MOLECULAR REARRANGEMENT

and

CLATHRATE STUDIES

A thesis

submitted to the University of Glasgow

in fulfilment of the requirements for

the degree of Doctor of Philosophy in

the Faculty of Science.

by

Joseph James McKendrick, B.Sc.

Department of Chemistry,

October 1974.

ERRATA

Page 14, line 13 : "2-formylbenzo(b)thiophene" should read "2-formylbenzo(b)selenophene".

Page 42, line 18 and page 43, line 1 should read "isation with Raney nickel gave 2-(β-naphthyl)- and 2-(α-naphthyl)butane respectively, which allow the alternative possibilities to be".

Page 44, line 3 : "Table 2" should read "Table 1".

Page 50 : "Figure 11" should read "Figure 6".

Page 88, line 2 : "dimension" should read "dimensions".

Page 117, line 26 : "enatiomorphous" should read "enantiomorphous".

Page 119, line 23 : "refelcted" should read "reflected".

Page 141, line 18 : "dimethylmercury" should read "diethylmercury".

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. D.D. MacNicol for his constant interest and helpful advice throughout the course of this work. I am also indebted to the technical staff of the Chemistry Department, in particular to Mr. J. Gall and Mrs. F. Lawrie for the recording of ^{1}H n.m.r. and infrared spectra respectively. Finally, I would like to thank Dr. R.K. Mackenzie for his assistance in the typing of this thesis.

CONTENTS

SUMMARY

Cyclodehydration of 4-methyl-4-phenylthiopentan-2-one by polyphosphoric acid (PPA) at ca. 100°C gave not only the expected 2,2,4-trimethyl-2H-thiachromene but also the ring-contracted 2-isopropyl-3-methylbenzo(b)thiophene as the other major volatile product. Gel permeation chromatography allowed the separation of these two compounds together with a third component identified as the corresponding 4H-thiachromene. The successful extension of the reaction to a series of substituted ketosulphides illustrated the potential of this novel rearrangement. The ring-contracted thiophenes were also produced on PPA treatment of the isolated thiachromenes indicating that the latter are intermediates in the reaction for which an ionic mechanism is proposed.

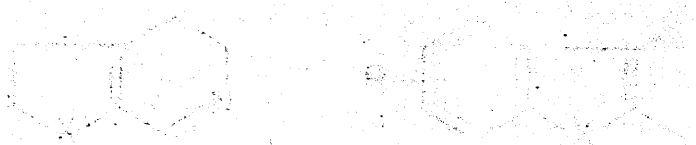
Section 2 describes a systematic study of the clathrate hosts, 4-p-hydroxyphenyl-2,2,4-trimethylchroman (Dianin's compound) and its sulphur analogue, compounds which are known to accommodate guest molecules in their approximately hour-glass shaped cavities. In an attempt to produce a new host with voids of markedly different geometry substitutions were made on the above thiachroman; introducing a methyl group para to sulphur led to a clathrate having a cage structure similar to that of the parent host while moving the methyl substituent meta to sulphur completely eliminated any inclusion behaviour. Most significantly, however, with an ortho methyl group one found a considerable alteration in crystal structure while still maintaining the ability to form stable clathrates. Ample demonstration of this change in cavity dimensions was provided by separately recrystallising the hosts from an equimolar mixture of cyclopentane, cyclohexane and cycloheptane, when it was found that the two new hosts showed a relatively increased tendency to include larger cycloalkanes. Introducing an

additional fused benzene ring and interfering with the hydrogen bonding were alterations which eliminated the clathrate-forming ability of the parent hosts.

An important extension to the use of clathrates has been made in the storage of materials which are difficult or hazardous to handle in their free state, this being highlighted by the formation of a stable crystalline adduct between 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman and dimethylmercury.

Section 1

Study of a Molecular Rearrangement.

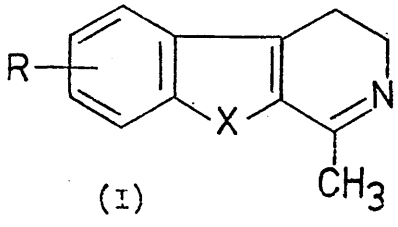


INTRODUCTION

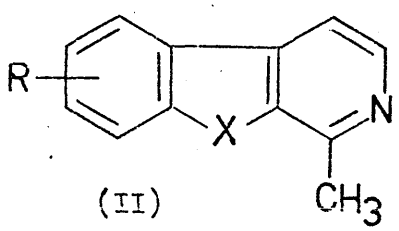
I. Interest in Benzo(b)thiophenes.

Although benzo(b)thiophene was first reported in 1893, it has received far less attention than thiophene; much of the early literature on this condensed thiophene is devoted to studies of 3-hydroxybenzo(b)thiophenes which are intermediates in the preparation of thioindigo dyes. The isosteric relationship between the latter and indigo was responsible for the rapid rise in their commercial importance after the announcement of the original synthesis by Freilander in 1906.

More recently this isosteric relationship between indole and benzo(b)thiophene has created considerable interest in the synthesis and pharmacological properties of benzo(b)thiophene analogues of biologically active indole derivatives; a recent review[1] by E. Campaigne *et al.* illustrates the broad spectrum of their biological activities. This group has directed much synthetic effort to the synthesis of sulphur isosteres of active indole derivatives. For example, since it was known that harmaline (Ia) and harmine (IIa) are active reversible inhibitors of monoamine oxidase, a series of



(I)

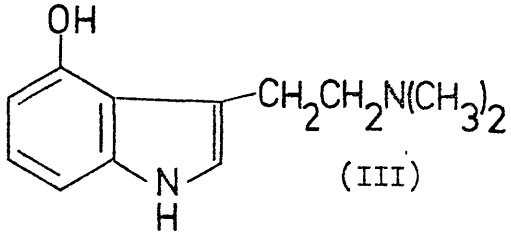


(II)

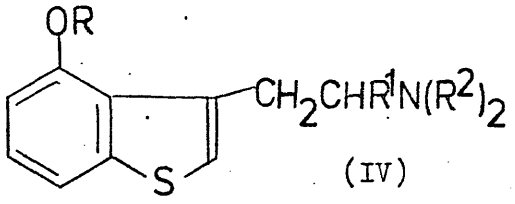
a; R = 7-OMe, X = NH
b; R = 7-OMe, X = S

sulphur analogues was prepared[2] and tested for pharmacological activity[3]; harmine and its benzo(b)thiophene analogue (IIb) were similar

in potency with respect to monoamine oxidase inhibition while sulphur substitution of the harmaline molecule led to a fiftyfold increase in potency. More recently Campaigne and Rogers have turned their attention to the sulphur isosteres of psilocybin and psilocin, two potent hallucinogenic substances isolated from certain mushrooms[4]; psilocin has been shown to have the structure (III)

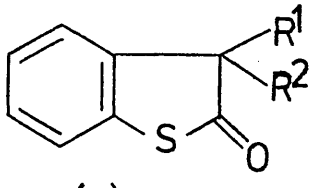


(III)

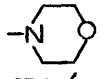


(IV)

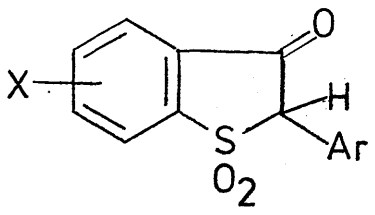
while psilocybin is the phosphate ester of (III). Along with the two sulphur isosteres were synthesised some O-methylated and N-demethylated derivatives; maximum pressor activity was observed with (IVa; R = Me, R^1 = Me, R^2 = H). Preliminary tests on the central nervous system activity of the two compounds (IVb; R = R^1 = H, R^2 = Me and IVc; R = R^1 = R^2 = H) have been carried out. Kikugawa and Ichino have evaluated numerous organic compounds including indoles and benzo(b)thiophens as platelet-aggregation inhibitors[5].



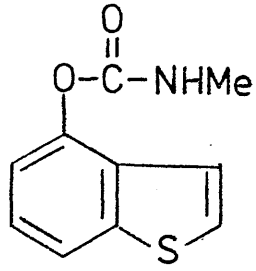
(V)

	R^1	R^2
a;	OH	
b;	OH	-NH-(p-CH_3)Ph
c;	OH	-NH-CH_2-CH_2-OH
d;	=CHC(O)Ph	
e;	=CHC(O)Me	

Derivatives (Va,b,d and e) but not (Vc) had strong inhibitory activity against both adenosine 5'-diphosphate and collagen-induced platelet aggregation. Already known for their anticoagulant and anti-inflammatory properties are 2-arylbenzo(b)thiophen-3(2H)-one 1,1 dioxides (VI)[6]. Hydroxybenzo(b)thiophenes have been used for the

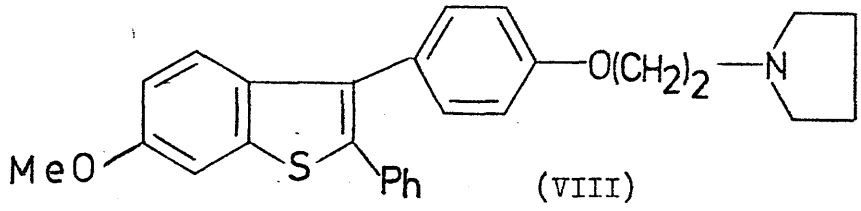


(VI)



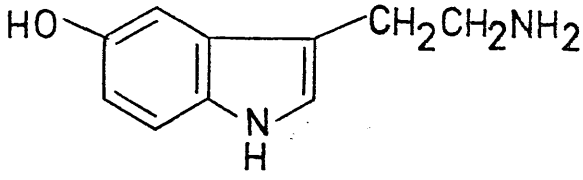
(VII)

synthesis of carbamates with insecticidal effects; one of them, mobam (VII), exhibits a favourable combination of insecticidal



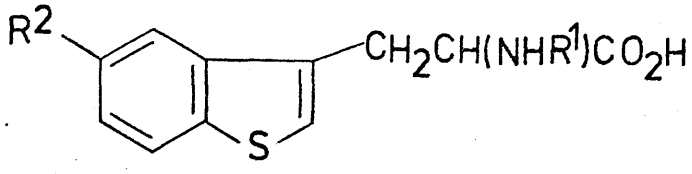
(VIII)

activity together with low mammalian toxicity[7]. Substituted diaryl derivatives of benzo(b)thiophene appear promising as antifertility agents, the highest activity being reported with (VIII)[8].



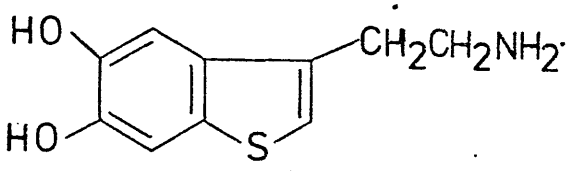
(IX)

Research with compounds related to the amino acid tryptophan has been extensive; in particular, substitution at position five has received considerable attention since 5-hydroxytryptophan has been shown to be transported across the blood-brain barrier as the precursor of 5-hydroxytryptamine (IX); the latter's presence in the brain has caused considerable speculation that it may be involved in mental disorders[9]. Chapman et al. have synthesised the benzo(b)thiophene isostere of tryptophan (X; R^1 = R^2 = H) and some 5-substituted derivatives (X; R^1 = H, R^2 = Me, Br, Cl or NO_2) in

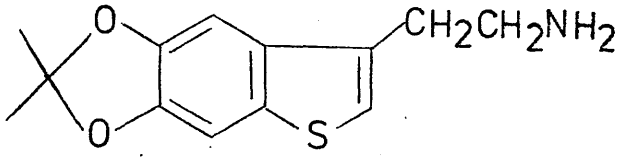


(X)

order to investigate how they affect the amount of 5-hydroxy-tryptamine in the brain[10]. The pharmacology of the latter has been compared with that of its benzo(b)thiophene, benzo(b)furan and indene isosteres[11], revealing that replacing the -NH in (IX) by O, S or CH_2 causes a significant decrease in potency. Knowing that 5,6-dihydroxytryptamine was a selective neurotoxin, Campaigne has synthesised its sulphur isostere[12] (XI) together with its isopropylidine derivative (XII). (XI) was found to have a marked



(XI)

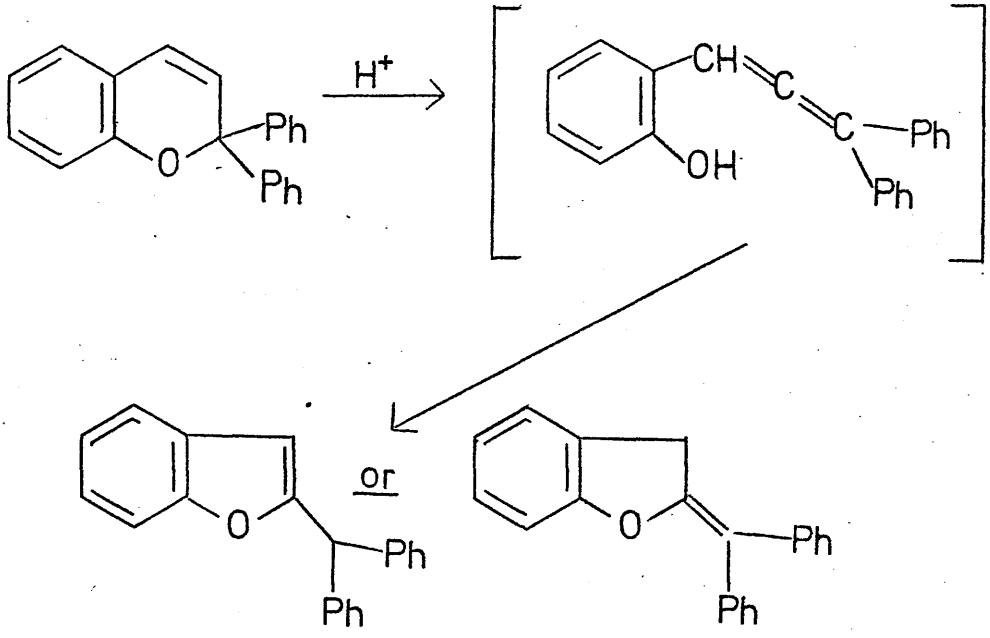


(XII)

effect on biogenic amine levels both centrally and peripherally while (XII) showed significant but opposite activity. Further synthetic work on tryptamine analogues[13] and related compounds has led Chapman to conclude that the benzo(b)thiophene nucleus is an effective carrier portion of these molecules[14]. These few systematic pharmacological studies of benzo(b)thiophene derivatives have uncovered potentially useful biological properties and it can, therefore, be anticipated that these initial leads will be further exploited in future.

II. Rearrangements Involving the Benzo(b)thiophene Nucleus.

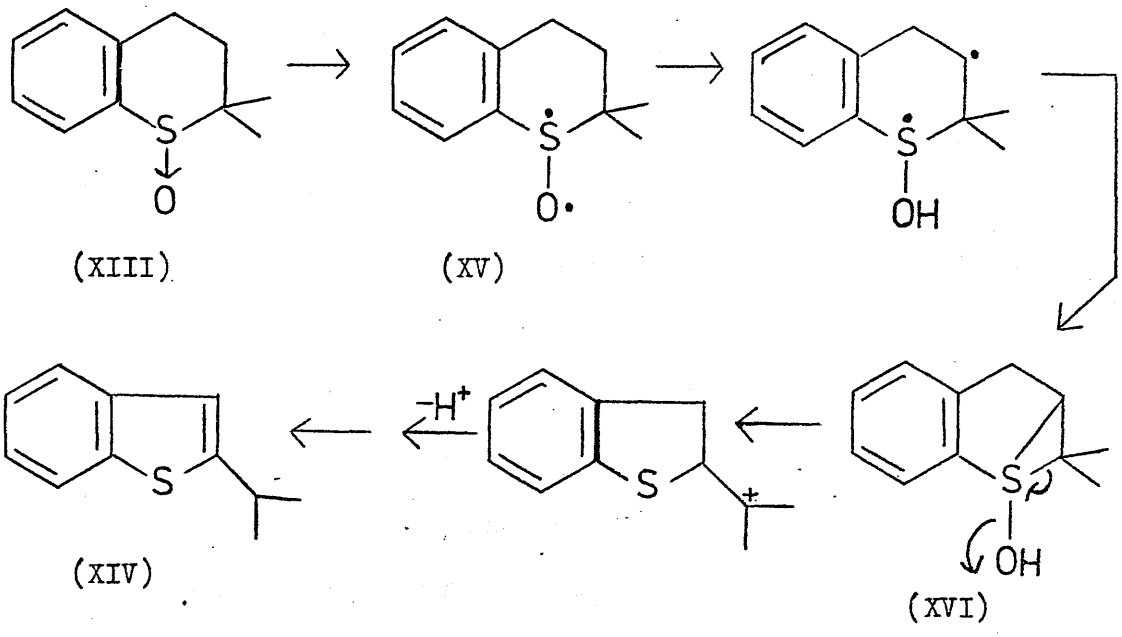
Several instances of the formation of the benzo(b)thiophene nucleus by a ring contraction process have been reported mainly during the last decade. Earlier work on chromenes by Lowenbein[15,16] has shown that 2,2-diphenylchromene isomerises in acetic acid to either a substituted benzofuran or an isomer with the carbon-carbon double bond exocyclic (Scheme 1).



