C, 71.7; H, 7.9. $C_{14}H_{18}O_3$ requires: C, 71.7; H, 7.6%).

IR: saturated ketone band at 1700.

(30) 2-(β-Naphthoxymethylene)-cyclohexanone (XXVI)

β-Naphthol (2.88 g), NaH (0.48 g, 50% in oil) and tosylate (XII) (5.6 g) were reacted as in Experiment 14 to

give (XXVI) (4.9 g; yield, 97%), b.p. 160-70°/0.1 mm (with decomposition).

IR (Fig. 31): α,β-unsaturated ketone band at 1690; double bond at 1645.

(31) 2-(β-Naphthoxymethyl)-cyclohexanone (XXVII)

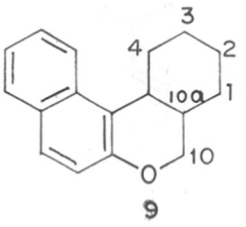
(XXVI) was hydrogenated as in Experiment 15 to give (XXVII) (0.81 g; yield, 80%), m.p. 78-79° (Found: C, 80.3; H, 7.3. $C_{17}H_{18}O_2$ requires: C, 80.3; H, 7.1%).

IR (in CCl_4): saturated ketone band at 1720.

(32) Cyclodehydration of (XXVII)

The ketone (XXVII) (0.81 g) was added to 70% $HClO_4$ (2 ml) cooled in an ice bath. The mixture was stirred at room temperature for 2 hrs. and then worked up as in Experiment 3 to give the chroman (XXVIII) (0.318 g; yield, 42%). The product was purified by passing over Grade IV neutral chromatographic alumina and eluting with pet. ether (60-80°). The product on distillation (b.p. 160°/0.1 mm) gave (XXVII) m.p. shrinks at 88°, melts at 90-95° (Found: C, 85.6; H, 8.0. $C_{17}H_{18}O$ requires: C, 85.7; H, 7.6%).

NMR



(XXVIII)

(a) a 7 proton band for the methylene protons centered at 1.49

(b) a two proton multiplet for one of the C_4 methylene protons and the C_{10a} methine proton, centered at 2.15 and 2.35

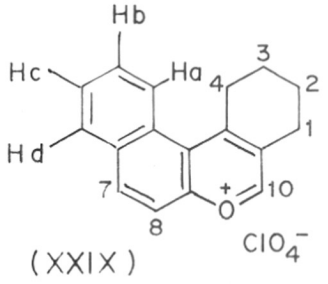
(c) a one proton band for the C_{4a} methine proton centered at 3.22

(d) a two proton multiplet for the O-CH_2 group centered at 4.25

(e) a multiplet for the six aromatic protons centered at 7.32

The $HClO_4$ layer gave the perchlorate (XXIX) (0.307 g; yield, 29%) m.p. 198-200° (Found: Cl, 10.1. $C_{17}H_{15}ClO_5$ requires: Cl, 10.6%).

NMR (Fig. 27) in trifluoroacetic acid



(XXIX)

(a) a 4 proton band for C_2 and C_3 methylene protons at 2.23

(b) a 2 proton band for the C_1 and C_4 axial protons at 3.31

(c) a 2 proton band for C_1 and C_4 equitorial protons at 4.05

(d) a doublet for the C_7 proton at 7.99 ($J_{H_7-H_8}$ = 9.5)

(e) a multiplet for Hb, Hc, Hd centered at 8.08

(f) a doublet for the C_8 proton at 8.6 ($J_{H_8-H_7}$ = 9.5)

(g) a multiplet for Ha centered at 8.92

(h) a sharp singlet for the C_{10} proton at 9.14

(33) 5,6-Benzo-9-oxa-1,2,3,4,9,10,4a,10a-octahydrophenanthrene (XXVIIIA)

The perchlorate (XXIX) (250 mg) was reduced with

$NaBH_4$ and subsequently hydrogenated as in Experiment 18 to give (XXVIIIA) (0.124 g; yield, 70%), b.p. 160°/0.1 mm; m.p. 81-83° (Found: C, 85.8; H, 8.0. $C_{17}H_{18}O$ requires: C, 85.7; H, 7.6%).

NMR: Same as (XXVIII) (see discussion).

(34) 2-(Anilinomethylene)-cyclohexanone (XXX)

To a solution of aniline (1.86 g, 0.02 mole) in benzene (10 ml) was added a solution of the tosylate (XII) (2.818g; 0.01 mole) in benzene. The reaction mixture was left overnight at room temp. and then filtered to remove aniline salt of p-toluenesulphonic acid. The filtrate was washed with water, concentrated and cooled when it gave (XXX) (1.05 g) m.p. 145-46°.

IR (CCl_4) (Fig. 32): N-H band at 3190; carbonyl band at 1655.

(35) 2-(m-Anisidinomethylene)-cyclohexanone (XXXII)

Compound (XXXII) was prepared as above starting from m-anisidine (2.46; 0.02 mole) and tosylate (XII) (2.8 g; 0.01 mole) (0.62 g; m.p. 118-119°).

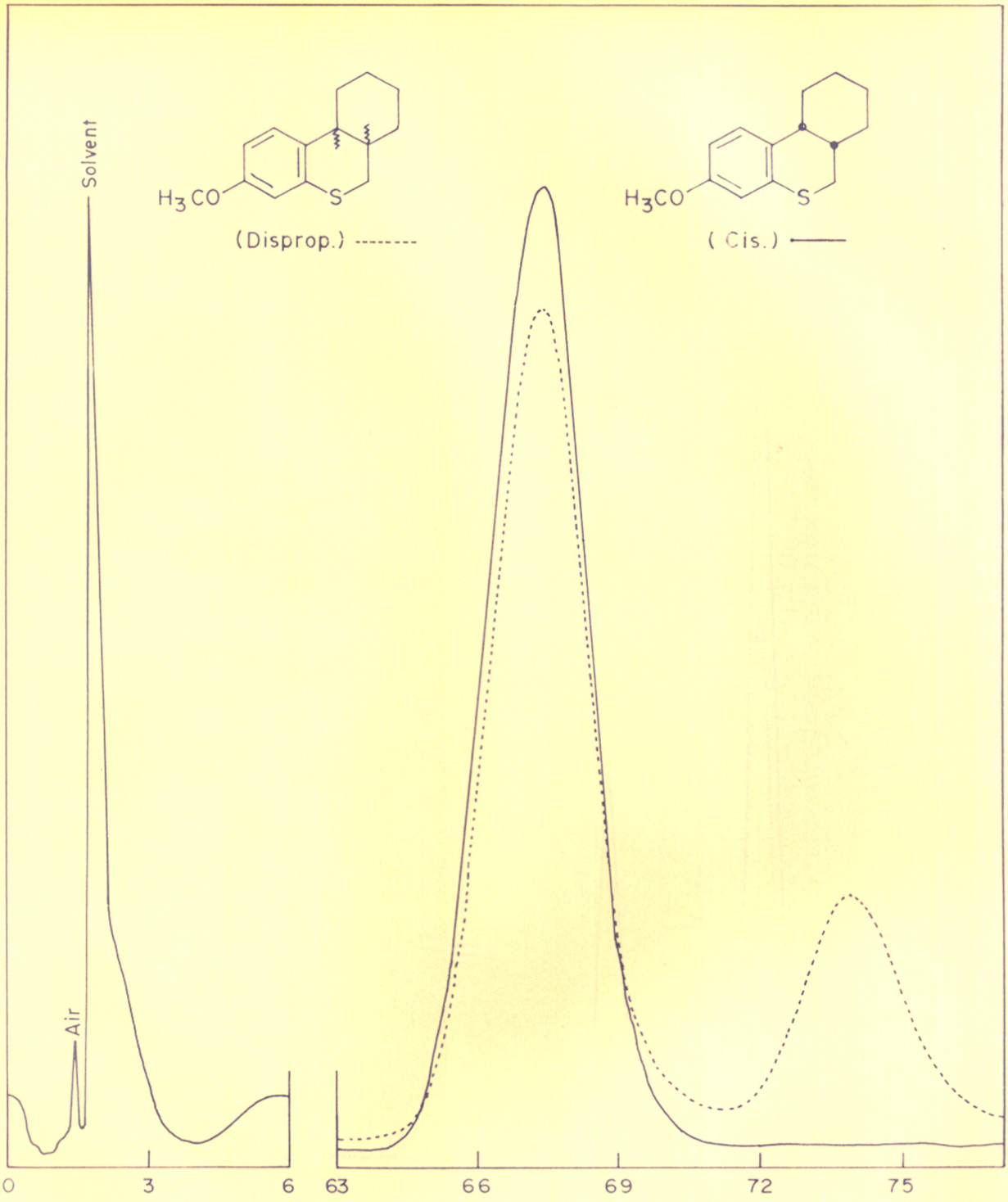
IR ($CHCl_3$) (Fig. 33): NH band at 3190; carbonyl band at 1665.

CONCLUSION

The above studies on the stereochemistry of hydride transfer reaction show that a higher degree of stereospecificity is observed in the disproportionation of thiachromenes than the corresponding chromenes. It may be concluded from these observations that the sulphur atom plays a distinct role in directing the course of hydride attack.