Scheme 1.

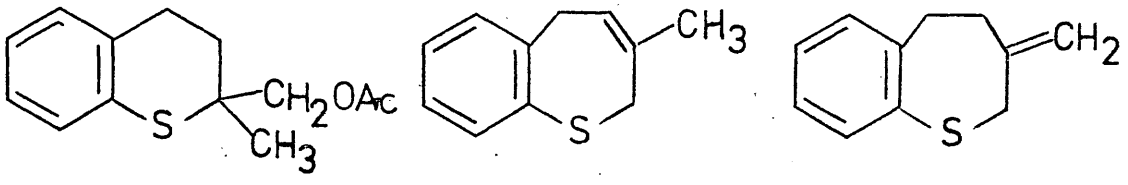
When considering rearrangements giving benzo(b)thiophene derivatives it is convenient to separate non-photochemical from photochemical reactions; many of the latter involve irradiation of sulphoxides, the first reported case being in 1966 when Archer and Kitchell irradiated a benzene solution of 2,2-dimethylthiachroman-1-oxide (XIII) and obtained 2-isopropylbenzo(b)thiophene (XIV) as the major product[17]. Following the photolysis by GLC allowed the detection of small amounts of the corresponding sulphide and sulphone, formed by disproportionation of the sulphoxide. The proposed mechanism for the rearrangement of (XIII) to (XIV) involves

initial excitation of the sulphoxide to the excited state species represented by (XV), followed by intramolecular hydrogen abstraction to give, after recombination of the radicals, the intermediate (XVI);



(XIII) (XV) (XIV) (XVI)

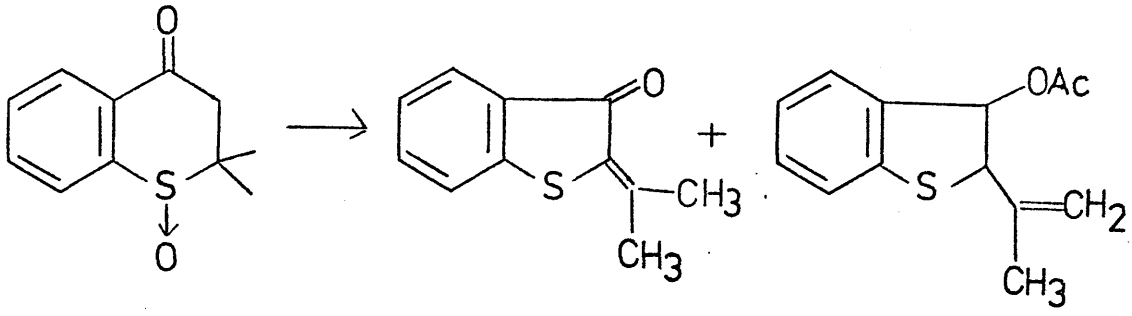
this undergoes decomposition to (XIV) as shown. The introduction of sensitizers led to a different array of products, suggesting that the rearrangement occurs by way of an excited state which differs from the excited state of the sensitized experiments. Refluxing (XIII) in acetic anhydride gives an 80% yield of (XVII)[18] but refluxing in xylene gives no reaction, showing that the presence of



(XVII) (XVIII) (XIX)

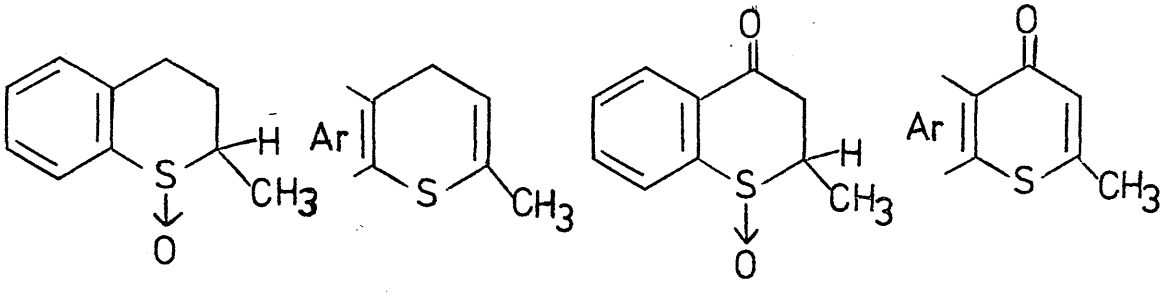
an electrophile is essential; the addition of small quantities of water to the acetic anhydride caused a decrease in the yield of (XVII)with concomitant formation of the olefinic compounds (XVIII) and (XIX) and the two products resulting from disproportionation.

Only disproportionation was observed when a little concentrated hydrochloric acid was added to the anhydride. The effect of introducing a carbonyl was studied by subjecting the ketosulphoxide



(XX) (XXI) (XXII)

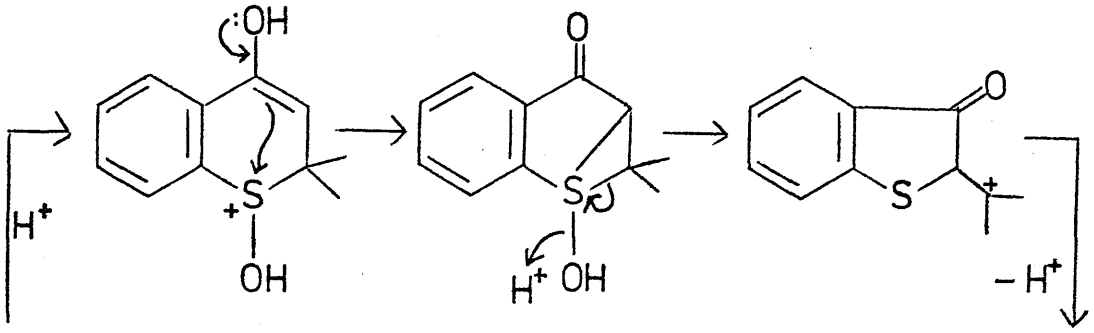
(XX) to similar conditions; only the ring contracted products (XXI) and (XXII) were formed and not those arising from oxidation of the methyl groups (the addition of acid again caused disproportionation). Sulphoxides, for example (XXIII) and (XXIV), which possess a hydrogen on the α-carbon and in which the carbon-sulphur bond is not subjected to steric constraint, give, on acetic



(XXIII) (XXV) (XXIV) (XXVI)

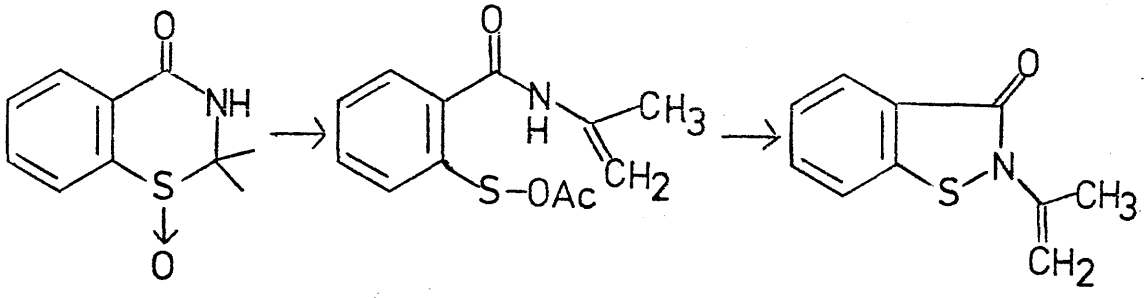
anhydride treatment, a Pummerer reaction; the products (XXV) and (XXVI) were obtained from (XXIII) and (XXIV) respectively in near quantitative yield. The authors suggest that reactions of (XIII) and (XX) can be described in terms of an elimination followed by addition of the sulphenyl derivative to the generated double bond; in the case of (XIII) the double bond will be formed by loss of a proton from one of the methyl substituents at the 2-position while (XX) will prefer to lose an activated proton from C_3.

Archer and Kitchell, however, suggest a mechanism whereby the above ring-contraction proceeds through an intermediate (XXVII)[17] analogous to (XVI) in the photochemical process. Morin and Spry



(XX) (XXVII) (XXI)

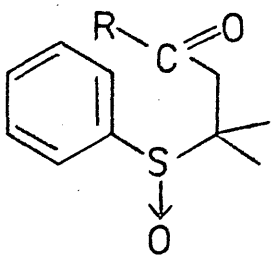
have extended the scope of the reaction by studying the action of acetic anhydride on nitrogen-containing cyclic sulphoxides[19] and, simultaneously, provide further evidence that formation of an intermediate sulphenic acid is involved. Treatment of (XXVIII) with Ac_2O containing 1% NaOAc under reflux gave a mixture of two



(XXVIII) (XXIX)

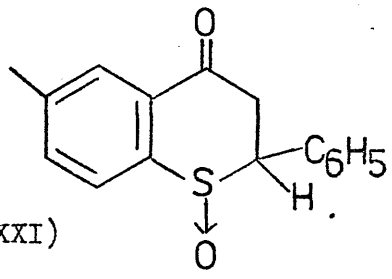
products, the major one being (XXIX), a transformation proceeding by an initial elimination to the intermediate as shown. In contrast with the dimethylthiachroman system the sulphenic acid moiety does not add to the generated double bond but is trapped by the neighbouring nitrogen atom forming a stable cyclic sulphenamide. If, however, the nitrogen is tertiary instead of secondary, this trapping is impossible and subsequent double bond addition occurs. Acyclic sulphoxides, (XXX, R = OH, OMe, or NH_2) give, as the only sulphur-containing product isolated, diphenyl disulphide formed

by the phenylsulphenic acid reacting with itself. These studies

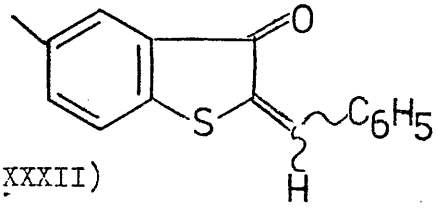


(XXX)

have prompted Still and Thomas[20] to report photochemical rearrangements of substituted thiachroman-4-one 1-oxides of which the 2-substituted derivatives (XX) and (XXXI) give as the sole identifiable products the ring-contracted products (XXI) and (XXXII) respectively; thus the conversion of (XX) into (XXI) has



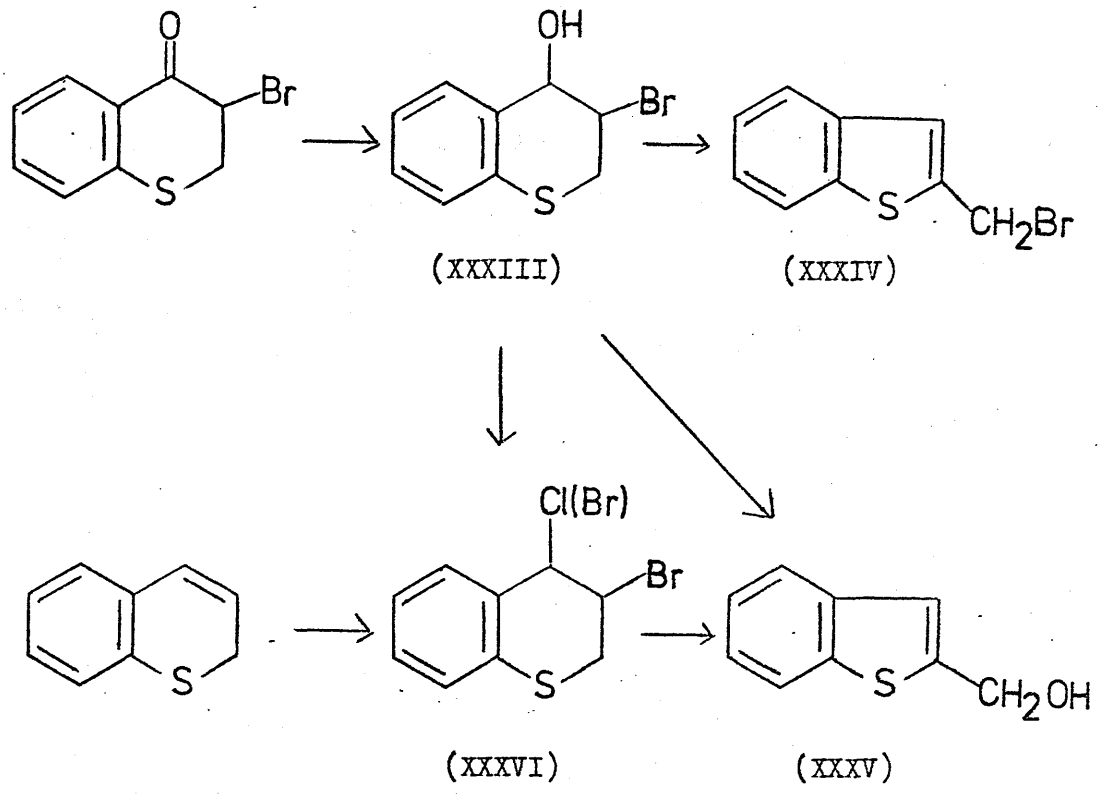
(XXXI)



(XXXII)

been achieved photochemically and non-photochemically. In contrast to 2-methylthiachroman-4-one 1-oxide (XXIV), which gave a Pummerer reaction on acetic anhydride treatment, 6-methyl-2-phenylthiachroman-4-one 1-oxide (XXXI) undergoes ring contraction on photolysis. The 3,3-dimethyl derivative gave three products, namely isobutyrophenone, 2-benzoylisobutyraldehyde and benzoic acid while 3-methyl-2-phenylthiachroman-4-one 1-oxide, the only compound bearing substituents at both the 2- and 3- positions, gave 1,1-dibenzoylethane as the only product in 35% yield. The above results lead one to conclude that an unsubstituted 3- position is necessary in order to obtain compounds with the benzo(b)thiophene nucleus.

This framework can also be obtained from 1-thiachromans by ring contraction as reported by Hofmann and Salbeck[21]; sodium borohydride or lithium aluminium hydride reduction of 3-bromo-1-thiachroman-4-one gives a high yield of the chromanol (XXXIII)

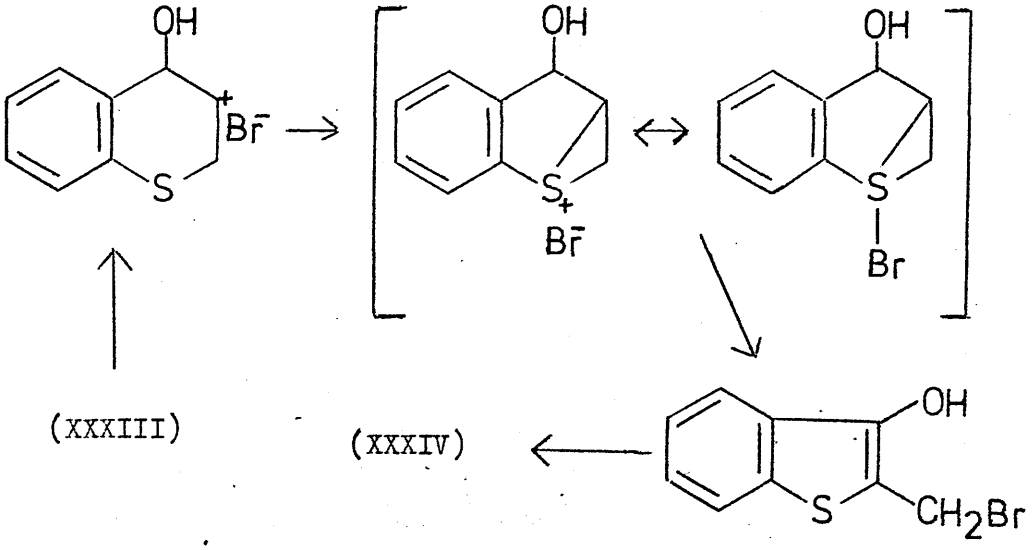


(XXXIII) (XXXIV)

(XXXVI) (XXXV)

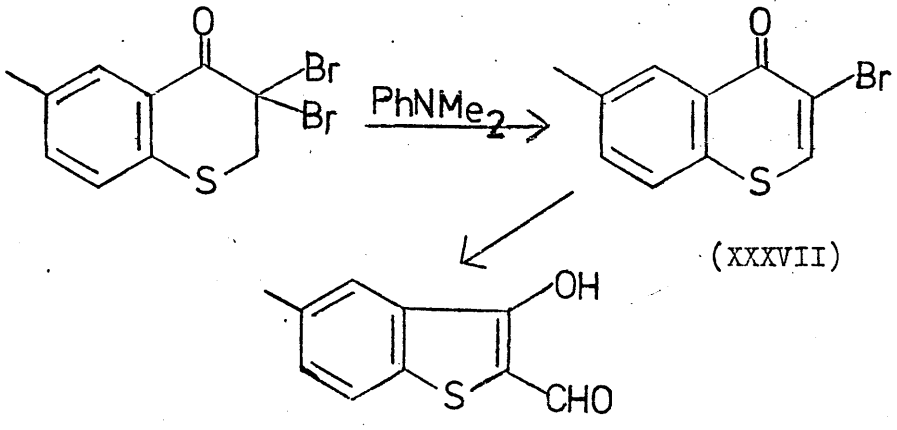
which, when refluxed in dioxane or distilled with potassium hydrogen sulphate at 0.1mm Hg, rearranges with loss of water to 2-bromomethylbenzo(b)thiophene (XXXIV). Using aqueous dioxane produces (2-benzo(b)thienyl)-methanol (XXXV). trans-3,4-Dihalogeno-1-thiachromans, which can be prepared from the chromanol or from the known 1-thia-2H-chromene, also form (XXXV) with loss of halogen hydride on heating in aqueous dioxane. 3-Bromo-2-methyl-1-thiachroman-4-ol likewise rearranges on heating in dioxane to 2-(α-bromoethyl) benzo(b)thiophene but in aqueous dioxane further elimination of hydrogen bromide occurs giving 2-vinylbenzo(b)thiophene. The authors cannot decide how the rearrangement is initiated but a carbonium ion at the 3-position once formed, will be stabilised by neighbouring group participation of the thioether group (Scheme 2). Support for the participation of an intermediate thiiranium ion comes from the observation that the acetate of (XXXIII) does not rearrange, the acetoxy group on C-4 evidently stabilising the carbonium ion on C-3; the same argument can be used to explain

the stability of the 3,3-dibromo- and 3-bromo-3-methyl-1-thia-4-chromanols. A related reaction has been known since 1925 when Krollpfeiffer[22] treated the thiachromone (XXXVII) with sodium ethoxide, giving in good yield, 2-formyl-3-hydroxy-5-methyl-

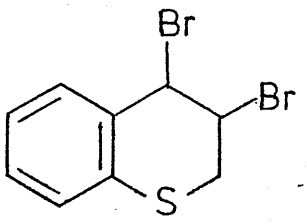


Scheme 2.

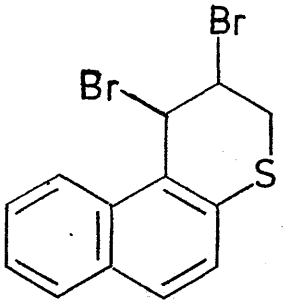
benzo(b)thiophene; replacing the 6-methylthiachromone with the 5,6-dibenzo derivative gave 2-formyl-3-hydroxynaphtho(2,1-b)thiophene under the same conditions. The mechanism of Hofmann and Salbeck can also be used to explain the ring-contraction which trans-3,4 dibromothiachroman (XXXVIII) undergoes on hydrolysis in aqueous acetone alone or containing an equimolar quantity of potassium hydroxide[23] with the formation of 2-hydroxymethyl



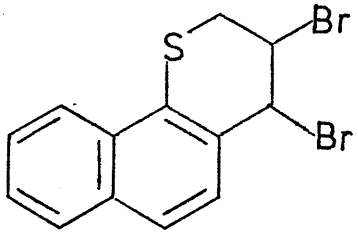
benzo(b)thiophene (XXXV). trans-1,2-Dibromo-2,3-dihydro-1H-naphtho (2,1-b)thiapyran (XXXIX) and trans-3,4-dibromo-3,4-dihydro-2H-naphtho(1,2-b)thiapyran (XL) also suffer this rearrangement on treatment with aqueous acetone giving 2-hydroxymethylnaphtho (2,1-b)thiophene and 2-hydroxymethylnaphtho(1,2-b)thiophene respectively. Ring contraction of (XXXVIII) and (XXXIX) is also



(XXXVIII)



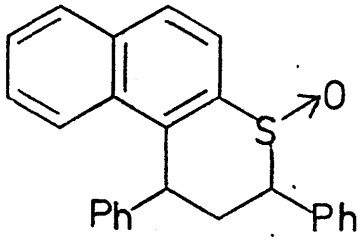
(XXXIX)



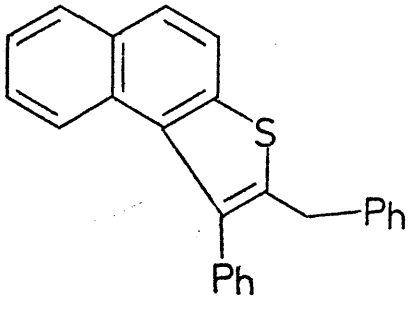
(XL)

accomplished in methanol giving the respective 2-hydroxymethyl derivatives.

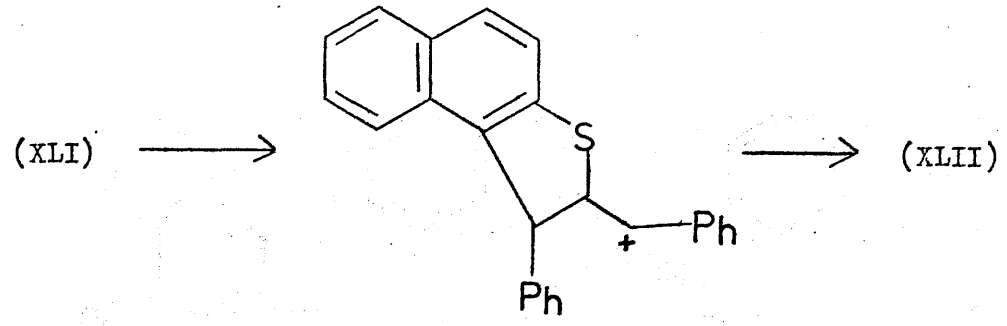
These extended ring systems have been the subject of a recent study by Schultz and Schlessinger[24], their results giving experimental backing to the mechanism proposed by Archer and Kitchell for the conversion of (XIII) to (XIV). Irradiation of a benzene solution of any isomer of the sulphoxide (XLI) resulted in the

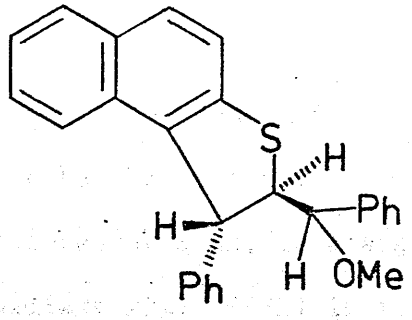


(XLI)



(XLII)

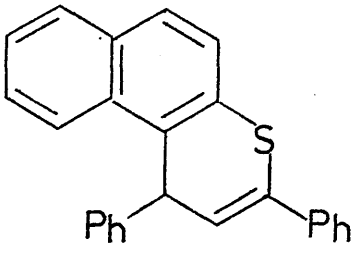




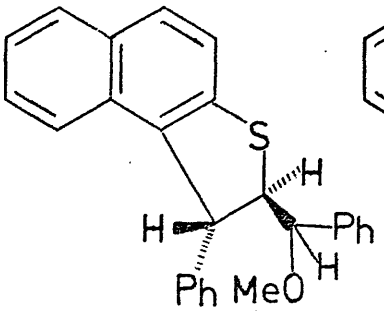
(XLIII)

formation of 2-benzyl-3-phenylnaphtho(2,1-b)thiophene (XLII), along with trace quantities of the corresponding sulphide and sulphone; the analogous mechanism invokes the intermediate shown, the presence of which was confirmed by irradiating the sulphoxide isomers in a nucleophilic solvent, namely benzene-methanol, resulting in the formation of a single methanol incorporated product (XLIII) plus small amounts of the above sulphide and sulphone. Further proof of the route came from deuterium labelling studies which showed that only the proton on the β-carbon was lost in the process (XLI) to (XLIII). It is possible that dehydration of the intermediate corresponding to (XXVII) could give the vinyl sulphide (XLIV), which in a second photochemical step might produce either (XLII) or (XLIII). This can be discounted since (XLIV) prepared

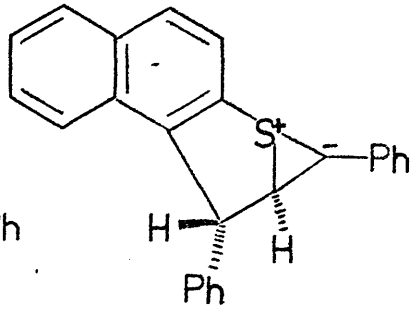
by the Pummerer reaction on the sulphoxide[25], produced neither the



(XLIV)



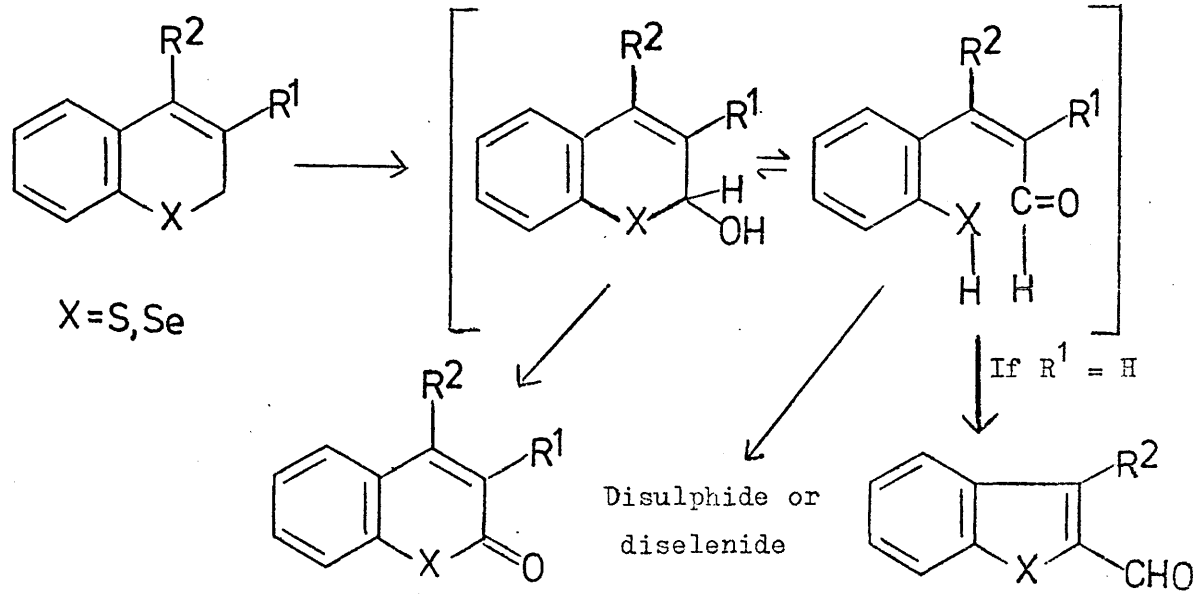
(XLV)



(XLVI)

thiophene when irradiated in benzene, nor the β-methoxysulphide (XLIII) when irradiated in benzene-methanol. The product in the latter case appears to be a diastereoisomer of (XLIII) and, following lengthy interconversions, is assigned the structure (XLV), for which the intermediate ylid (XLVI) is tentatively suggested by the authors.

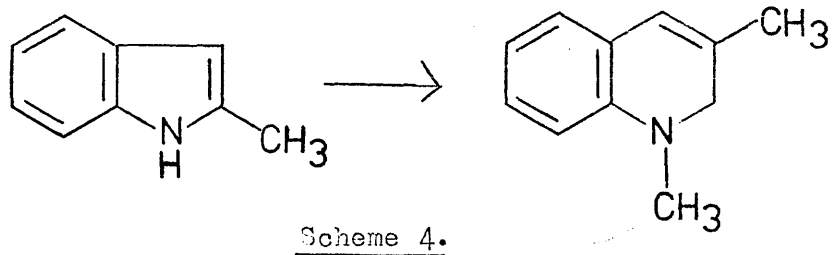
Less complex systems have been shown to rearrange during selective oxidation by selenium dioxide[26]; while attempting the preparation of coumarins from the corresponding chromenes, it was found that a selenachromene having a C-3 hydrogen gives, on treatment with this reagent in refluxing pyridine, an 80% yield of 2-formylbenzo(b)thiophene whereas the sulphur analogue gives



Scheme 3.

yields of this magnitude only if refluxing dimethylformamide is employed. The ease of formation of the 1-thia and 1-selena coumarins can be interpreted by supposing the reaction goes via a hemiacetal which will be in tautomeric equilibrium with the open chain aldehyde (Scheme 3); the proportion of the latter form is dependent not only on the temperature and on the environment but also on the heteroatom, the selenium derivative being easier to open than the sulphur. Further oxidation of the hemiacetal leads to the coumarins while the aldehyde can easily lead to a benzo(b)thiophene or benzo (b)selenophene when there is a removable hydrogen α to the carbonyl; prepared by this method were 2-formylbenzo(b)thiophene and its selenium analogue, along with 2-formyl-3-methylbenzo(b)selenophene and 2-formyl-3-phenyl-5-methylbenzo(b)selenophene. A ring contraction has been noted by Bellinger *et al.*[27] during the reduction of selenachroman-4-one when, as well as the expected selenachroman, there is formed 2,3-dihydro-2-methylbenzo(b)selenophene; the oxygen and sulphur isosteres do not give this rearrangement.

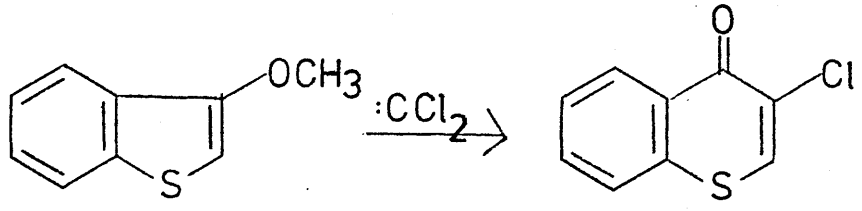
So far we have dealt with ring contractions, the opposite process being almost unknown in the chemistry of benzo(b)thiophene, unlike indole derivatives which ring expand to furnish quinolines, sometimes in excellent yield. For example Fischer and Steche[28] observed that, when 2-methylindole was heated with 2 equivalents of methyl iodide, 1,3-dimethyl-1,2-dihydroquinoline is formed in 80%



Scheme 4.

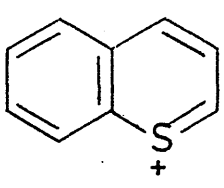
yield (Scheme 4); the ring enlargement is general but the reaction mechanism is not clearly understood. Ring expansion by the reaction with dichlorocarbene, of benzo(b)thiophene failed[29] but more

recently[30], 3-methoxybenzo(b)thiophene has been shown to react with this carbene, giving a fair yield of 3-chlorothiachromone

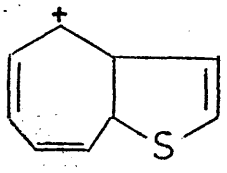


Scheme 5.

(Scheme 5). Enlargement of the benzene ring has been accomplished by Sullivan and Pettit[31] while attempting to prepare the benzthiapyrylium cation (XLVII) from benzo(b)thiophene; stable salts of



(XLVII)



(XLVIII)

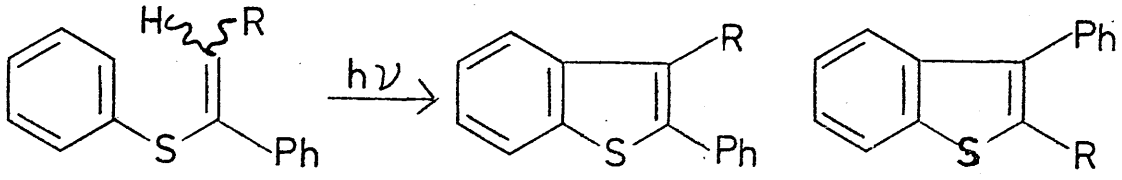
an organic cation are isolated but their properties do not correspond to those reported for (XLVII) and it has been shown that the compounds are in fact salts of the thienotropylium cation (XLVIII), an aromatic system isoelectronic with the benztropylium cation.

III. Preparation of Benzo(b)thiophenes.

A recent review[32] gives a comprehensive survey of the standard routes to benzo(b)thiophenes, most of which involve polyphosphoric acid promoted cyclisations, common starting materials being (arylthio)acetaldehyde dialkylacetals, (arylthio)acetones , aryl phenacyl sulphides and S-arylthioglycolic acids. It is to be noted that benzo(b)thiophenes are not formed in the phosphorous pentoxide treatment of thiachromanols, the sole product being

thiachromenes[33].