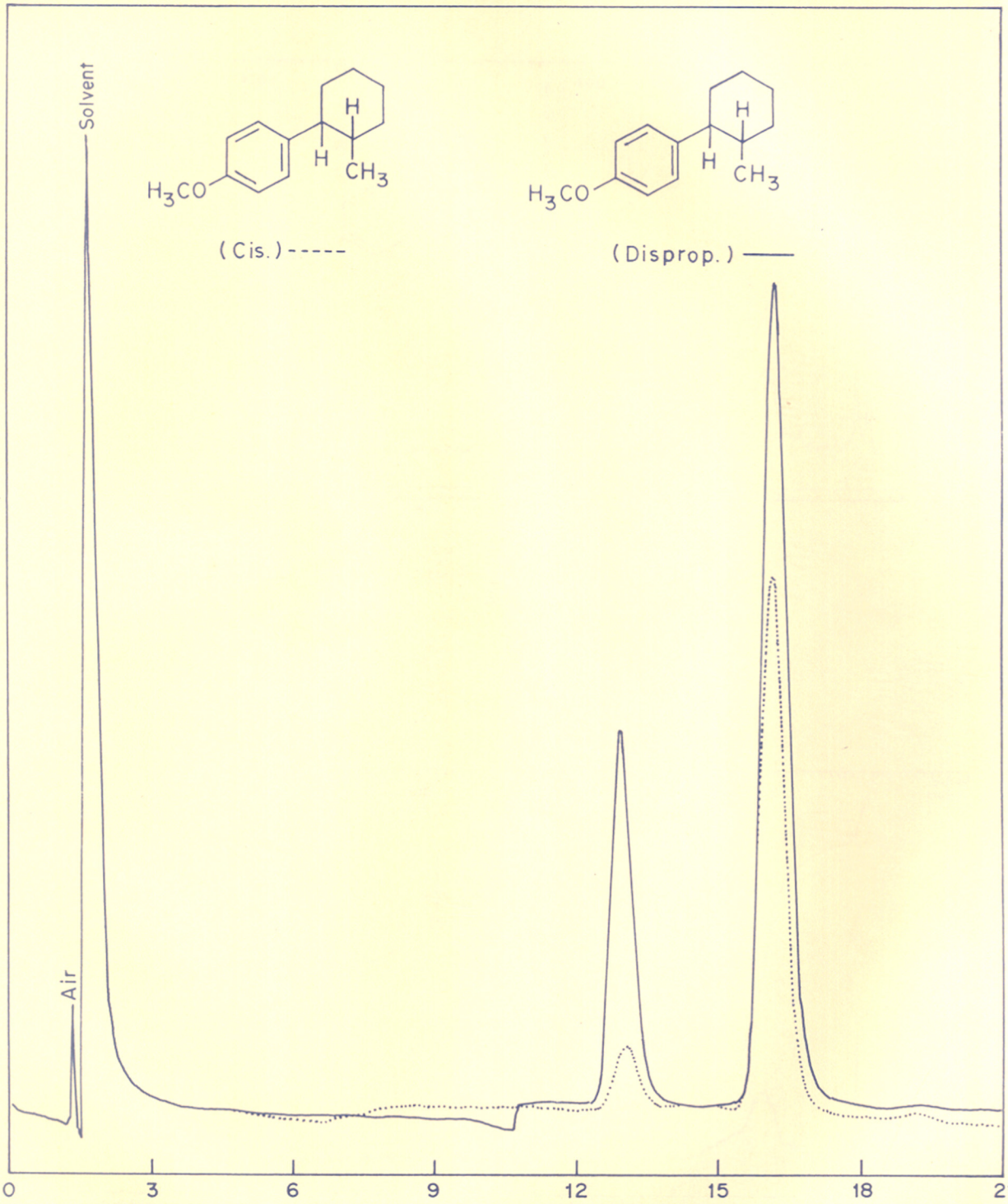
A stereospecific method for the preparation of cis 2-aryloxymethylenecyclohexanone and cis-2-arylaminomethylenecyclohexanone is described.

ILLUSTRATIONS



COLUMN: 20% APIEZON L/CHROMOSORB W + 0·25 % Me_2SiCl_2 ; COLUMN TEMP.: 285 °C.
FLOW RATE: 60 ml/min. ; CARRIER GAS: He ; CHART SPEED: 20"/hr.

FIG. 11.



COLUMN: 20% APIEZON L/CHROMOSORB W + 0·25% Me SiCl ; COLUMN TEMP.: 285 °C.
FLOW RATE: 60 ml /min. ; CARRIER GAS: He ; CHART SPEED : 20"/hr.

FIG. 12.

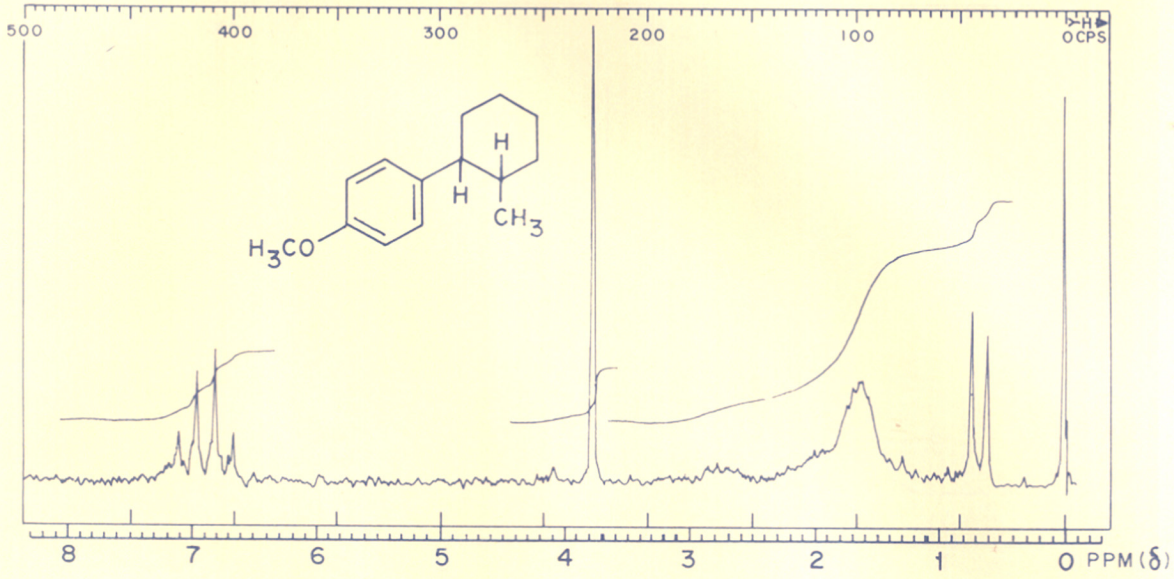

500
400
300
200
100
0 CPS
H
H
CH3
H3CO
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 13.

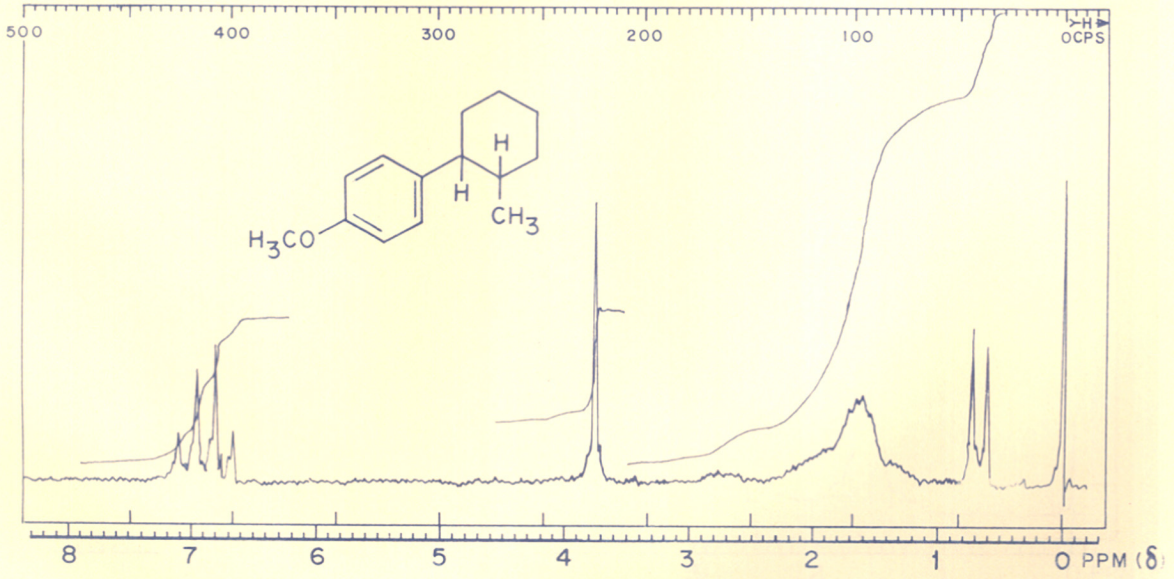

500
400
300
200
100
0 CPS
H
H
CH3
H3CO
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 14.

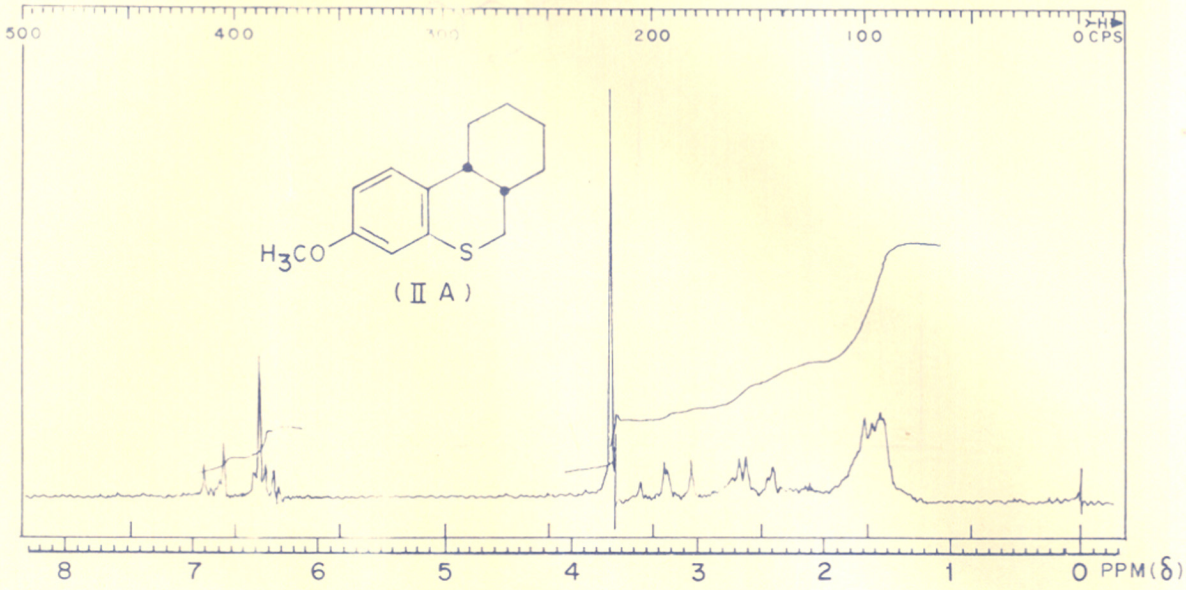

500
400
200
100
0 CPS
H_3CO
S
(II A)
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 15.

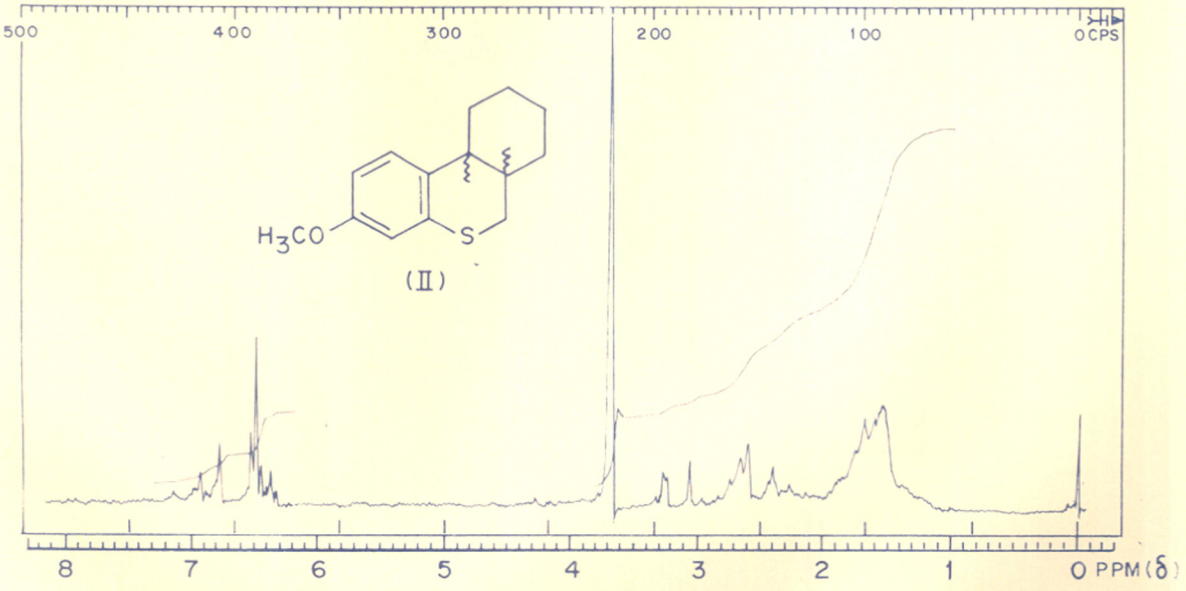

500
400
300
200
100
0 CPS
H_3CO
S
(II)
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 16.

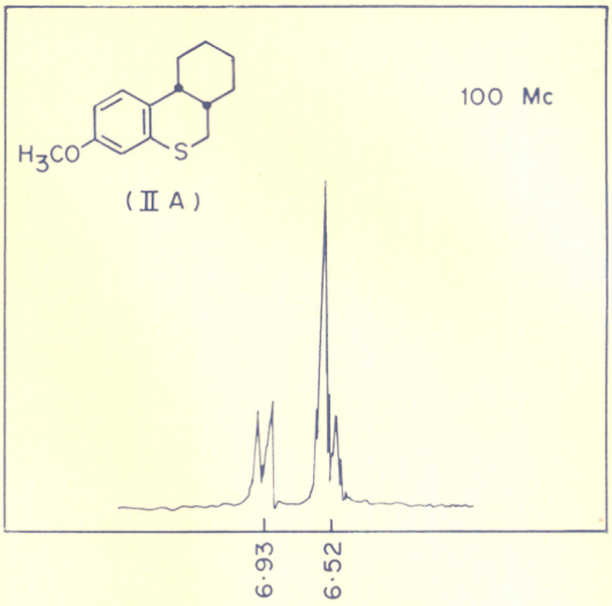
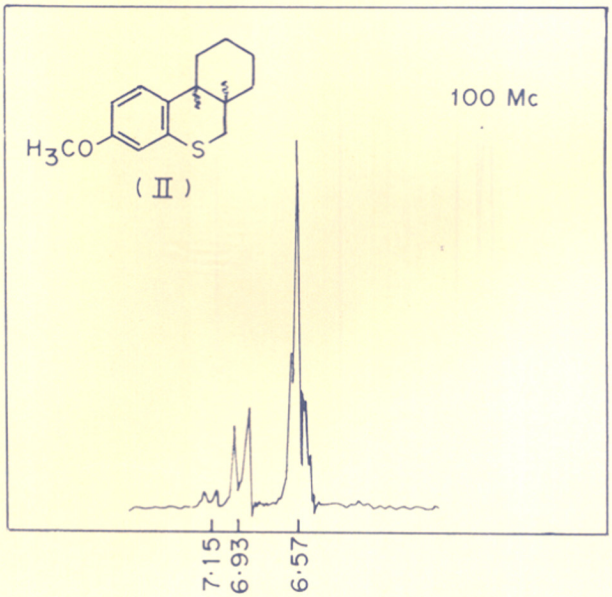
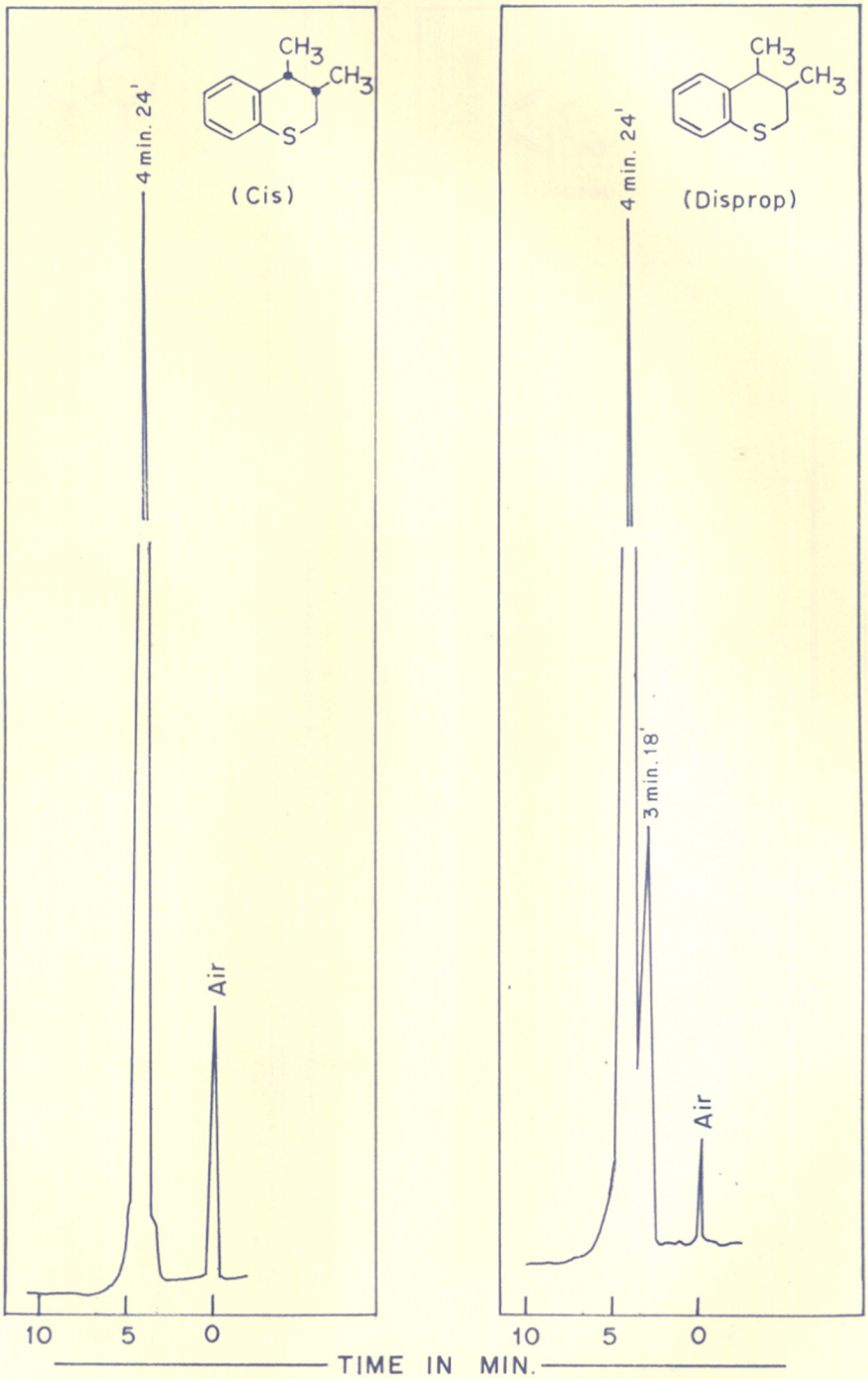