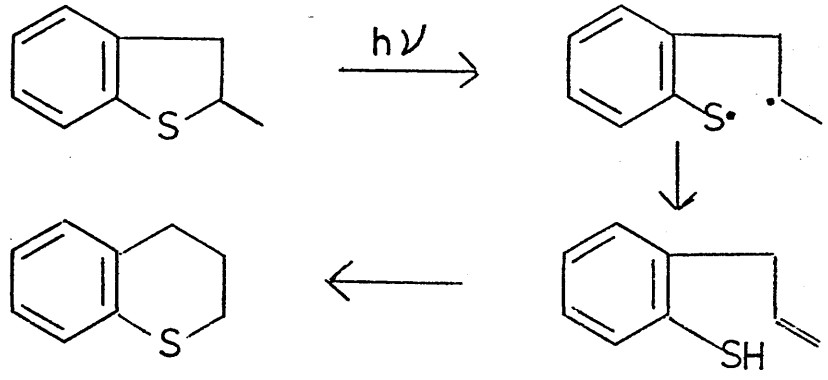
Less frequently, cyclisations to some benzo(b)thiophenes have been achieved photochemically, although the yields are generally much poorer. Additionally, one must guard against the possibility of groups migrating during the reaction thus leading to unexpected products. For example (XLIX; R = H) on photolysis gives both (L; R = H)



(XLIX) (L) (LI)

and the abnormal product (LI; R = H)[34]; an analogous product mixture was obtained from 1-phenyl-1-phenylthioprop-1-ene (XLIX, R = CH_3), whereas phenylthioethenes substituted in the α position with hydrogen or methyl gave only normal products.

Photolysis of a benzene or heptane solution of 2-methyldihydrobenzo(b)thiophene[35] gives thiachroman as the major product and



Scheme 6.

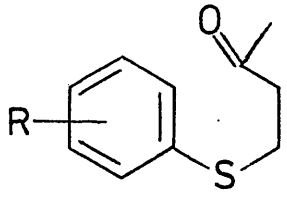
minor amounts of 2-methylbenzo(b)thiophene arising from disproportionation of the intermediate diradical (Scheme 6); furthermore dihydrobenzo(b)thiophene itself could be photolysed to benzo(b)thiophene, yields of up to 55% being obtained when the

reaction was carried out in solvents capable of producing radicals, for example CCl_4 or $CHCl_3$.

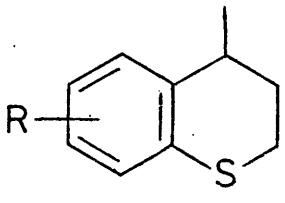
The addition of substituted thiophenols to acetylenedicarboxylic acid and its methyl ester has been used as a route to benzo(b) thiophenes[36]; the reaction is solvent dependent, for example in cold ethyl acetate both the acid and its ester added to thiophenol as well as its p-methyl and p-chloro derivatives, whereas no reaction took place in cold methanol while refluxing methanol gave a mixture of the desired product plus some vinyl sulphide intermediate.

IV. The Work of B.D. Tilak.

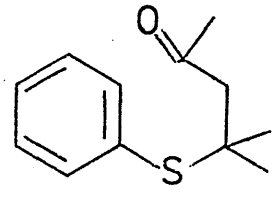
Of particular relevance to the rearrangement reaction to be described later is the work on sulphur heterocycles by Tilak's group. In a proposed synthesis of 4-methylthiachromans[37] a series of arylketo-sulphides (LII), prepared by piperidine-assisted Michael addition of aromatic thiols to methyl vinyl ketone, were cyclised with polyphosphoric acid (PPA), the expected thiachromenes then being catalytically reduced to the desired products. However,



(LII)



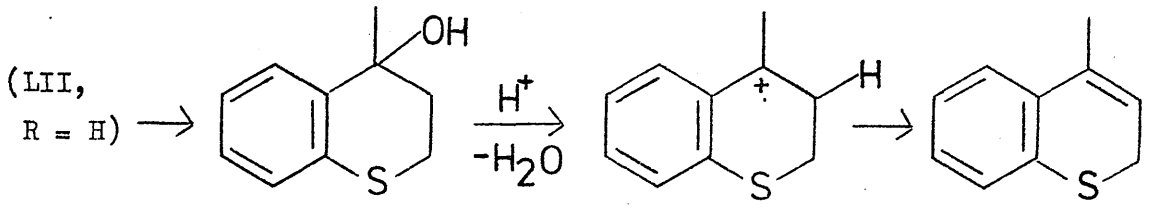
(LIII)



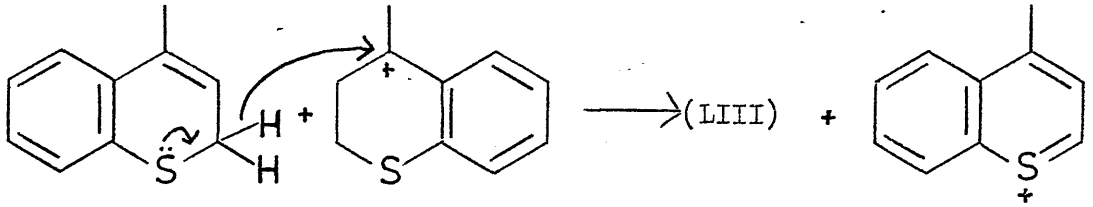
(LVI)

PPA treatment always gave directly a fair yield of the thiachromans (LIII; R = H, 6-, 7-, 8-Me, 6-, 7-, 8-OMe, or 6-Cl) together with benzthiapyrylium salts (LV). Since the reaction with PPA at 90°C of

the corresponding thiachromanols and thiachromenes, synthesised by an alternative route, gave the thiachromans, it was proposed that the cyclodehydration of the keto-sulphides proceeded through the thiachromanols and thiachromenes on the way to the thiachromans.



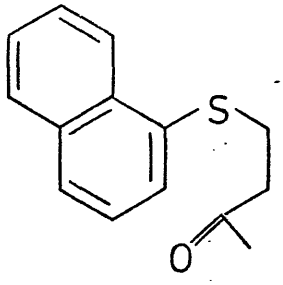
(LIV)



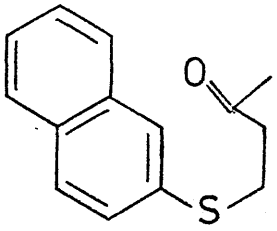
(LV)

To explain these facts a mechanism was proposed in which an essential step is the intermolecular hydride shift from the 2-carbon atom of one molecule of the thiachromene to the 4-carbonium ion position of another molecule which has been protonated. Similarly the reactions with 2,4-dimethylthiachromanol and 2,4-dimethyl thiachromene gave 2,4-dimethylthiachroman, but with (LVI) only the thiachromene, (a compound incapable of undergoing disproportionation) is produced, thus supporting the idea that hydride transfer from the 2-position is involved. Also, one should obtain a deuterium replacement of one of the protons at C-3 of (LIII; R = H) when the reaction is conducted in deuterated PPA, this being substantiated by Vaidya's nuclear magnetic resonance study[38] of Tilak's products. However, the spectrum of the product obtained from PPA treatment of 2,4-dimethylthiachromanol is unsatisfactory for the structure proposed while no data appears for the thiachromene supposedly produced during the PPA cyclisation of (LVI). Later work by

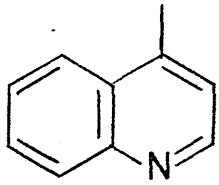
Tilak[39] makes no mention of n.m.r. and relies on ultraviolet absorption as the sole spectroscopic tool for product identification; considerable effort was devoted to investigation of the dyes obtained from the benzthiapyrylium salts formed simultaneously with the thiachromans but, nevertheless, several valuable extensions were made in the scope of the original reaction. A greatly increased number of ketosulphides substituted in the benzene ring were found to give the appropriate thiachromans on PPA treatment, while (LVII)



(LVII)



(LVIII)

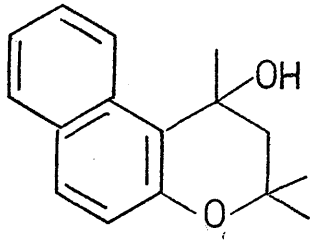


(LIX)

and (LVIII) gave 4-methyl-7,8-benzothiachroman and 4-methyl-5,6-benzothiachroman respectively.

Muljiani, Tilak's colleague, observed a similar disproportionation when the dehydration of 4-methylchroman-4-ol with PPA gave only 4-methylchroman - however, the use of anhydrous copper sulphate produced the expected 4-methylchrom-3-ene[37]. Tilak went on to demonstrate an analogous series of reactions with nitrogen heterocycles[40], methyl 2-phenylaminoethyl ketone giving lepidine (LIX) and 1,2,3,4-tetrahydrolepidine in nearly equal proportions as well as traces of 1,2-dihydrolepidine. Further work on the oxygen series[41] considered the perchloric acid catalysed disproportionation of a 3,4-disubstituted chromene, where cis/trans isomerism in the resulting chroman would occur depending on which side of the planar carbonium ion hydride addition occurred; in the instance of 3,4-dimethylchrom-3-ene the intermolecular hydride transfer was found to be non-stereospecific, a 50:50 mixture of cis- and trans-

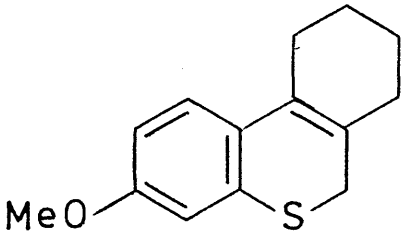
3,4-dimethylchroman being obtained. Again, when hydride transfer is impossible, only one product is formed, for example (LX) with



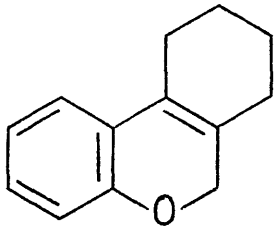
(LX)

perchloric acid gave only 2,2,4-trimethylnaphtho(2,1-b)pyran.

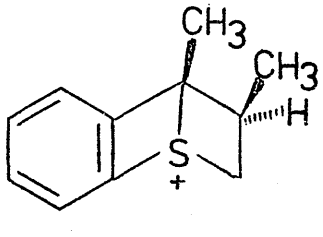
In contrast stereoselectivity is encountered in the sulphur series[42], for example perchloric acid treatment of 3,4-dimethyl-thiachrom-3-ene gives 85% cis- and 15% trans- isomer of the appropriate thiachroman; with tricyclic compounds the situation is more complicated because of the further steric effects imposed due to the greater rigidity of the tricyclic system, for example (LXI) gave 77% of the ring B/C cis-isomer of the thiachroman compared with 65% of the ring B/C cis-isomer of the chroman from



(LXI)



(LXII)



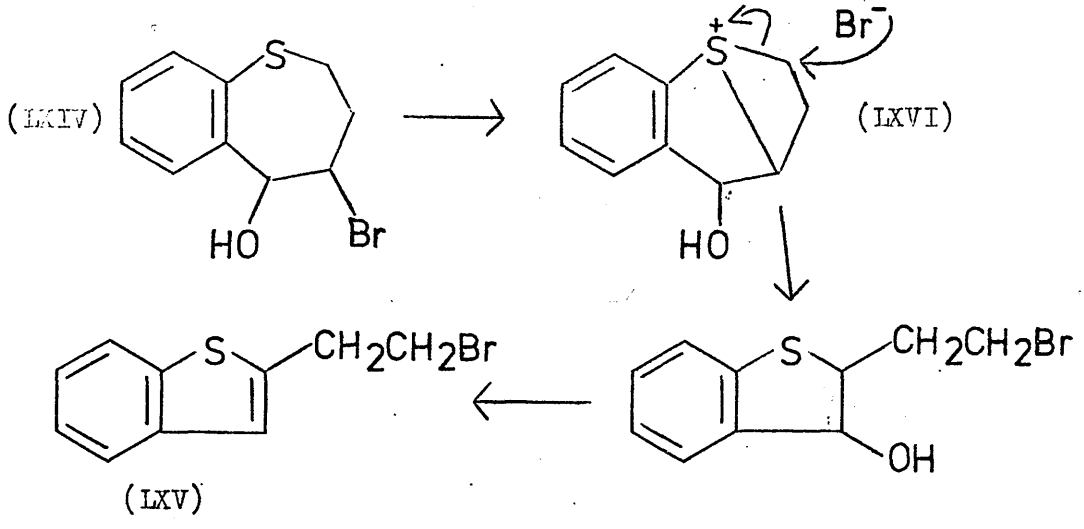
(LXIII)

(LXII). In view of the fact that in the oxygen series 3,4-dimethyl-chroman is formed as only an equal mixture of cis/trans isomers, it appears that the substituents at C-3 and C-4 of such systems are not the only stereochemically controlling factors for hydride transfer. Rather, some other mechanism appears to be operating in the sulphur series; a possibility is sulphur atom participation in the carbonium ion formed by protonation of the thiachromenes to give an intermediate sulphonium ion (LXIII). Protonation at C-3

from one face of the molecule, say α, would occur simultaneously with overlap, on the opposite face, of the sulphur lone pair with the p-orbital of C-4. This would lead to the stereochemistry of the sulphonium ion (LXIII) in which the two methyl groups are cis to each other. Subsequent hydride attack would then take place at C-4 from the side opposite to the newly formed C - S bridge, leading to a thiachroman in which the methyl groups are predominantly cis; the stereochemistry of the final product is governed primarily by the stereochemistry of protonation of the thiachromene.

Note added in proof.

Chatterjee and Sen.[68] have reported the formation of a benzo-(b)thiophene derivative by ring contraction of a benzo(b)thiepin;

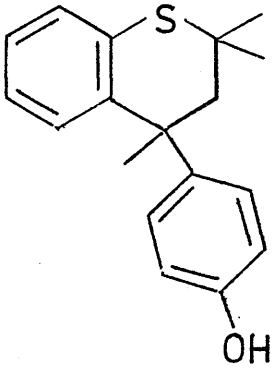


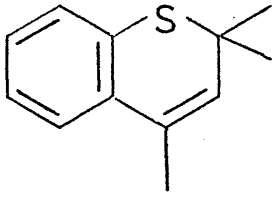
(LXV)

the cis-bromohydrin (LXIV), when refluxed in dioxane for 15 hours or treated with $KHSO_4$ under vacuum, gave (LXV) in near quantitative yield. The authors invoke the intermediate (LXVI) in a mechanism analogous to that of Hofmann and Salbeck[21].

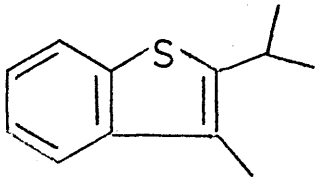
RESULTS AND DISCUSSION

In connection with our clathrate studies we wished to add phenol to 2,2,4-trimethylthiachromene (7) as a route to the clathrate host material 4-p-hydroxyphenyl-2,2,4-trimethyl-thiachroman. On attempting Tilak's preparation[39] of (7) we obtained,





(7)

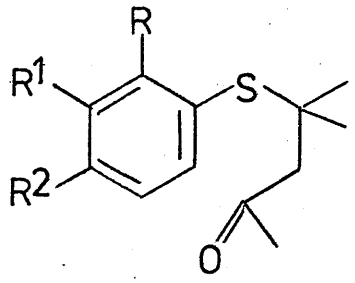


(13)

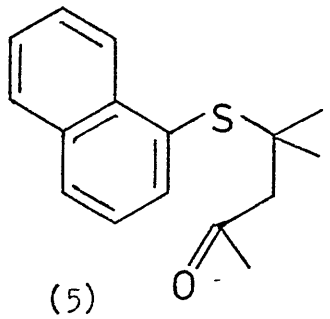
instead of the sole reported product, a mixture which proved difficult to separate and, consequently, a different approach to the clathrate was employed. Subsequent investigation of the above product array led to the identification of the substituted benzo(b)thiophene (13), the presence of which suggested a novel ring contraction process and a possible new route to benzo(b)-thiophene derivatives. There then followed a study to illustrate the generality of the reaction and to ascertain the effect of varying certain parameters such as temperature.