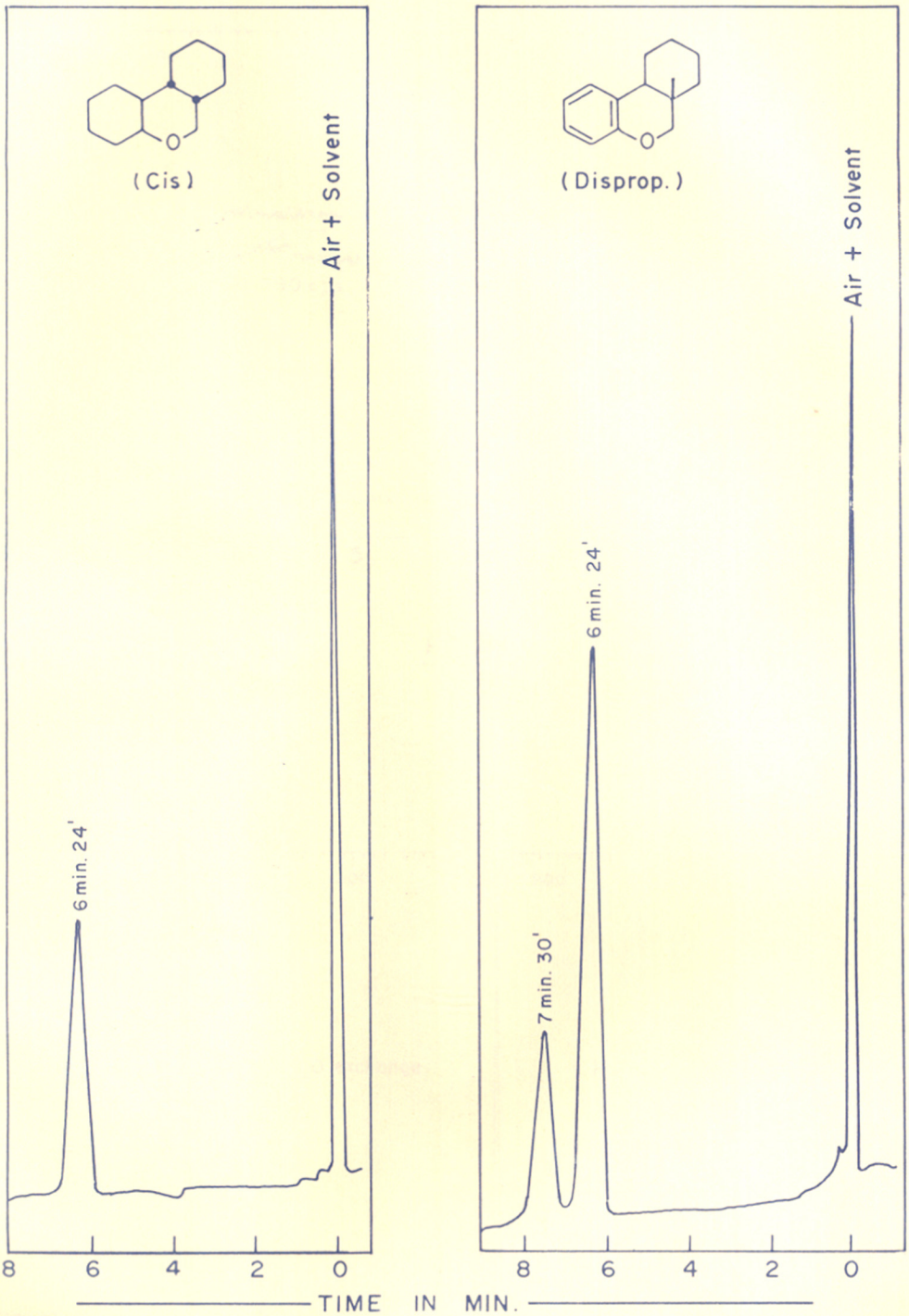
FIG. 17.





COLUMN: 20% DIETHYLENE GLYCOL POLYSUCCINATE/FIRE BRICK. COLUMN TEMP.: 200°C.
FLOW RATE: 60 ML./MIN. CARRIER GAS: H_2. CHART SPEED: 6"/hr.

FIG. 18.



COLUMN: 30% TUNG OIL / CHROMOSORB W. COLUMN TEMP.: 185°.
FLOW RATE : 100 ml./min. CARRIER GAS : H_2. CHART SPEED : 15"/hr.

FIG. 19.

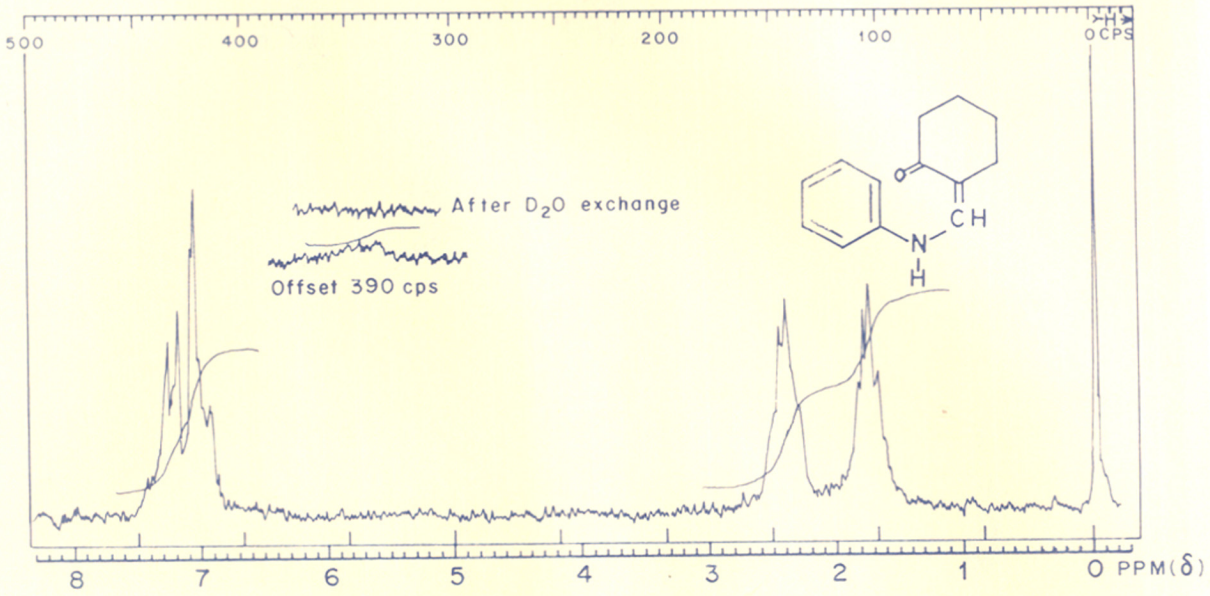

500
400
300
200
100
0 CPS
After D_2O exchange
Offset 390 cps
O
CH
N
H
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 20.

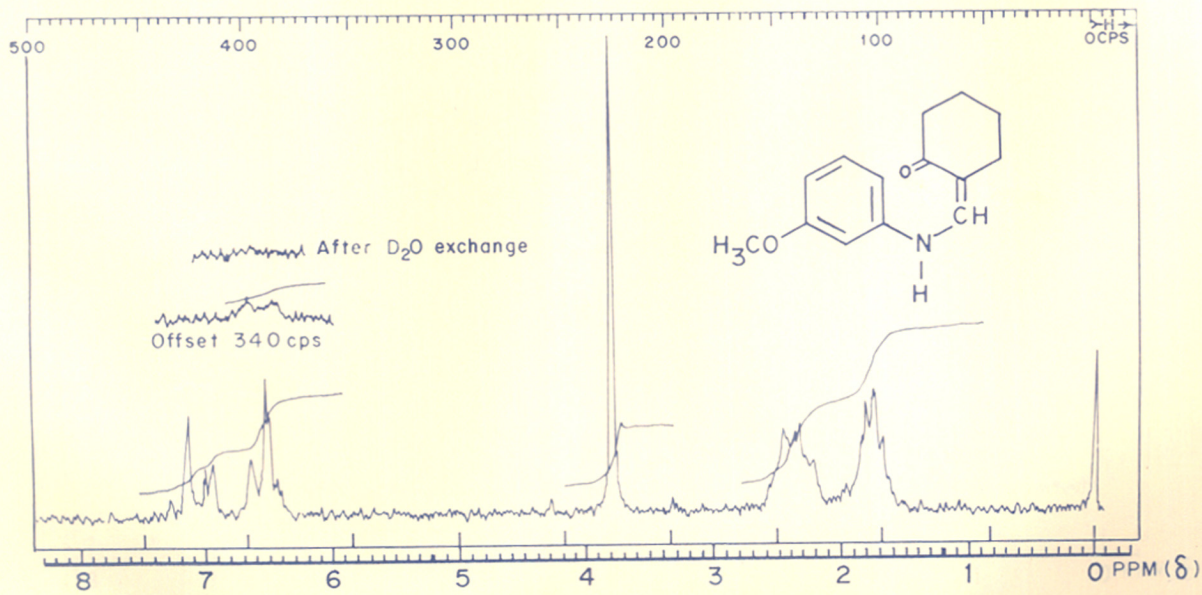

500
400
300
200
100
0 CPS
After D_2O exchange
Offset 340 cps
H_3CO
O
CH
N
H
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 21.

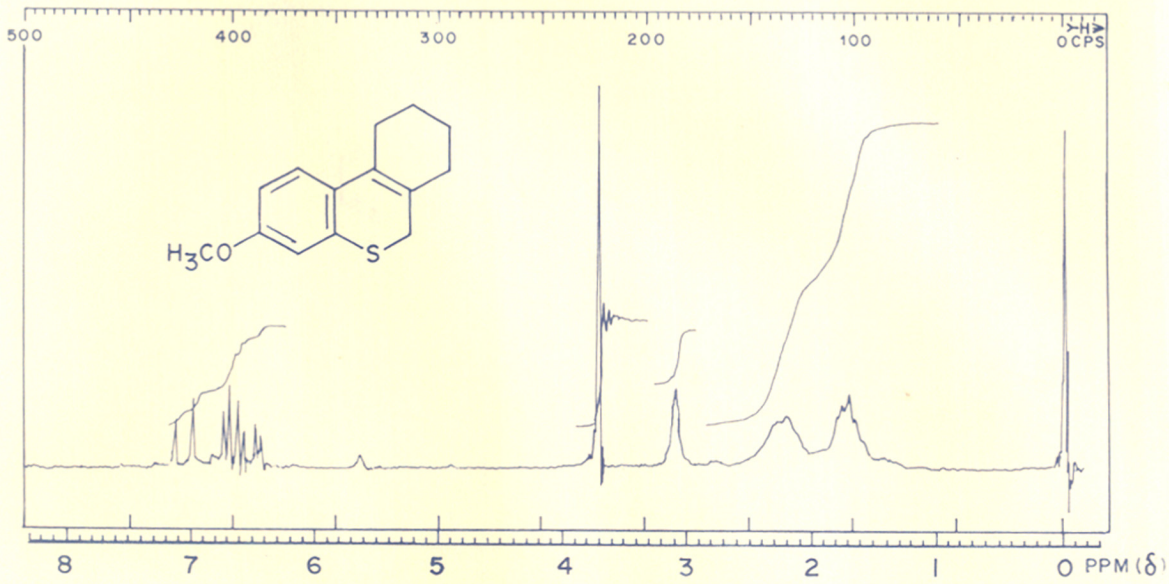

500
400
300
200
100
0 CPS
H_3CO
S
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 22.

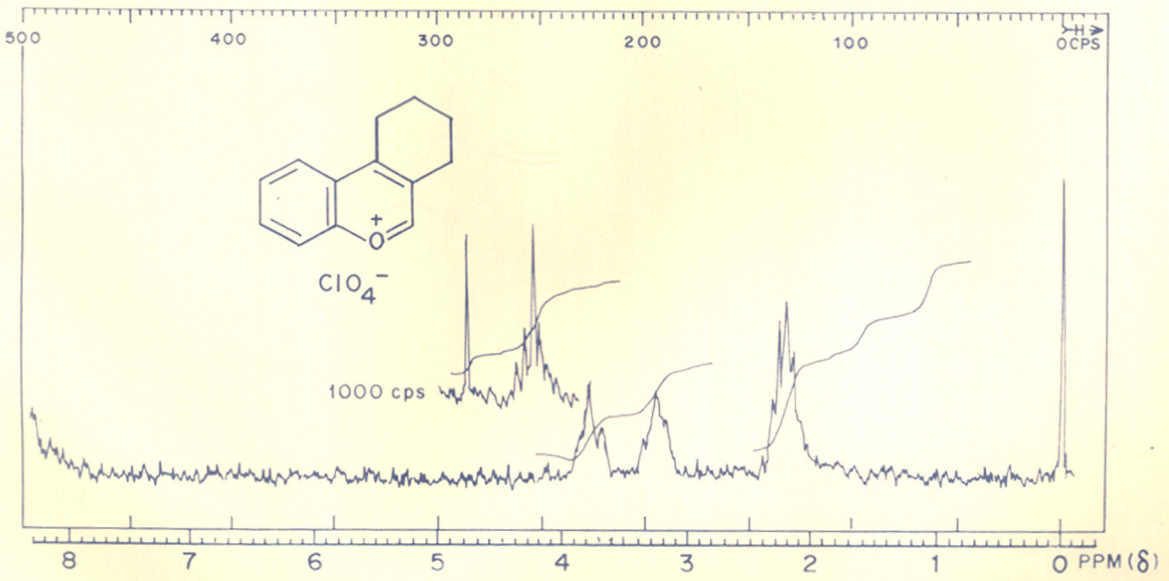

500
400
300
200
100
0 CPS
O
ClO_4^-
1000 cps
8
7
6
5
4
3
2
1
0 PPM (δ)

FIG. 23.

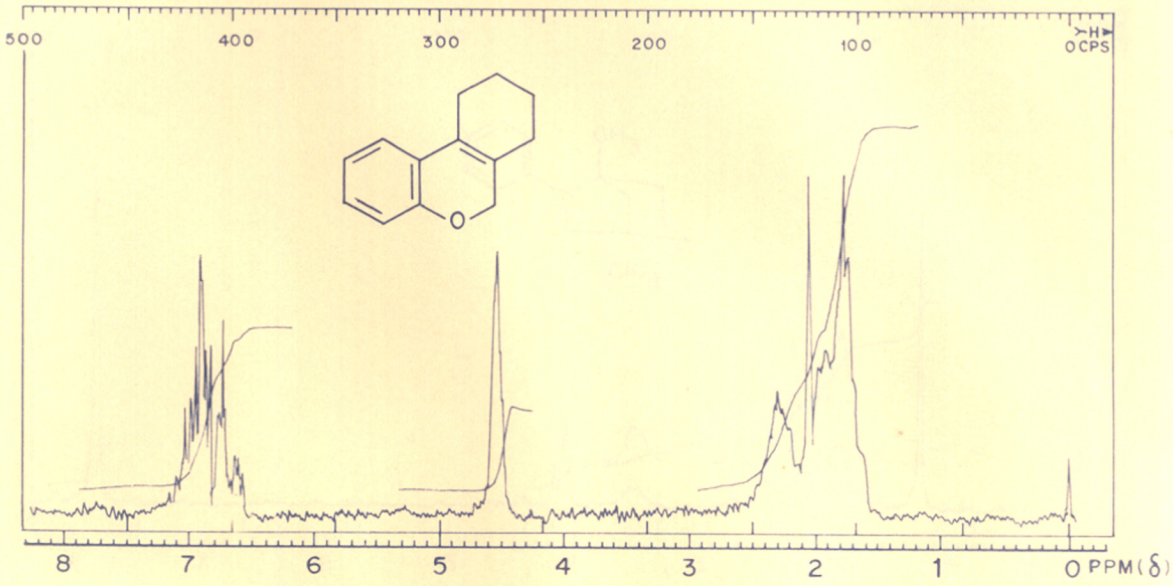

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 24.

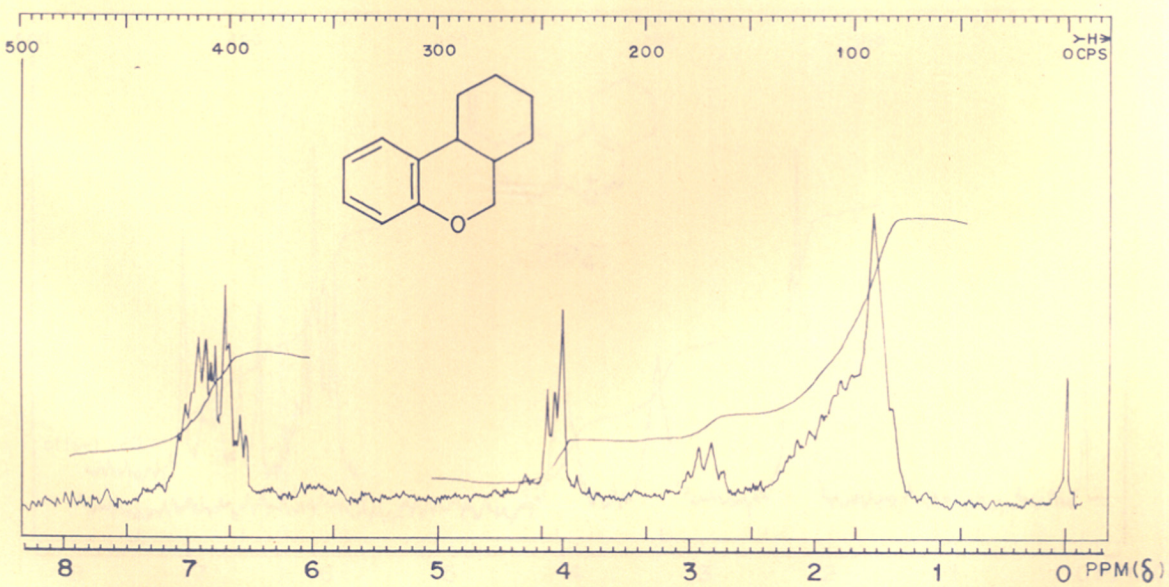

500
400
300
200
100
0 CPS
8
7
6
5
4
3
2
1
0 PPM(δ)

FIG. 25.