I. Preparation and Reaction of Ketosulphides with Polyphosphoric Acid.

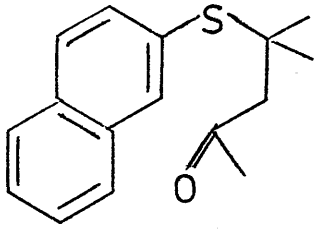
A series of ketosulphides (1)-(6) were readily prepared by piperidine-catalysed Michael addition of the appropriate aryl mercaptan to mesityl oxide - all the thiols were commercially available and required only distillation or recrystallisation before use; since the ketone was in excess the progress of the reaction



(1); R = R^1 = R^2 = H
(2); R = Me, R^1 = R^2 = H
(3); R = R^2 = H, R^1 = Me
(4); R = R^1 = H, R^2 = Me



(5)

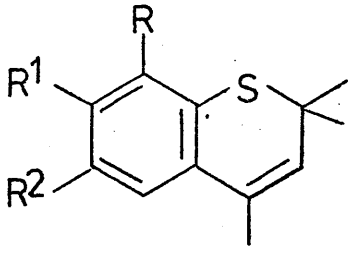


(6)

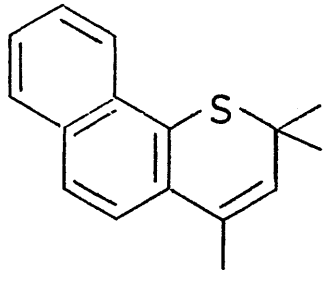
could be conveniently followed by withdrawing reaction samples and monitoring, by n.m.r. or i.r., the disappearance of the thiol. The keto-sulphides, purified by distillation, all gave satisfactory elemental analyses and their spectral characteristics were consistent with their various structures (see experimental section). When it came to cyclising these compounds with polyphosphoric acid (PPA), a few trial runs soon showed the necessity to standardise the conditions as far as possible; because of the varying qualities of commercial PPA, the decision was taken to use only freshly prepared samples, synthesised by heating phosphorous pentoxide with orthophosphoric acid at 150°C for 1 hour, and furthermore, in view of its extremely hygroscopic nature, to take strict precautions against the entry of water vapour, for example, a mercury sealed stirrer was employed and evaporation from the water bath was minimised by a surface layer of molten paraffin wax.

The keto-sulphides (1)-(6) were each added in one lot to the PPA at room temperature, and the reaction vessel placed in the pre-heated water bath at 99(±1)°C. Having been stirred mechanically for three hours the reaction mixtures were allowed to regain room

temperature before being poured into iced water and extracted with ether. Following base and water washing, the solvent was evaporated leaving brown oils which were vacuum distilled; generally a distillation was required initially to separate most of the high boiling polymeric material, a characteristic of all PPA-catalysed cyclisations, while on subsequent distillations fractionation of the several components was attempted. Preliminary n.m.r. studies of the fractions soon revealed that none of the keto-sulphides had undergone clean cyclisation and so, in addition to the expected 2H-thiachromenes (7)-(12), there was formed as the other major



(7); R = R^1 = R^2 = H
(8); R = Me, R^1 = R^2 = H
(9); R = R^2 = H, R^1 = Me
(10); R = R^1 = H, R^2 = Me



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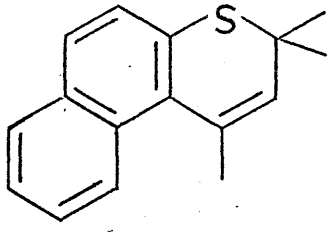
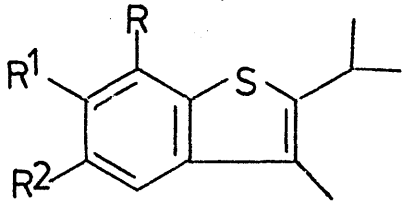
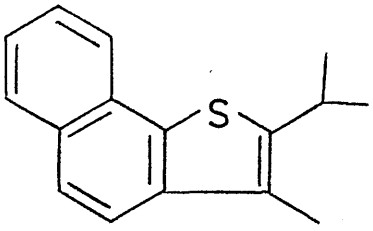


(12)

volatile products the condensed thiophenes (13)-(18); also in a



(13); R = R^1 = R^2 = H
(14); R = Me, R^1 = R^2 = H
(15); R = R^2 = H, R^1 = Me
(16); R = R^1 = H, R^2 = Me



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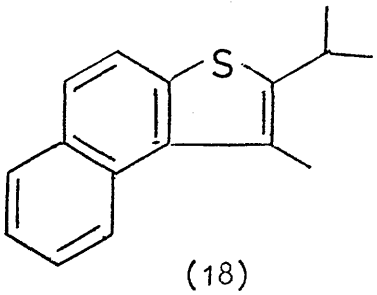
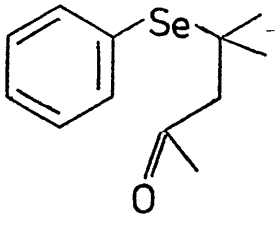


(18)

few cases significant quantities of a third component were observed and later identified as the 4H-thiachromenes. Table 1 gives the relative percentages of the major products from PPA treatment of keto-sulphides (1)-(6) as estimated (±)10%) from integration of 60MHz or 100MHz ^{1}H n.m.r. spectra - in all cases other minor products were detected.

In an attempt to futher extend the scope of the reaction two compounds, in addition to those previously mentioned, were reacted with PPA in the standard way, namely the ketoselenide (21) and the ketosulphide (22), the latter prepared by condensing thiophenol



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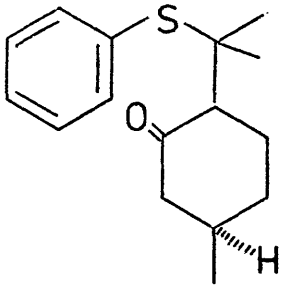

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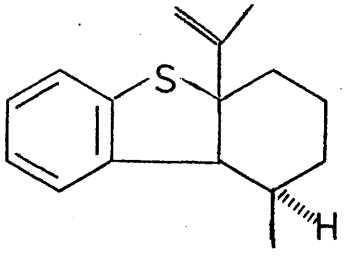


(23)

with (+)pulegone. The product from (21) was mainly polymeric, but its ^{1}H n.m.r. spectrum contained a peak in the olefinic region at 4.51τ and a doublet, J = 1.5 Hz, at 7.90τ, indicating that at least a little cyclisation to a selenachromene had occurred. Dropping the reaction temperature by 25°C, in the hope of avoiding polymer formation, was unsuccessful with neither cyclisation showing any benzo(b)selenophene detectable by ^{1}H n.m.r. Interest in (22) arises from the observation that simple ring closure would produce a

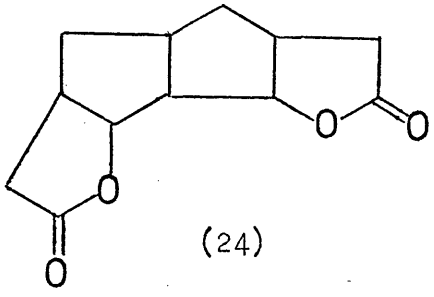
Table 1. Relative percentages of major products from PPA treatment of ketosulphides (1) - (6).

Compound Number.	Material recovered (%).	2H-thiachromene.	4H-thiachromene.	ring-contracted product.
1	23	15	15	70
2	22	60	(a)	40
3	29	60	5	35
4	24	40	30	30
5	33	95	(a)	5
6	38	20	(a)	80

(a) : present in, at most, trace quantities (< ca 5%).

tricyclic structure with the newly-formed double bond at the ring junction, while a possible course of ring contraction would require proton loss from one of the gem-dimethyls to give (23). The usual reaction conditions and work up yielded a brown oil, the distillation of which gave two distinct fractions; ^{1}H n.m.r. of the lower boiling component, although revealing an olefinic proton at 4.15τ, was very low on aromatic resonances, thus eliminating (23). The later fraction showed only aromatic peaks and a plethora of signals in the region 7.6 - 9.1τ, which could arise only from polymeric material. Under these conditions, the ketosulphide has presumably undergone a retro-reaction to produce an isomer of pulegone with the carbon-carbon double bond in a different position in order to account for the olefinic resonance.

While these studies were in progress, Eaton and Mueller[43] described the conversion of (24) to the bis-enone (25), brought about by heating (24) with fifty times its weight of PPA at 75°C for five days; the authors' opinion of PPA as "an exasperating reagent, impossible to handle efficiently or stir effectively"



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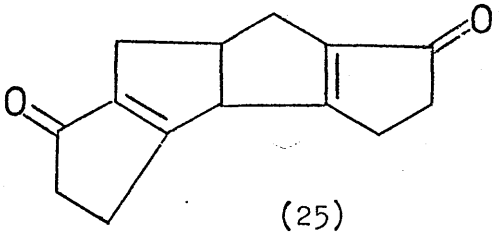


(25)

was in part responsible for their attempt to discover a new, easily-manipulated cyclisation medium. This was found in trifluoromethanesulphonic acid containing 5 wt.% of phosphorous pentoxide, a combination which achieves the same yield of (25) in only 2 days at room temperature. Further work in the same laboratory has shown that a still superior reagent is a solution of 5 - 10 wt.% of P_2O_5 in ordinary methanesulphonic acid. In trying to determine whether a specific cyclisation agent is essential for the rearrangement

being considered here, the ketosulphide (1) was heated with this novel mixture under the same conditions as before; ^{1}H n.m.r. of the gum obtained on work-up revealed the formation of 2,2,4-trimethyl-2H-thiachromene, but neither the 4H- isomer or the ring-contracted product appeared to have been formed. Similarly, a sample of (1) saturated with dry gaseous HCl and left in a stoppered flask for a considerable length of time (ca. 18 months) became a red viscous liquid, which on work-up and distillation, yielded impure 2H-thiachromene, no other isomers being observed. Thus it would appear that the ring-contraction occurs only when PPA is the reagent employed, at least under the conditions tried.

II. Separation of the Products from PPA Treatment of Ketosulphides (1)-(6).

Repeated vacuum distillations of the products achieved some degree of separation with the thiachromenes being the major component of the early fractions while the benzo(b)thiophenes predominated as the temperature was increased, the late fractions tending to be contaminated by some low-boiling polymeric material; the small scale of the distillation precluded the use of a spinning-band column. Thin layer chromatography in numerous solvent systems was of no assistance in the attempted separation of the products with only a single spot (Rf $\sim$0.8 in $CHCl_3$) being observed. Since it is known that most sulphides give crystalline complexes with mercuric chloride, it was hoped that the dropwise addition of an alcoholic solution of the mixture to a saturated alcoholic mercuric chloride solution would preferentially precipitate one of the components as its complex from which the pure compound could be regenerated by treatment with base; unfortunately no precipitation occurred. Lack of success also arose in an attempt to selectively enclathrate

one component in thiourea. Although preparative scale G.L.C. was unfruitful, separation on an analytical scale was achieved with a 6ft. column of 1% OV-17; the G.L.C. trace (Figure 1) of fraction one of the distillate of the product obtained from PPA treatment of ketosulphide (1) reveals the presence of the two isomeric thiachromenes with similar retention times, together with a later peak, subsequently assigned to the benzo(b)thiophene (13).

It was thought that the separation problem might be got round by altering the reaction conditions, for example, changing the cyclisation temperature may result in the formation of only one product; this met with limited success in that a temperature rise of 25°C produced a higher proportion of the ring-contracted product but the overall recovery of volatile material was decreased with the concomitant formation of larger quantites of polymeric material - conversely, lowering the temperature to 90°C led to an increased yield of the 2H-thiachromene. The G.L.C. trace (Figure 2) of the corresponding 90°C product fraction illustrates the higher proportion of the 2H-thiachromene compared with the 4H-isomer and the benzo(b)-thiophene. Lengthening the reaction time produces only a negligible difference in the product ratios, with a slight decrease in the overall recovery. Compound (3), as a representative ketosulphide, was subjected to the same reaction conditions except that the time was doubled to six hours; the proportion of 2,2,4,7-tetramethyl-2H-thiachromene formed remained constant while that of the 4H- isomer fell marginally, a balancing slight increase being noted for the ring-contracted product.

The early abhortive separations led us to consider less conventional separation procedures and attention was turned to liquid-gel chromatography, a technique now experiencing widespread acceptance in contrast to its early limitation to biological systems. The stationary phase for this type of chromatography

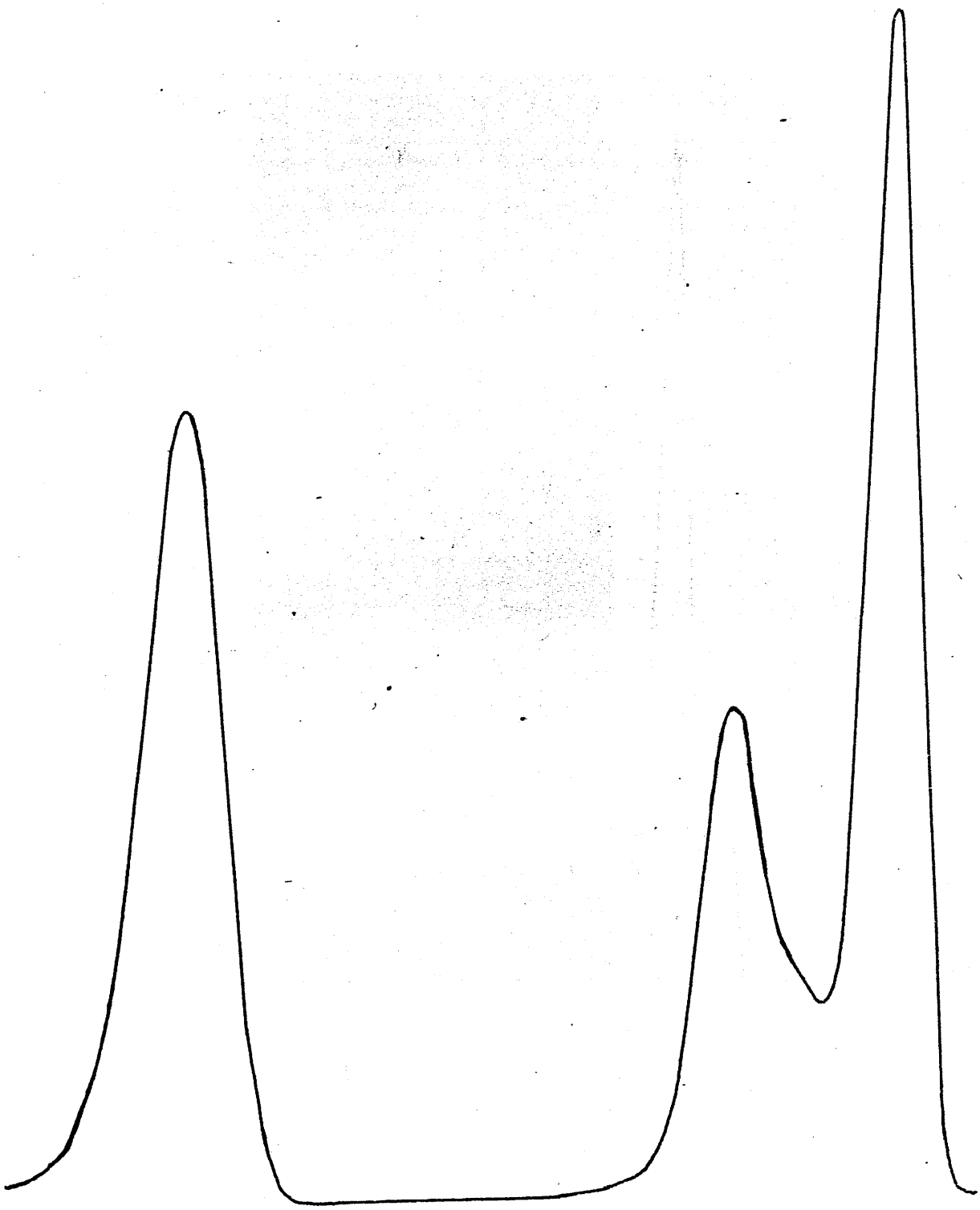


Figure 1. G.L.C. trace of fraction one of the distillate of the product obtained from PPA treatment at 100°C of the ketosulphide (1). Conditions :- 6 ft column 1% OV-17, temperature 100°C.

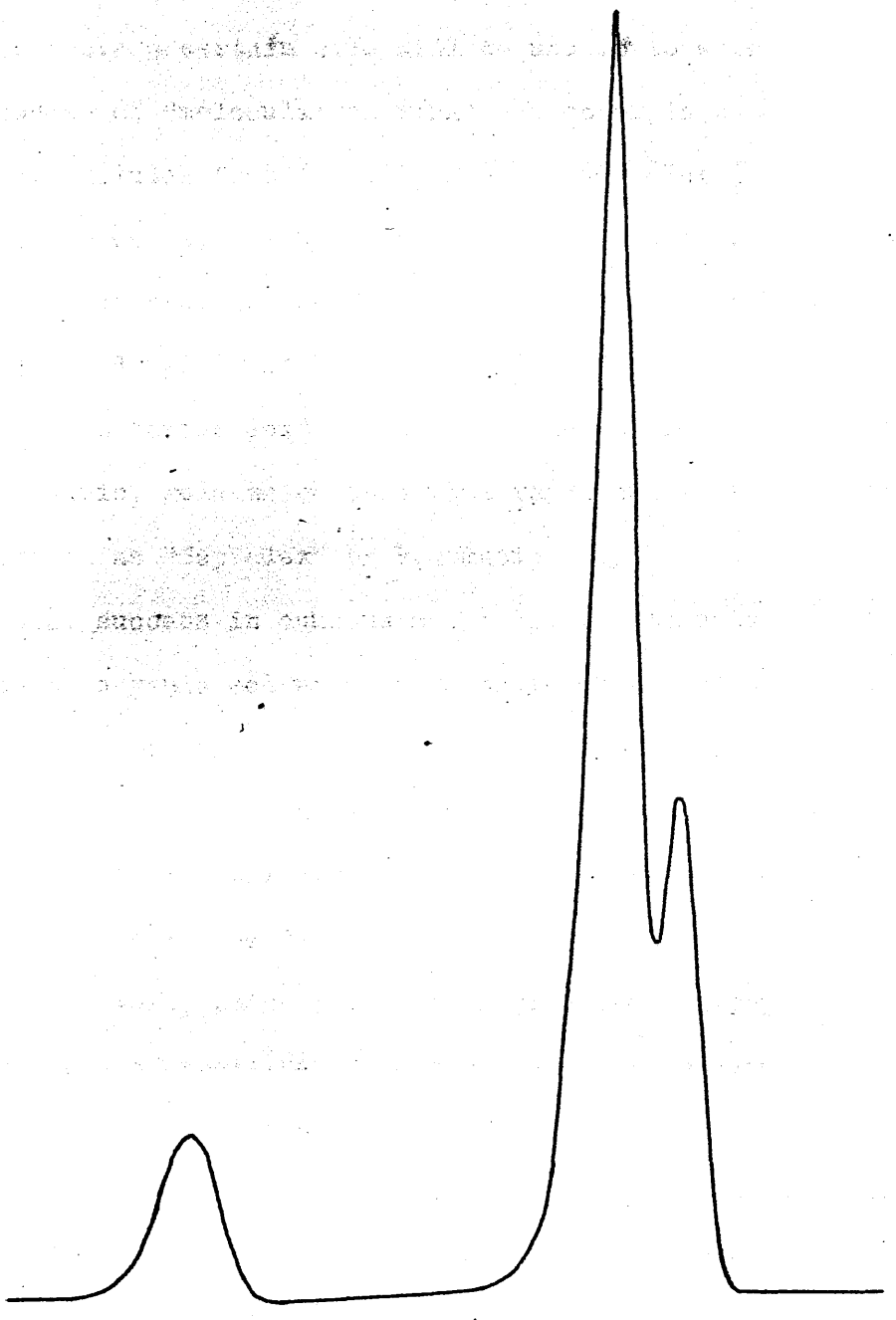


Figure 2. G.L.C. trace of fraction one of the distillate of the product obtained from PPA treatment at 90°C of the ketosulphide (1). Conditions:- 6 ft column 1% OV-17, temperature 100°C.

is formed by the incorporation of solvent into particles of polymeric substances possessing a cross-linked structure; depending on the nature of the polymer and the degree of crosslinking, molecules above a certain size will be unable to enter the gel, and a process of "molecular sieving" can occur, in which large molecules, excluded from the gel, are rapidly eluted, in contrast with small molecules which can diffuse into the gel. The first significant advances in the field of gel chromatography concentrated on the development by Porath and Flodin[44] of systems based on the polysaccharide dextran, cross-linked by reaction with epichlorohydrin, gels which underwent rapid commercial development when marketed as "Sephadex" by Pharmacia.

Initial success in aqueous media led to attempts to extend their use to organic solvents where they were found to be unsuitable on account of their inability to swell under conditions of low polarity. To overcome this limitation one approach adopted the substitution of the free hydroxyl groups of the Sephadex products in an attempt to reduce the polarity of the gel matrix; Flodin reported that acetylation of Sephadex produced a lipophilic derivative, capable of swelling in solvents such as toluene and chloroform but later, it was realised that ether derivatives were preferable to esters since the former are less labile to hydrolysis. Pharmacia developed the β-hydroxypropyl ether of Sephadex, and this is now available commercially as "Sephadex LH-20"; as well as exhibiting the standard molecular sieving process, this gel presents a number of interesting gel-solute interactions which allow molecules of approximately the same size to be separated on the basis of their differing affinities for the gel. The latter mechanism proves attractive to organic chemists whose molecules show less variation in size, whereas gel filtration is highly effective for the analysis of polymer preparations, an area where

the requirement is not high selectivity but rather a system capable of handling a wide range of molecular weights.

With gel chromatography in organic solvents, the variability of polarity of both eluant and gel matrix is superimposed on the molecular sieving effect and three areas may be distinguished[45]:-

1). Straight-phase partition, where the gel is more polar than the solvent, and compounds are eluted in order of their (increasing) polarity;

2). Gel filtration, where the gel and solvent have the same polarity characteristics and elution is in order of decreasing molecular size of the solutes;

3). Reversed-phase partition, where the gel is less polar than the solvent, and compounds are eluted in inverse order of their polarity.

The application of reversed-phase chromatography was hindered by the lack of generally useful stationary phases but, in an attempt to overcome this restriction, Ellingboe and Nystrom[46,47] developed the lipophilic-hydrophobic hydroxyalkoxypropyl derivative of Sephadex LH-20 by treating the commercial gel with NEDOX 1114, a saturated long chain olefin oxide containing 11-14 carbon atoms; this modified gel can be used both for straight-phase (for example with benzene as solvent) and reversed-phase (for example with methanol as solvent) chromatography, due to the simultaneous presence of hydroxyl groups and long alkyl chains-if the polarity of this gel and the solvent are matched, effects due to molecular sieving can be demonstrated. Variation in the solvent system and in the degree of gel substitution can be used to achieve different kinds of separation, while the chemical stability and inert nature of the gels mean that there is little or no irreversible adsorption of sample, thus allowing sensitive compounds to be analysed and permitting the repeated use of columns.

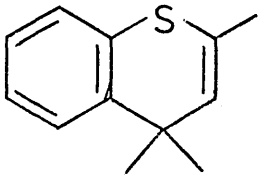
In any chromatographic process the behaviour of the compounds may be recorded either in an absolute manner, which is frequently difficult to estimate, or by trivial measurements, which are valueless for correlation; a compromise between these two extremes must provide ease of measurement, and also permit comparison of data from different sources. For T.L.C. and G.L.C. this is provided by Rf values and retention indices[48,49] respectively, while with liquid gel chromatography several terms have been used, but require several column parameters for their estimation. The only factor having a simple one-to-one relationship with the elution volume (Ve) of any sample is the total volume of the gel bed (Vt). Under comparable conditions of column preparation, a given sample should show a constant ratio (Ve/Vt) which is independent of column dimensions. An extension of this idea has been proposed[50] and the term "Standard Elution Volume" (SEV) has been defined as the hypothetical elution volume from a column having a bed volume of 100 arbitrary units - in practice this figure is obtained by multiplying (Ve/Vt) by a factor of 100, and is thus dimensionless;

$$S.E.V. = \left(\frac{Ve}{Vt}\right) \times 100$$

Encouraged by the potential of liquid-gel chromatography's capabilities, a 200 x 2.5 cm. column was constructed, and filled with Sephadex LH-20 modified with NEDOX 1114 according to Ellingboe and Nystrom[47]. In an attempt to isolate a pure sample of the thiachromene (7), fraction one of the distillation of the product obtained from PPA treatment of the ketosulphide (1) at 90°C was applied to the column and eluted with methanol, a flow rate of ~10 ml/hr being used. The first component of the mixture to be eluted was a colourless oil with a standard elution volume of about 145; after a short path distillation to remove some gel

particles which had been washed from the column, the analytically-pure sample was characterised spectroscopically as 2,2,4-trimethyl-2H-thiachromene (7). ^{1}H n.m.r. (τ, $CDCl_3$) showed a multiplet at 2.5 - 3.0 (aromatics), a quartet (J = 1.5 Hz) at 4.37 from the olefinic proton, a doublet (J = 1.5 Hz) at 7.92 from the olefinic methyl and a singlet at 8.64 from the gem-dimethyls, all in agreement with the proposed structure. The u.v. (EtOH) gave λ_{max} of 323 and 244 with a shoulder at about 281 nm, in accordance with Tilak's[39] result of Δ^3-thiachromenes showing characteristic maxima at 242 - 247 and 320 - 325, together with a shoulder around 272 - 283 nm (his thiachromans gave a characteristic peak at 255 - 257 and a shoulder or a peak at 280 - 295 nm).

Eluted just after (7), and well before any ring-contracted product, was a colourless oil (S.E.V. ~ 163), which, although analytically pure after a short path distillation, was never obtained completely free of minor impurities as revealed by ^{1}H n.m.r.; the latter bore a close resemblance to that of (7) with very similar resonance positions for the aromatic and gem-dimethyl protons, but the signals from the olefinic proton and the olefinic methyl had moved upfield to 4.53 and 7.99τ respectively. More dramatic differences were apparent in the u.v., there being shoulders at ~ 245 and 280 with a single maxima at 259 nm, and a complete absence of absorption at longer wavelengths. On this evidence this third major volatile product of the reaction was tentatively assigned the structure (19), 2,4,4-trimethyl-4H-thiachromene. Support for this



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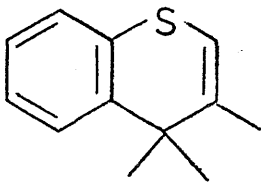


(26)

proposal comes from studies[33] on the parent molecules which show that the highest u.v. absorption from 4H-thiachromene occurs at 274 nm, while 2H-thiachromene, the isomer with the double bond in conjugation with the aromatic ring, exhibits maxima at 277, 298 (shoulder) and 327 nm. Furthermore, the reduced compound, thiachroman, has a single strong absorption at 259 nm (apart from weak shoulders at 299 and 310 nm), suggesting that the principal minor impurity in the sample of (19) eluted from the column is a thiachroman, a proposal substantiated when the mass spectrum of (19) revealed peaks, not only at m/e 190 as expected, but also at m/e 192 as required for $C_{12}H_{16}S$. Although indicating that this product has structure (19), the spectral data, so far obtained, does not conclusively eliminate the isomer (26); to achieve this, the nuclear overhauser enhancements (N.O.E.) of the olefinic proton resonance were measured employing a degassed CS_2 solution. The results were in keeping with formula (19), being 10% N.O.E. on irradiation of the olefinic methyl, and 28% N.O.E. for irradiation of the gem-dimethyl group - no positive N.O.E. effect would be expected with the latter irradiation if structure (26) were correct.

To isolate a pure sample of the ring-contracted reaction product, the third fraction of the distillate of the product obtained from PPA treatment at 100°C of the ketosulphide (1) was applied to the gel column, and eluted with methanol as before. The collected colourless oil, obtained pure after a short path distillation, has a most helpful ^1H n.m.r. spectrum (Figure 3); the doublet at 8.68 τ (J = 7 Hz) and, more particularly, the heptet at 6.63 τ (J = 7 Hz) allow the indentification of the sample as 2-isopropyl-3-methyl-benzo(b)thiophene (13). Compared with the thiachromenes, the aromatic resonances are significantly more diffuse, the low-field lines having been attributed to the protons on C_4 and C_7 in a recent high resolution analysis of the ^1H n.m.r. spectrum of benzo(b)thiophene

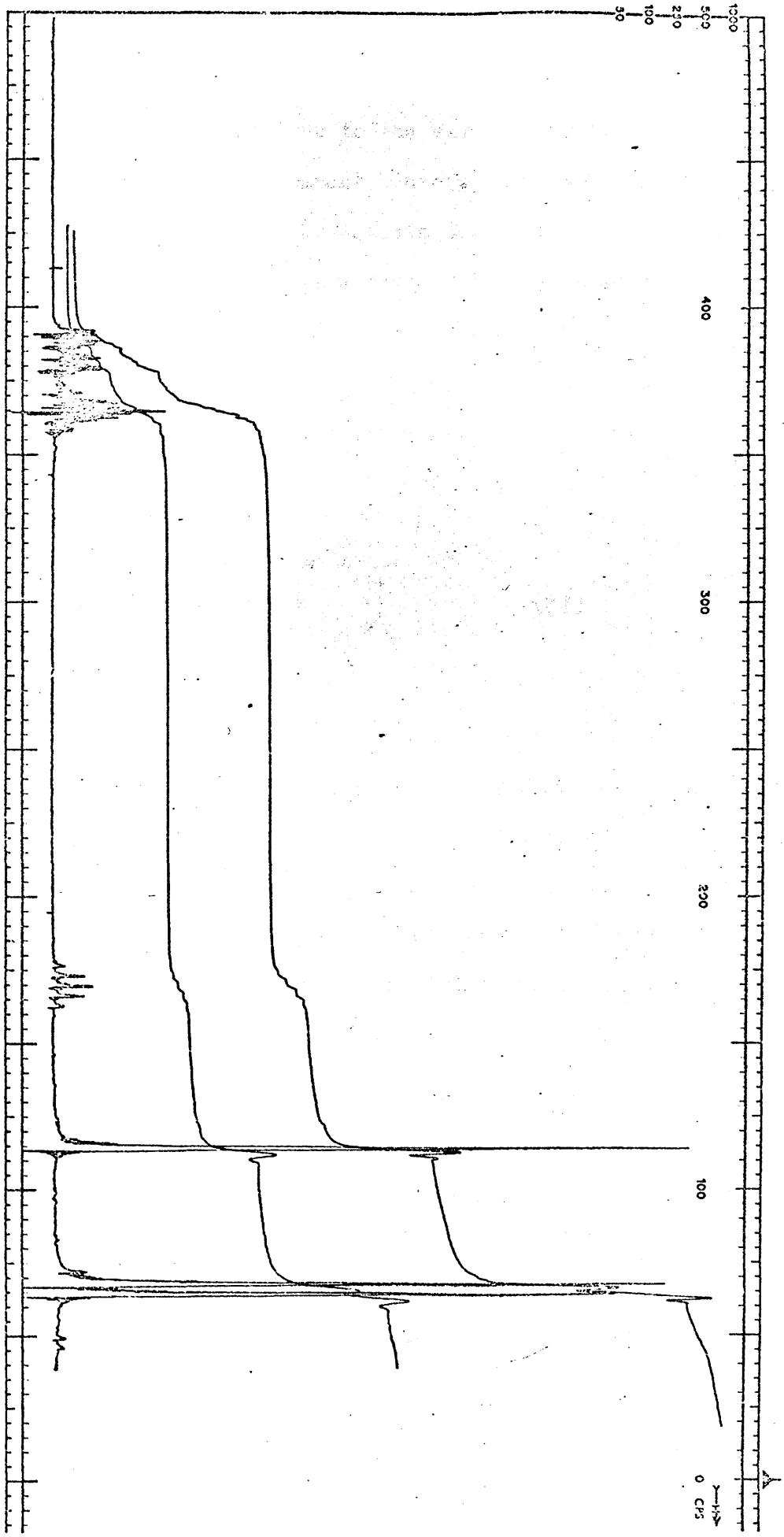
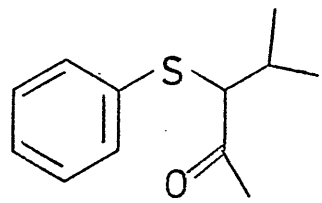


Figure 3. ^{1}H n.m.r. spectrum of 2-isopropyl-3-methylbenzo(b)thiophene.

itself[51]. Figures strongly indicative of the presence of this nucleus arise in the sample's u.v., where maxima occur at 233, 268, 290 and 299 nm, corresponding to the values of 227, 256, 289 and 298 nm reported[52] for the parent benzo(b)thiophene. The proposed structure was corroborated by satisfactory i.r., mass spectrum and an unambiguous synthesis, via a route first proposed by Werner[53]; sodium thiophenoxide was added to 3-bromo-4-methylpentan-2-one, prepared by bromination of iso-butylmethyl ketone according to Cardwell and Kilner[54], to give 3-phenylthio-4-methylpentan-2-one (27) as a colourless liquid. Cyclisation of (27) with PPA at 100°C gave a



(27)

high yield of 2-isopropyl-3-methylbenzo(b)thiophene, a material identical in all respects to that eluted from the column. As mentioned previously, the preparation of benzo(b)thiophenes often produces unexpected isomers in addition to the predicted products[34]; thus for example, when Dickinson and Iddon[55] attempted to prepare 3-methylbenzo(b)thiophene, migration of a methyl group occurred giving the required product and 2-methylbenzo(b)thiophene in a ratio of 5:1. As a check against similar migration taking place here, equal weights of synthetic material and (13) isolated from the column were mixed, and the ^{1}H n.m.r. spectrum recorded; even expansion of the doublet and heptet did not reveal any "shadowing", all lines appearing sharp and symmetrical, confirming the homogeneity of the sample.

As a probe of the purity of 2,4,4-trimethyl-4H-thiachromene obtained via gel chromatography, an ethyl acetate solution of the sample was applied to a 4 ft column of 1% OV-17 at 100°C; samples of pure 2,2,4-trimethyl-2H-thiachromene and 2-isopropyl-3-methyl-

benzo(b)thiophene were also run under identical conditions, and their retention indices[48] calculated by correlation with a series of C_{11} - C_{16} n-alkanes (Table 2). As expected, the most volatile

Table 2 . Retention Indices of Compounds Isolated from PPA Treatment of (1).