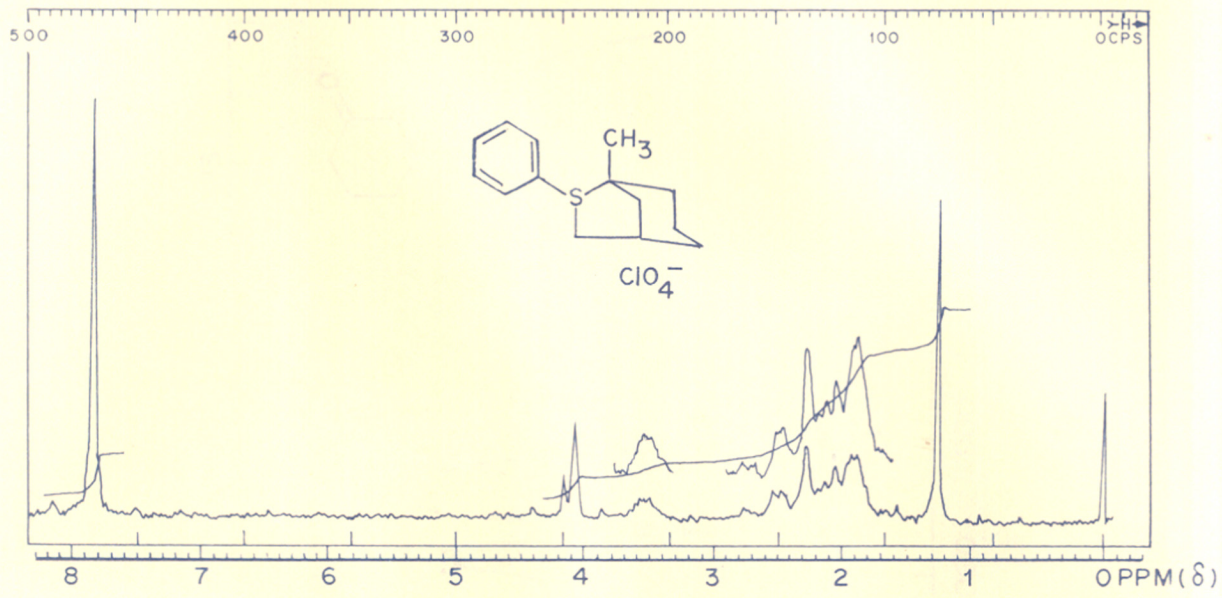

500
400
300
200
100
0CPS
CH3
S
ClO4−
8
7
6
5
4
3
2
1
0PPM(δ)

FIG. 26.

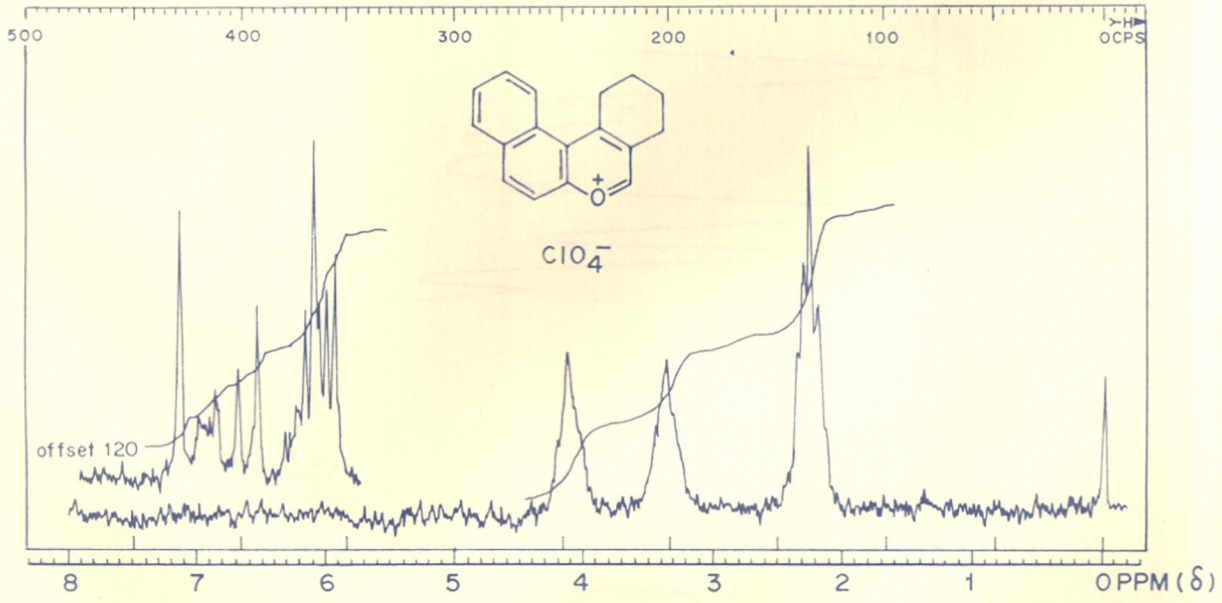

500
400
300
200
100
0CPS
O+
ClO4−
offset 120
8
7
6
5
4
3
2
1
0PPM(δ)

FIG. 27.

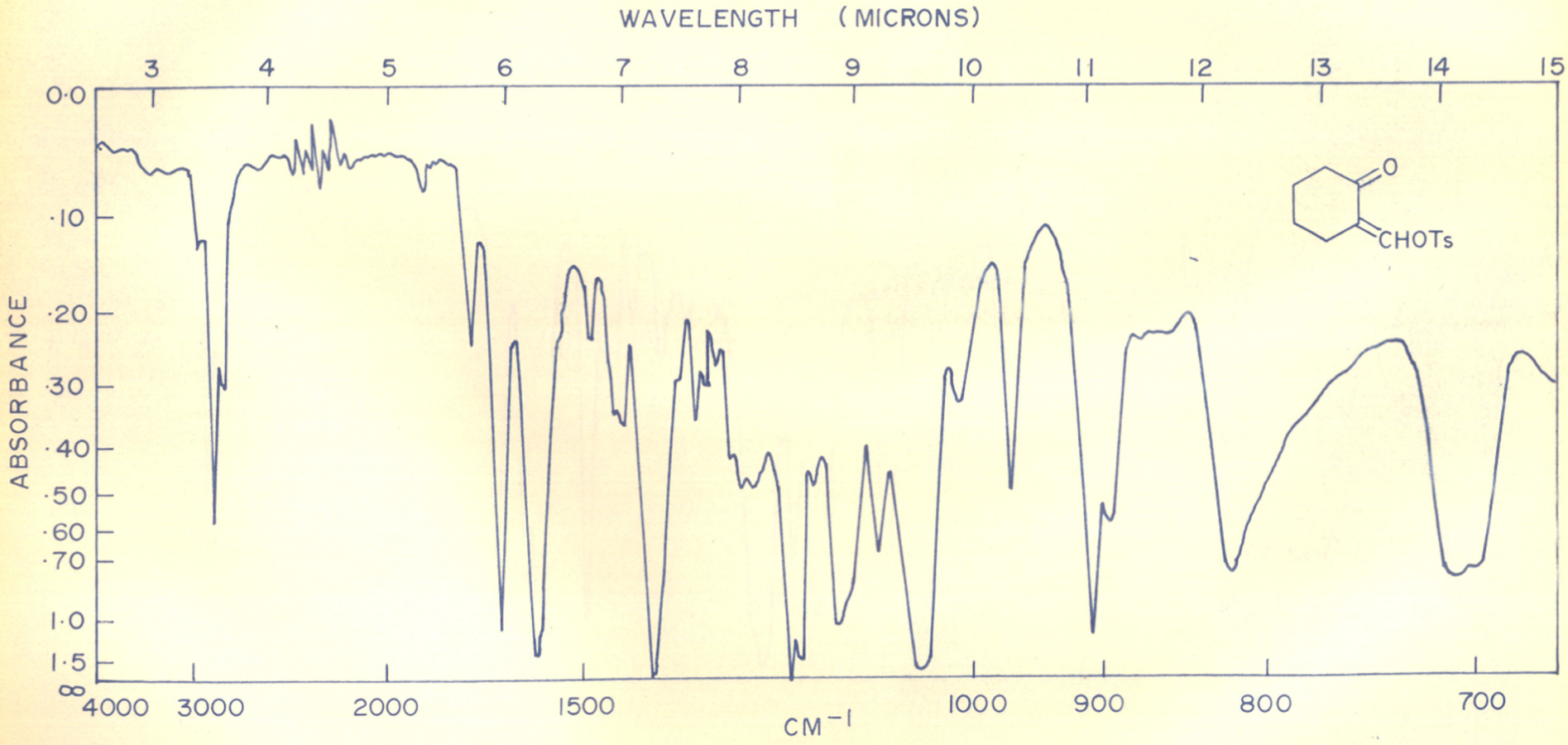

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
∞
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
O
CHOTs

FIG. 28.

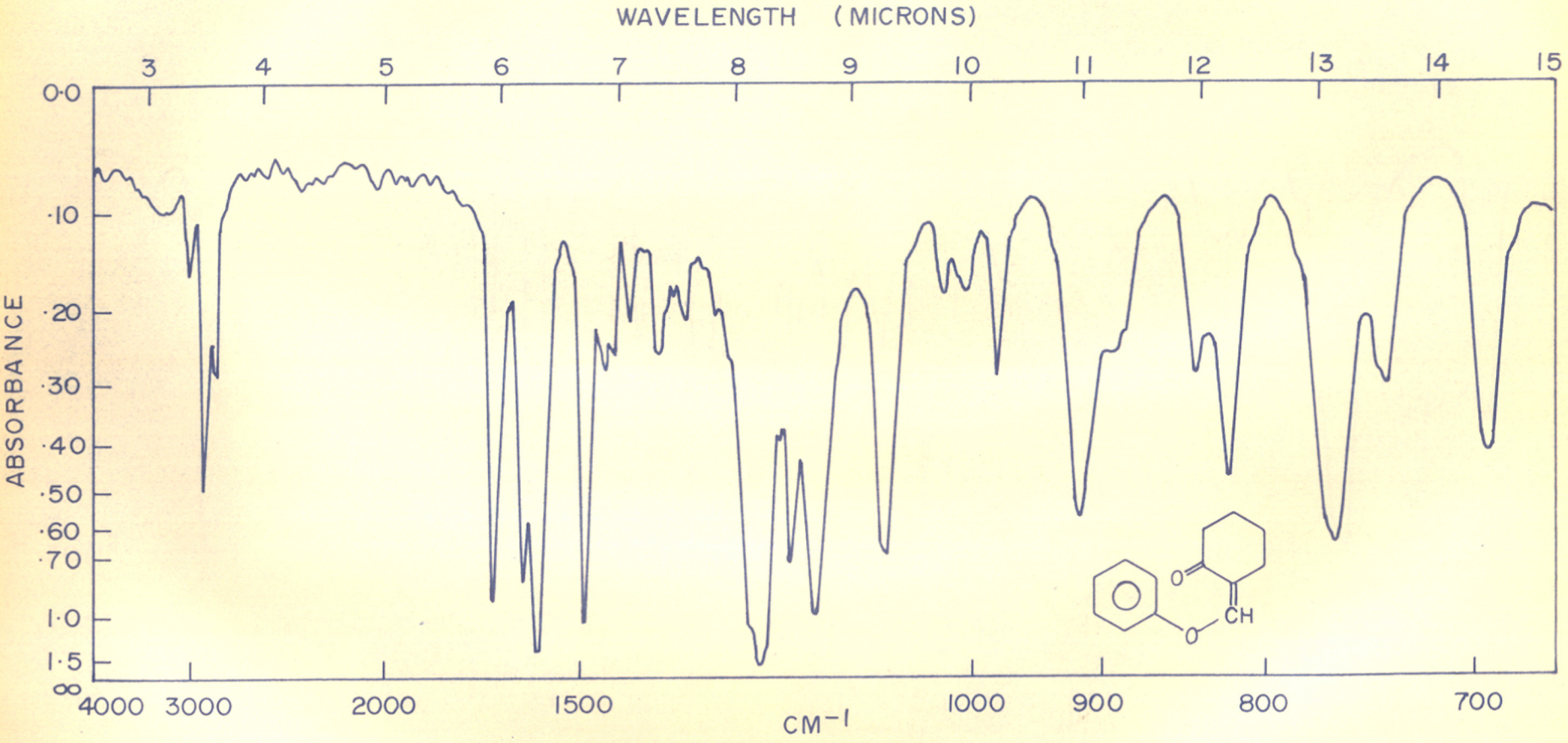

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
∞
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM-1
O
CH
O

FIG. 29.

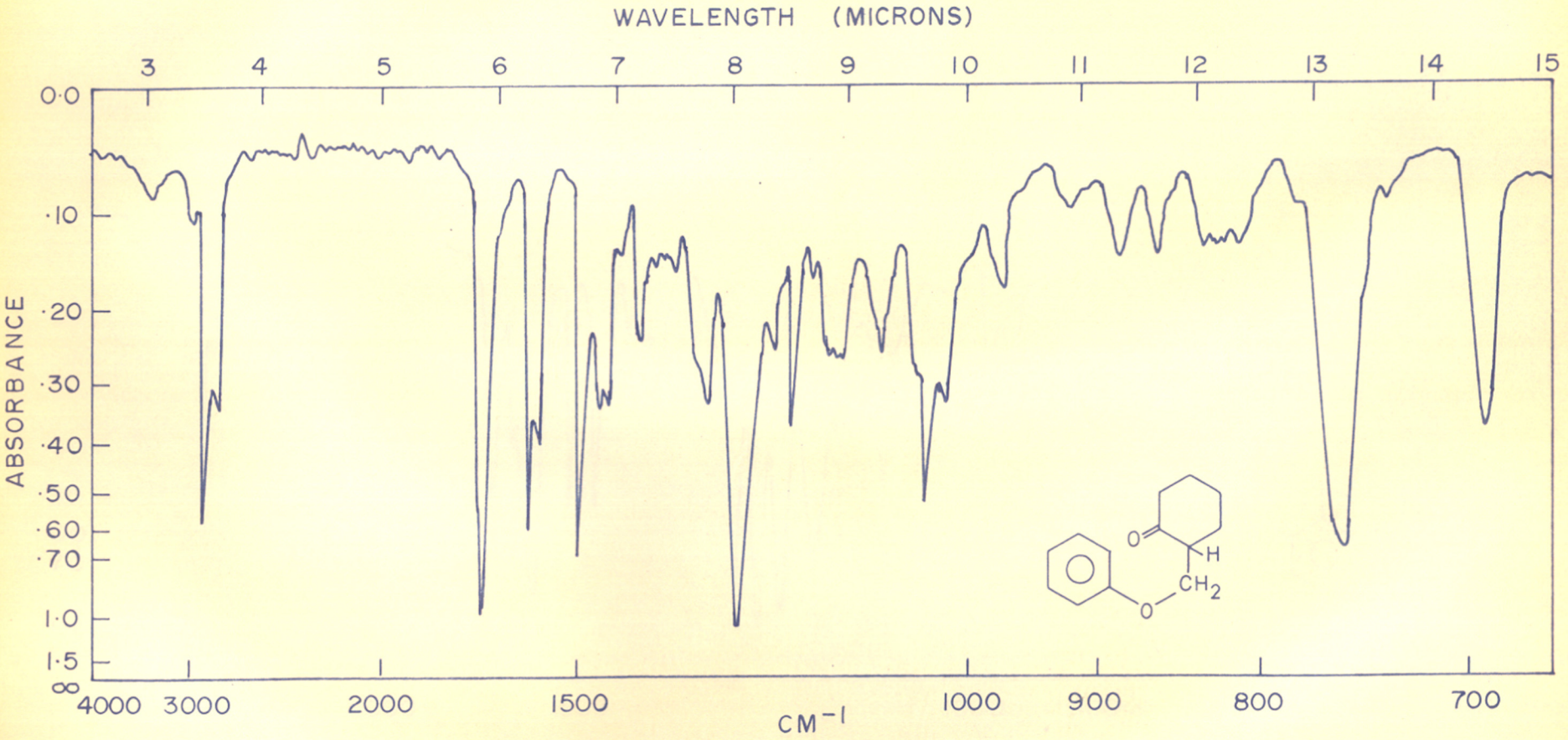

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
∞
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
O
H
CH2
O

FIG. 30.

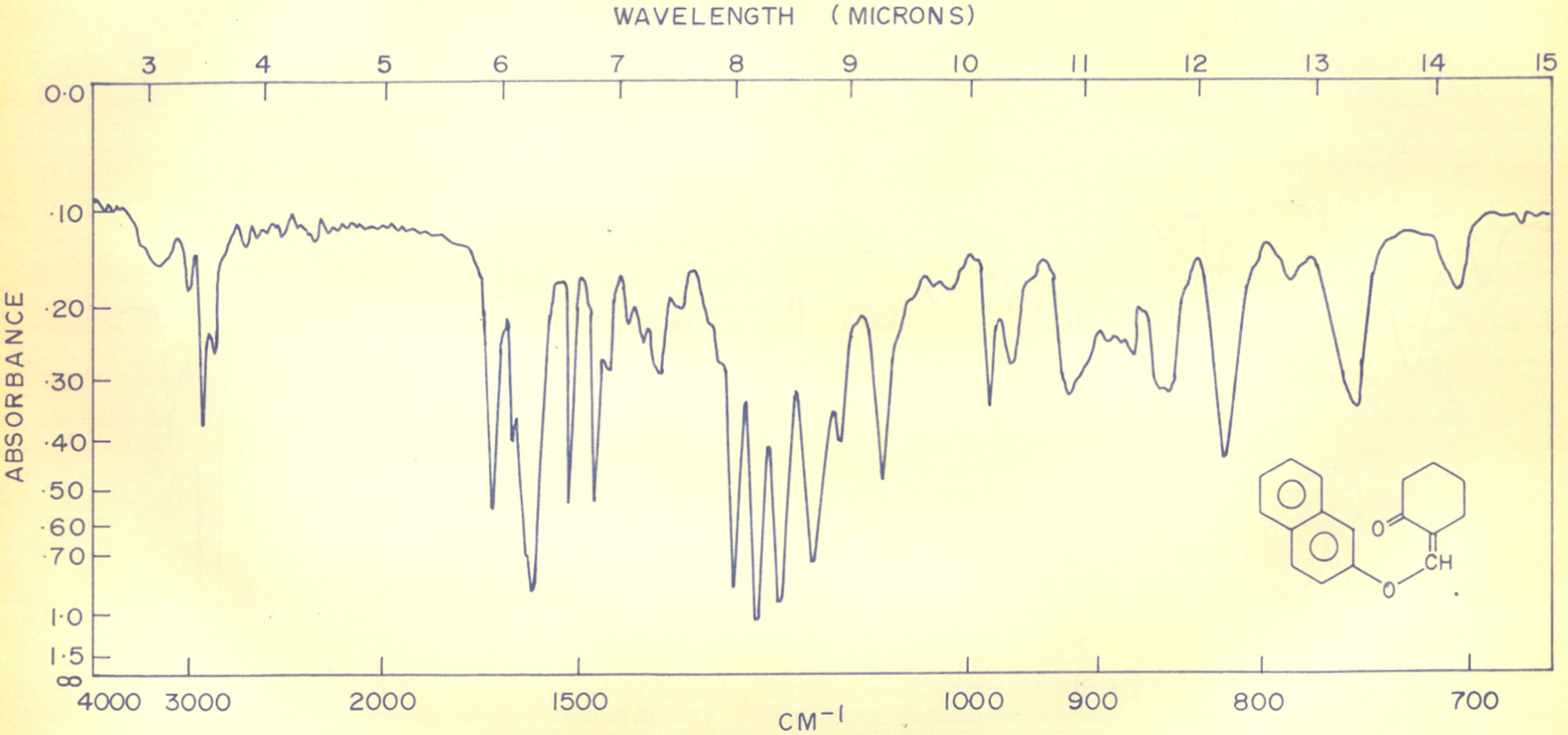

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
O
CH
O

FIG. 31.