Compound	Retention Index
2,4,4-trimethyl-4H-thiachromene	1590
2,2,4-trimethyl-2H-thiachromene	1615
2-isopropyl-3-methylbenzo(b)thiophene	1685

Conditions :- 4ft. column of 1% OV-17, temperature 100°C, argon flow 50ml/min.

sample was the 4H-thiachromene, followed closely by the 2H-thiachromene with the ring contracted product somewhat behind. G.L.C. of the 2,4,4-trimethyl-4H-thiachromene (Figure 4) did, in fact, reveal the presence of an impurity (retention index 1625) which was neither the 2H- isomer nor the benzo(b)thiophene.

As will be recalled, Tilak proposed that the PPA assisted cyclisation of the ketosulphides proceeded via the thiachromanols and the thiachromenes, to give the thiachromans[39], except in the special case where the absence of a hydrogen in the 2-position precluded disproportionation; as evidence for this pathway he subjected his suggested intermediates, prepared unambiguously, to the same reaction conditions as the ketosulphides, and isolated the expected, reduced compounds from the product array. Having successfully realised pure 2,2,4-trimethyl-2H-thiachromene by gel chromatography, it was anticipated that significant information about the mechanism of the rearrangement would be obtained by allowing a sample of this to undergo the reaction with PPA. As a prelude to this investigation, the separation of some further representative

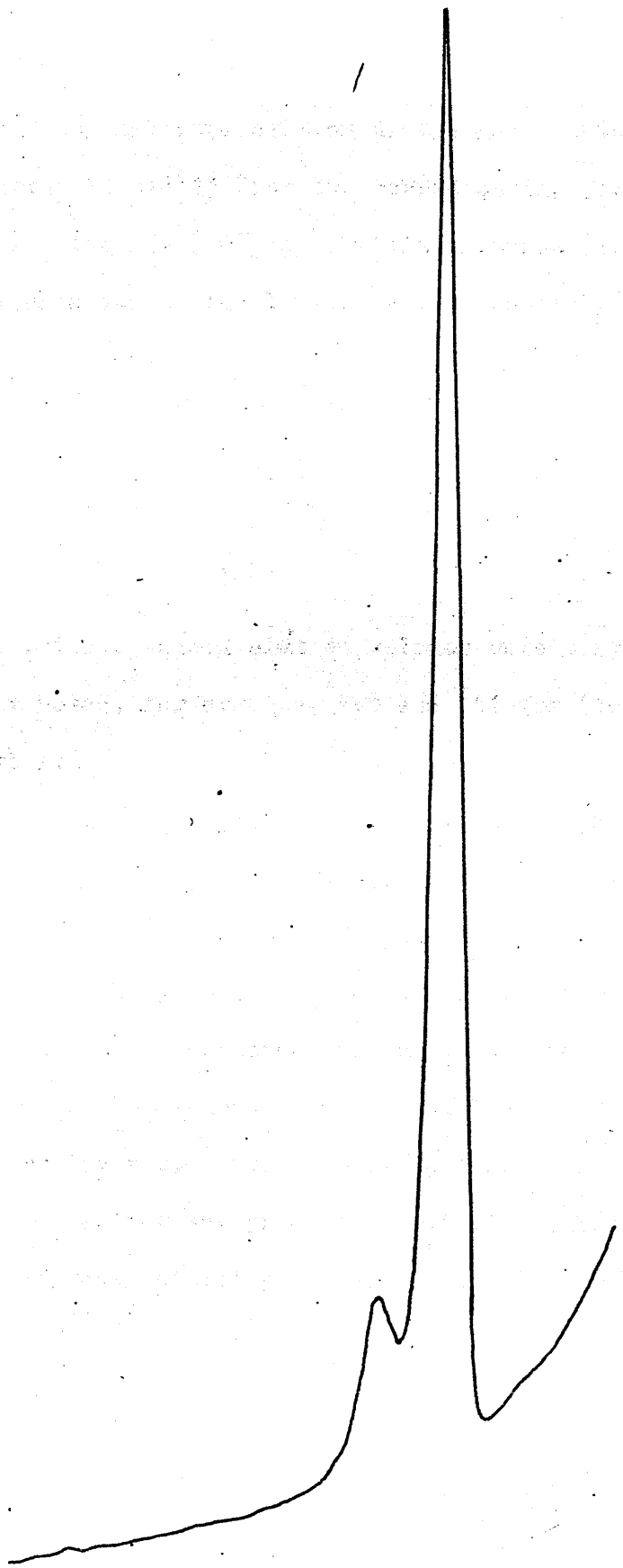
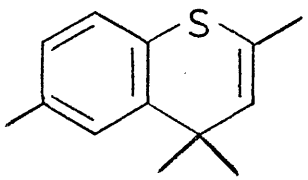


Figure 4. G.L.C. trace of (impure) 2,4,4-trimethyl-4H-thiachromene obtained by gel chromatography. Conditions :- 4 ft column of 1% OV-17, temperature 100°C, argon flow 50 ml/min.

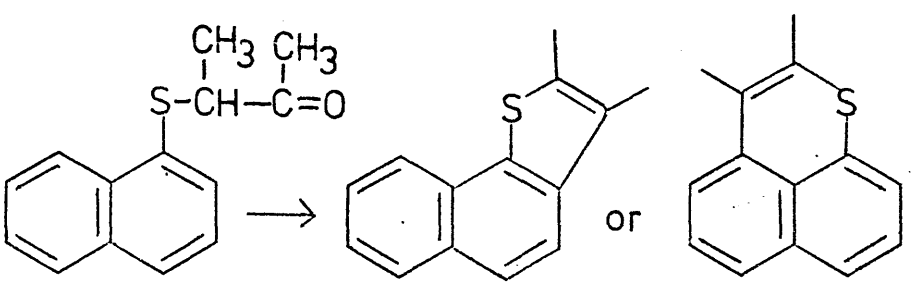
thiachromenes was embarked upon; the mixture obtained from (3) readily yielded a pure specimen of 2,2,4,7-tetramethyl-2H-thiachromene (9) by methanol elution of the gel column, while the product array (Table 1) from the corresponding para-isomer (4) enabled both the 2H- (10) and 4H-thiachromenes (20) to be isolated, although, once again, the latter was not entirely free of minor



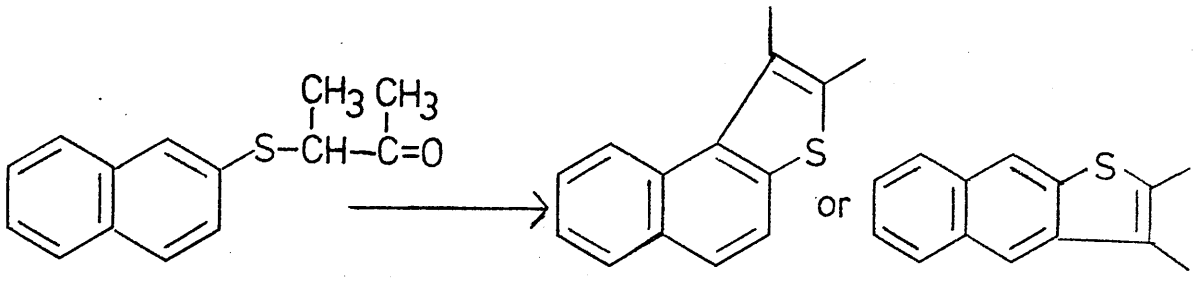
(20)

impurities. The standard elution volumes were similar to those previously noted, for example, 148 and 161 for (10) and (20) respectively.

With the reactants(5) and (6), both of which possess an additional fused ring, the mode of cyclisation constitutes an extra consideration, but, fortunately, several analogous situations have been described in the literature. An early instance[53] was the phosphorous pentoxide or zinc chloride catalysed cyclisations of 3-(α-naphthylthio)- and 3-(β-naphthylthio)butan-2-ones to form the respective 2,3-dimethylnaphtho(b)thiophenes (28) and (29); subjecting the products obtained to reductive desulphurisation with Raney nickel gave 2-(α-naphthylthio)- and 2-(β-naphthyl-

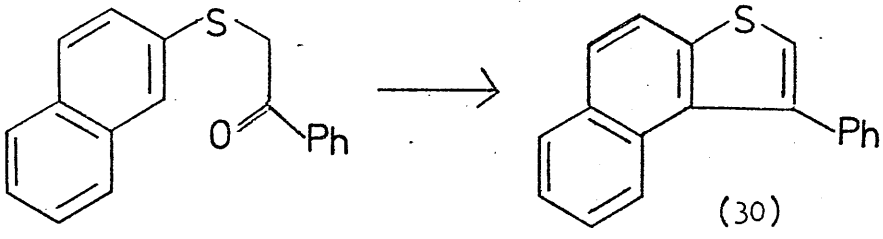


(28)



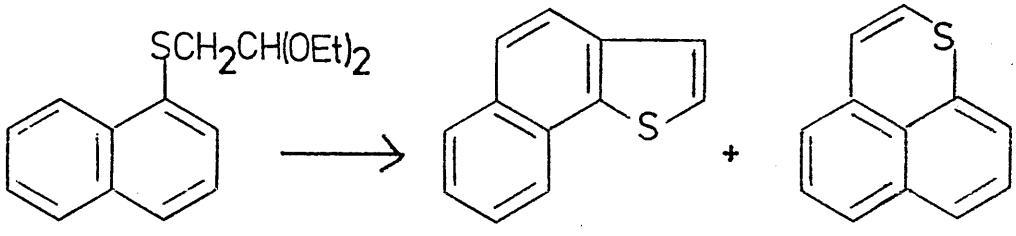
(29)

thio)butanes, which allow the alternative possibilities to be eliminated. Dann and Kokorudz[56] prepared 3-phenylnaphtho(2,1-b) thiophene (30) by PPA cyclodehydration of the corresponding naphthyl



(30)

β-ketosulphide, but for the 3-methyl analogue concentrated sulphuric acid was the reagent employed; very recently[57], however, both cyclisations have been accomplished in PPA, with no formation of the alternative products being reported. However, while the reaction of (6) should be straightforward, the α-isomer (5) may present more difficulty since Clarke[58] et al. encountered a mixture of naphtho(1,2-b)thiophene (31) and thiaphenalene (32) during



(31), 80%. (32), 20%.

the PPA cyclisation of (1-naphthylthio)acetaldehyde diethyl acetal - not suprisingly, they report the products as being "difficult to separate"; this experiment had previously been performed by Tilak[59] who reported the formation of only 8% of (32). In reality, any fears of obtaining a complex product array were unfounded, since

(5) gave predominantly 2,2,4-trimethyl-7,8-benzo-2H-thiachromene (11), with only trace quantities of the ring-contracted product (17) (Table 2). Conversely, the major product from (6) was 2-isopropyl-3-methylnaphtho(2,1-b)thiophene (18), with a reduced amount of the 2H-thiachromene (12). Neither (5) or (6) gave either of the 4H-thiachromenes in sufficient quantity to be observable by ^{1}H n.m.r., but significant increases were recorded in the percentages of material recovered. The distillate from (5) solidified on standing and recrystallisation gave a pure sample of (11), whereas gel chromatography was required for the separation of the products derived from (6). The structures of (17) and (18) were confirmed by comparison with samples prepared unambiguously via the same route as (13), but starting from naphthalene-1-thiol and naphthalene-2-thiol respectively instead of from thiophenol. Once again, the ^{1}H n.m.r. spectra of equal weights of synthetic material and samples eluted from the column were run to confirm the homogeneity of the mixture.

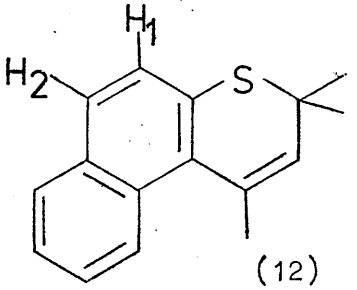
The ultra-violet absorption data for all the isolated thiachromenes is listed in Table 3, from which it can be seen that (7),(9) and (10) all exhibit similar maxima in the regions predicted by Tilak[39].

The longest wavelength absorption in the u.v. of (17), namely 347 nm (see experimental section) eliminates the possibility that (5) has undergone the alternative mode of cyclisation since thiaphenalene is known to give a λ_{max} at 420 nm[60]. Similarly, the structure of (18) is as expected, the other possibility being ruled out because the parent naphtho(2,1-b)thiophene absorbs at lower wavelengths than naphtho(2,3-b)thiophene[61] (304 nm compared with 352 nm in cyclohexane); the figures are also in accord with those quoted by Carruthers and Crowder[62].

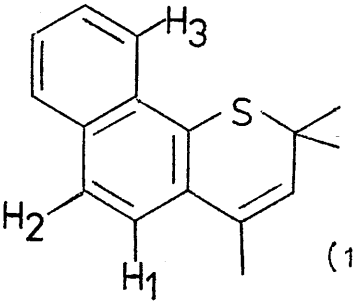
Table 3. Ultra-violet data of isolated thiachromenes.

Compound number.	λ_{max}(EtOH), (log ε).
(7)	323 (3.13), ~281 (sh), 244 (4.29)
(9)	322 (3.07), ~284 (sh), 248 (4.27)
(10)	328 (3.11), ~280 (sh), 244 (4.22)
(11)	~354 (sh), ~343 (sh), 330 (3.28), ~320 (sh), 279 (4.07), ~274 (sh), 252 (3.90), 232 (4.03)
(12)	352 (3.41), 325 (3.66), 313 (3.70), 276 (4.26), 260 (4.52), 234 (4.41)

The ^{1}H n.m.r. data of all the products formed from PPA treatment of (1)-(6) is listed in Table 4; the spectra of pure compounds gave the expected integration ratios, as did (19) and (20). Expansion of the aromatic region of (12) (Figure 5) reveals an AB quartet centred at 2.53τ (J = 9 Hz) from H_1 and H_2, a feature



(12)



(11)

which would be absent had the alternative cyclisation occurred Similarly, the AB quartet in (11) is highlighted when irradiation of the low-field proton H_3 is performed (Figure 6).

III. Reaction of Thiachromenes with PPA.

The first indication that the thiachromenes might be capable of undergoing ring-contraction came from the variation of product ratio (7):(13) with temperature - higher temperatures favouring, and lower temperature disfavouring, the benzo(b)thiophene. Accordingly representative thiachromenes (7),(9),(11) and (12), isolated by gel chromatography, or crystallisation in the case of (11), were treated with polyphosphoric acid at 100°C, the scale being reduced by about a factor of 100. With (11), both the weight of PPA and the reaction time were increased in view of the low percentage of the ring contracted-product formed from (5). The ^{1}H n.m.r. spectra were recorded on the products, thus allowing the percentage rearrangement to be calculated (Table 5); as with the ketosulphides, the product distribution has a marked dependence on the structure of the starting material, but in the case of the thiachromenes almost quantitative recoveries were achieved, the only compounds present being the

Table 4. ^{1}H n.m.r. data of products from PPA treatment of (1) - (6).

Compound number.	Aromatic H.	Olefinic H.	Aromatic methyl.	Olefinic methyl.	$C(CH_3)_2$.
(7)	2.5 - 3.0 (m)	4.37 (q, J = 1.5)	-	7.92 (d, J = 1.5)	8.64 (s)
(8)[b]	c	4.46 (q, J = 1.5)	7.70 (s)	7.94 (d, J = 1.5)	8.64 (s)
(9)	2.7 - 3.2 (m)	4.43 (q, J = 1.5)	7.70 (s)	7.92 (d, J = 1.5)	8.60 (s)
(10)	2.7 - 3.2 (m)	4.34 (q, J = 1.5)	7.66 (s)	7.89 (d, J = 1.5)	8.61 (s)
(11)	1.65-1.85 (m,1H) and 2.1 - 2.7 (m,5H)	4.32 (q, J = 1.5)	-	7.79 (d, J = 1.5)	8.54 (s)
(12)	1.9 - 2.8 (m)	4.23 (q, J = 1.5)	-	7.70 (d, J = 1.5)	8.61 (s)
(19)[b]	2.5 - 3.0 (m)	4.53 (q, J = 1.5)	-	7.99 (d, J = 1.5)	8.64 (s)
(20)[b]	2.7 - 3.3 (m)	4.59 (q, J = 1.5)	7.69 (s)	8.01 (d, J = 1.5)	8.63 (s)

(a) : values of the coupling constants, J, are in Hz.

(b) : shifts measured from ^{1}H n.m.r. spectrum of mixture.

(c) : range not accurately determined from ^{1}H n.m.r. spectrum of mixture.

Table 4. (contd). ^{1}H n.m.r. data of products from PPA treatment of (1) - (6).