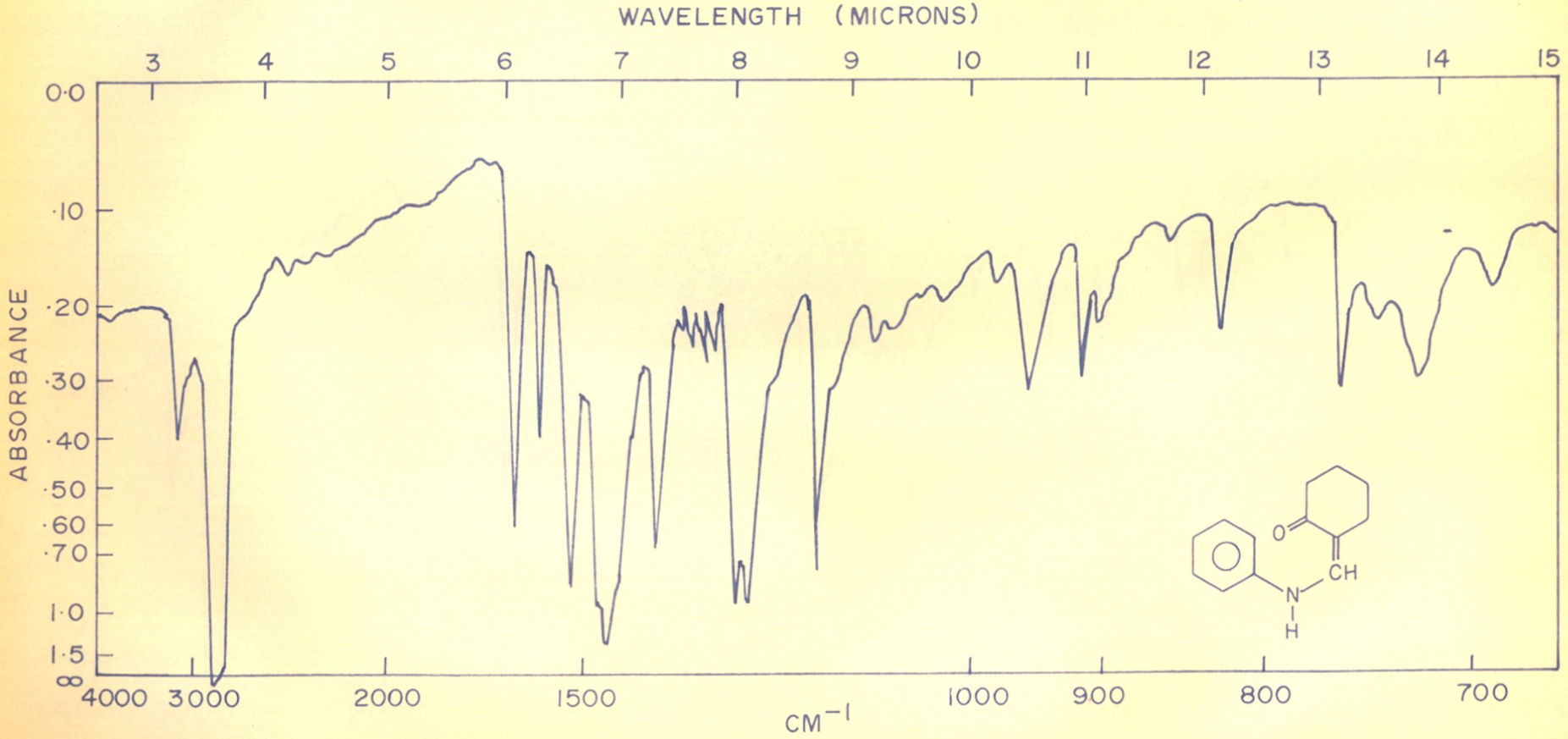

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
∞
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
O
CH
N
H

FIG. 32.

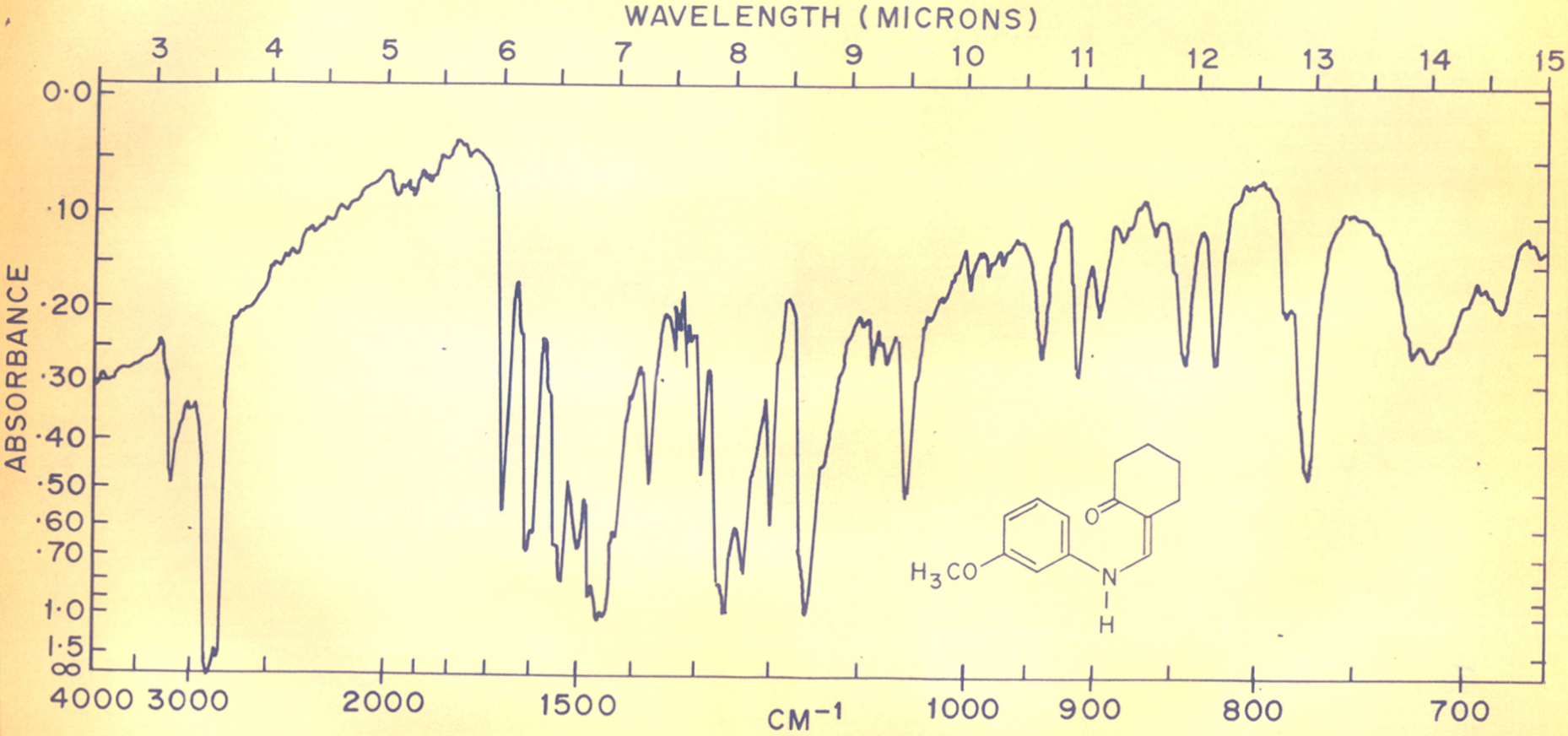

WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·60
·70
1·0
1·5
ABSORBANCE
4000
3000
2000
1500
CM-1
1000
900
800
700
O
H3CO
N
H

FIG. 33.

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I acknowledge with thanks the timely assistance rendered by the Glass Blowing Section of N.C.L.

Lastly I thank the donors of Petroleum Research Fund for a grant, and the Council of Scientific and Industrial Research for the award of a fellowship.

Statement required to be submitted under Rule 0.413
of the University of Bombay

No part of this work has been submitted for a degree or diploma or other academic award. The literature concerning the problems investigated has been surveyed, and all the necessary references are given. The experimental work has been carried out entirely by me. In accordance with the usual practice, due acknowledgement has been made whenever the work presented is based on the results of other workers.

Z. Muljiani.

Poona, 19.1.1968.

(Miss) Zainab Muljiani
Candidate

Prof. B. D. Tilak
Research Guide