Compound number.	Aromatic H.	$-CH(CH_3)_2-$	Aromatic methyl.	Olefinic methyl.	$C(CH_3)_2-$
(13)	2.1 - 3.0 (m)	6.63 (hept, J = 7)	-	7.73 (s)	8.68 (d, J = 7)
(14)[b]	c	6.61 (hept, J = 7)	7.51 (s)	7.71 (s)	8.67 (d, J = 7)
(15)[b]	c	6.59 (hept, J = 7)	7.53 (s)	7.70 (s)	8.66 (d, J = 7)
(16)[b]	c	6.61 (hept, J = 7)	7.55 (s)	7.73 (s)	8.69 (d, J = 7)
(17)	1.8 - 2.7 (m)	6.54 (hept, J = 7)	-	7.61 (s)	8.58 (d, J = 7)
(18)	1.2 - 1.4 (m,1H) and 2.0 - 2.7 (m,5H)	6.48 (hept, J = 7)	-	7.21 (s)	8.60 (d, J = 7)

(a) : values of the coupling constants, J, are in Hz.
(b) : shifts measured from ^{1}H n.m.r. spectrum of mixture.
(c) : range not accurately determined from ^{1}H n.m.r. spectrum of mixture.

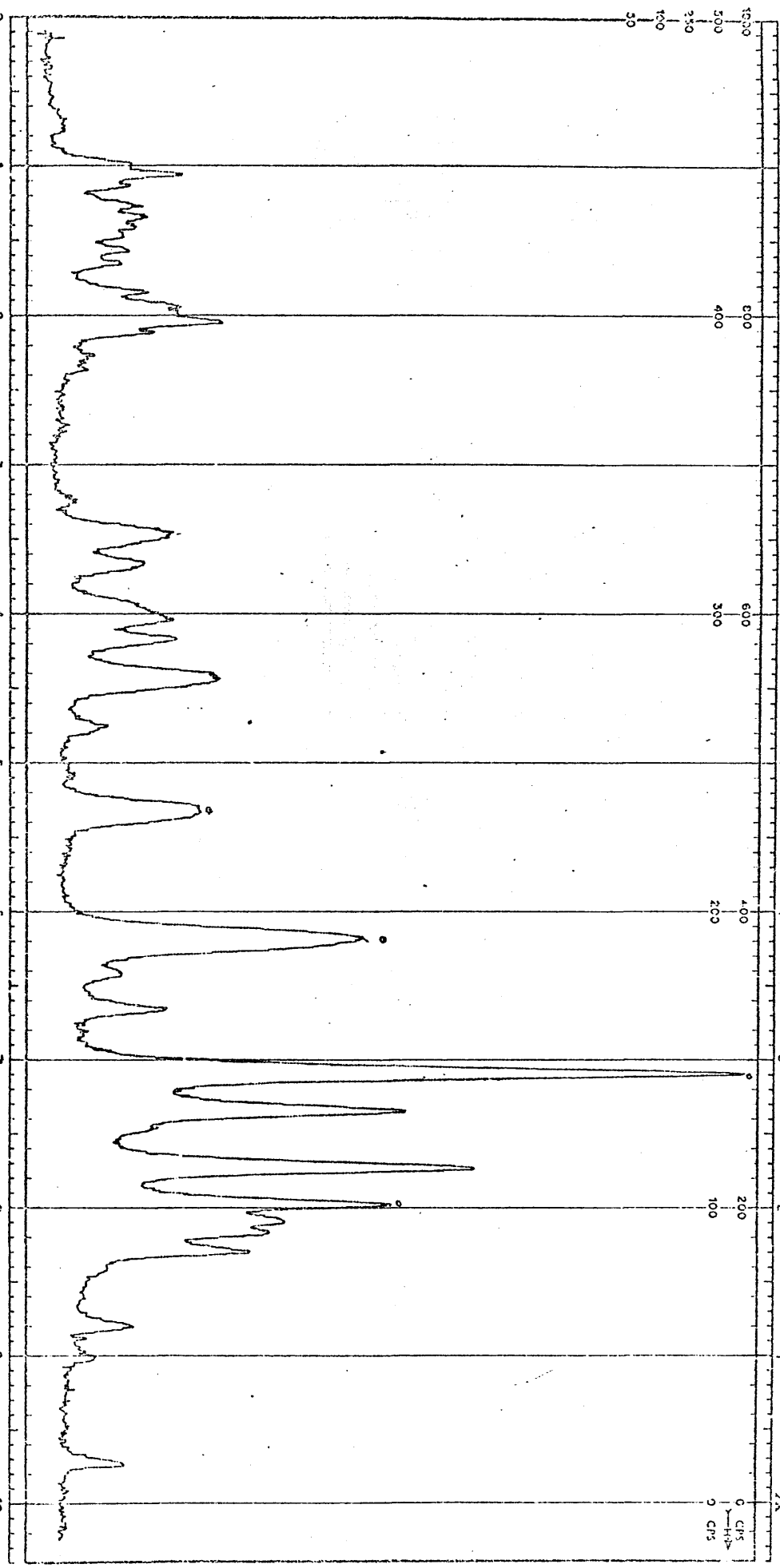


Figure 5. Expansion of the aromatic region of the ^{1}H n.m.r. spectrum of (12).

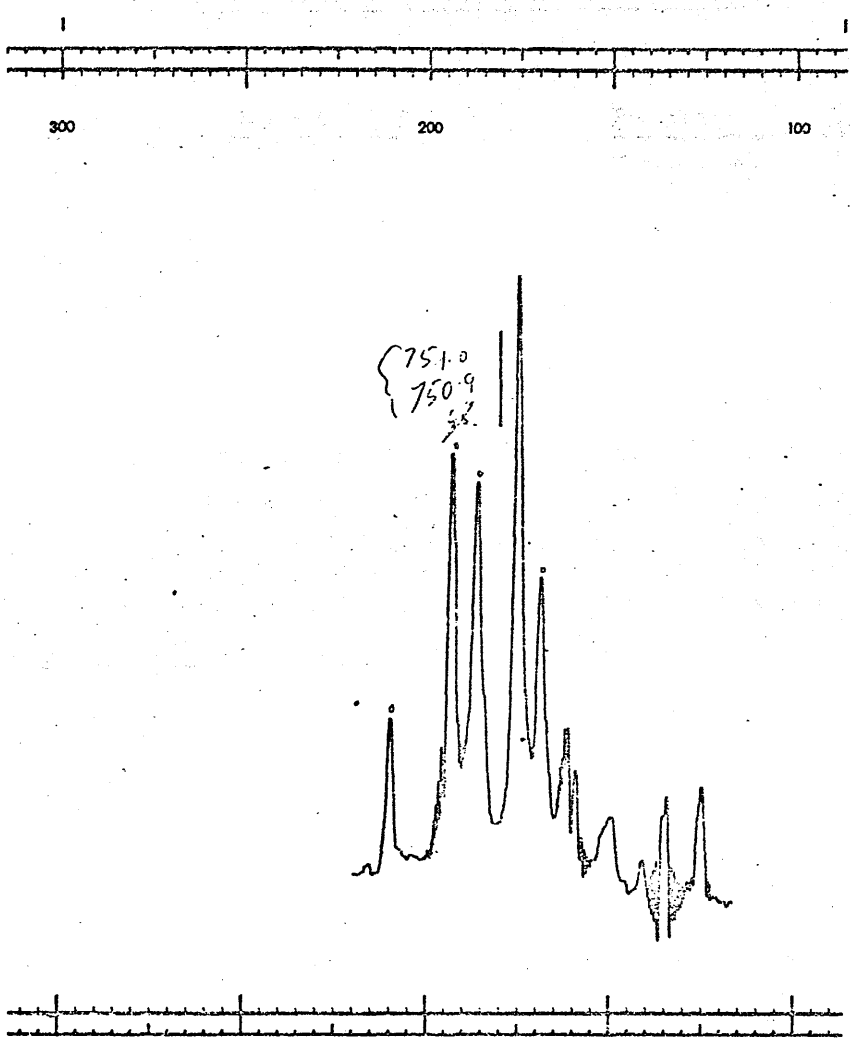


Figure 11. Expansion of the aromatic region of the ^{1}H n.m.r. spectrum of (11).

starting thiachromenes and the ring-contracted isomers.

Table 5. Rearrangement of Thiachromenes with PPA.

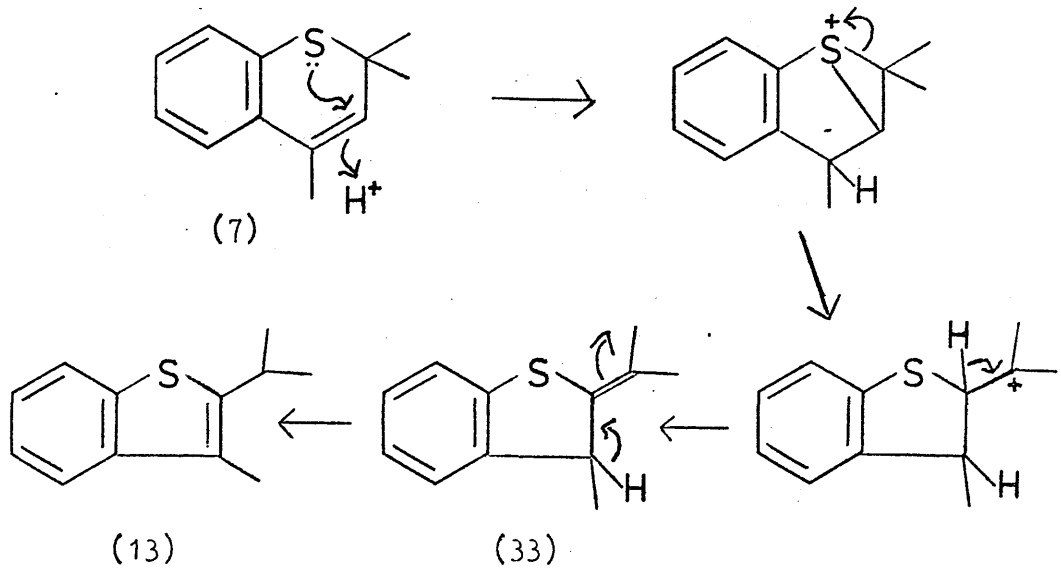
Compound Number.	Weight of P_2O_5(g)/ g. Reactant.	Reaction Time (hr).	%Rearranged*
(7)	4	3	40
(9)	4	3	17
(11)	15	8	61
(12)	4	3	91

* Given ($\pm$5%) from integration of 100 MHz ^{1}H n.m.r. spectrum.

IV. The Mechanism of the Rearrangement.

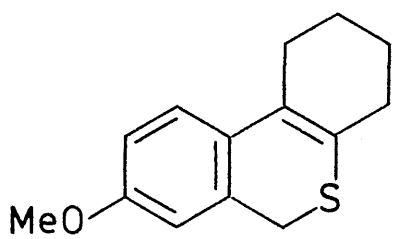
While a mechanism involving free radical intermediates seems improbable (see Introduction, II), it should not be dismissed out of hand, and, consequently, the reaction of ketosulphide (1) with PPA at 100°C was carried out in the probe of a Decca X3 spectrometer;* spectra were recorded at regular intervals, but no signals attributable to organic radicals were observed, this indicating the presence of an ionic pathway. Since the thiachromenes rearrange in PPA to give the ring-contracted products, it would appear that they are intermediates on the way from the ketosulphides to the benzo(b) thiophenes, just as Tilak's[37] thiachromenes were intermediates in the formation of the thiachromans; disproportionation as observed by Tilak is, however, precluded here as a result of there being no hydrogens on C-2.

* We thank Dr. A.L. Porte for this measurement.



Scheme 1.

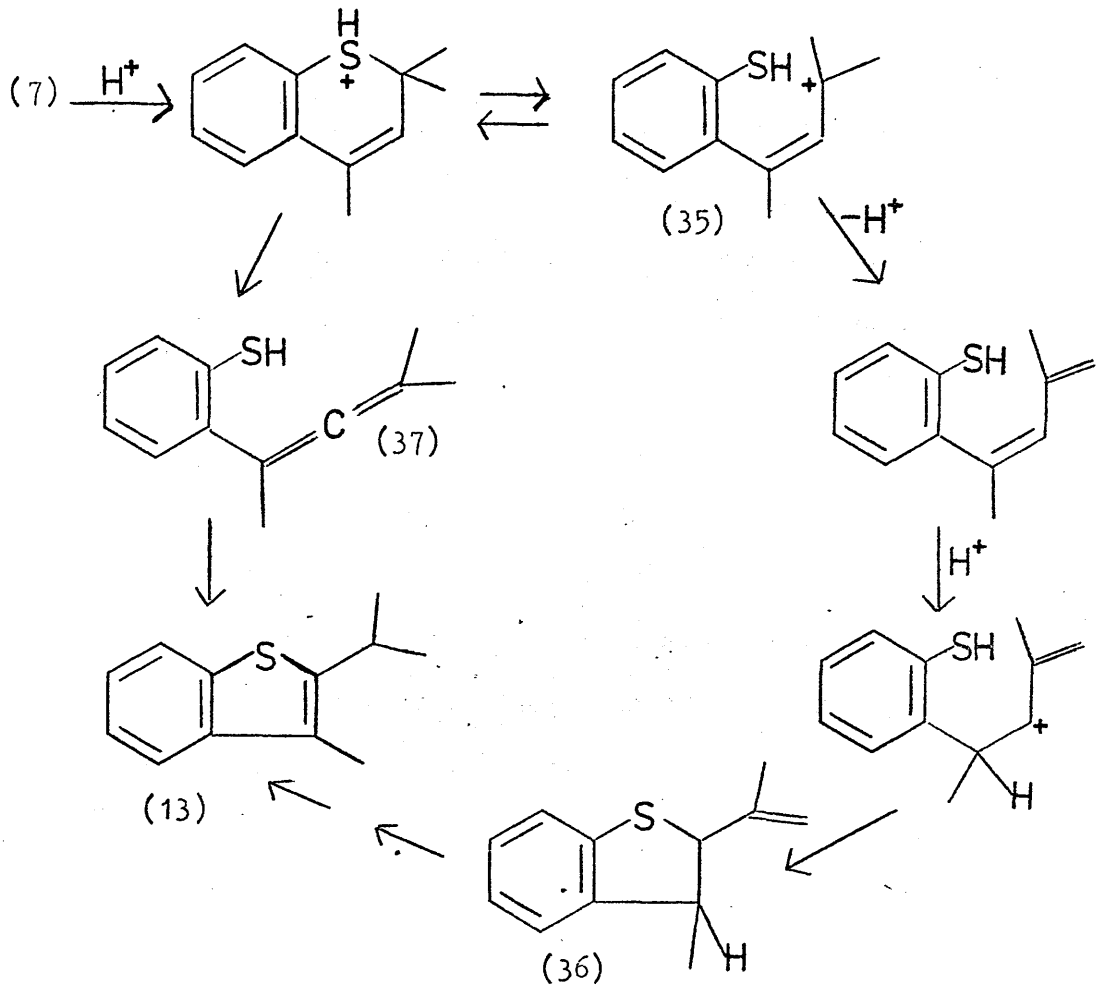
A likely ionic mechanism involves protonation by PPA at C-4 of the thiachromene, (e.g. (7) shown in Scheme 1), forming a thiiranium ion in a similar fashion to that proposed by Hofmann and Salbeck[21], and later adopted as an intermediate in the perchloric-acid catalysed disproportionation of (34)[63]; thiiranium ions as reaction intermediates have been reviewed by Mueller[64].



(34)

Subsequent ring opening of this species leads to a tertiary carbonium ion, which, following proton loss, gives rise to the benzo(b)thiophene nucleus by double bond isomerisation.

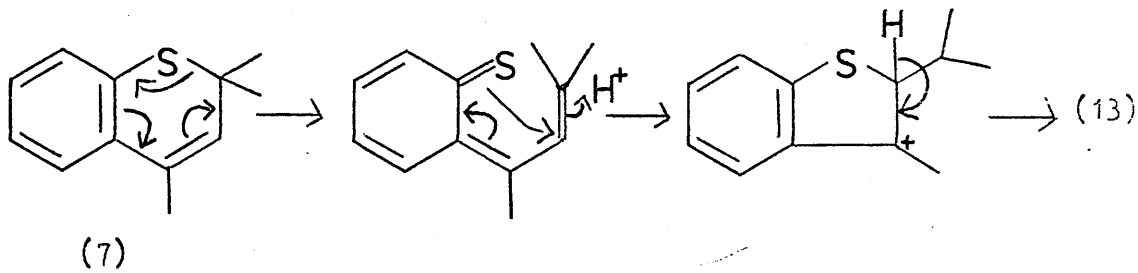
Alternatively, thiachromene protonation could occur on the sulphur, leading to the resonance-stabilised allylic carbonium ion (35); proton loss, followed by reprotonation and ring-closure produces (36), from which (13) is formed by double bond isomerisation (Scheme 2). Identical initial protonation can give rise to the allene



Scheme 2.

(37), capable of cyclising directly to the required product in an analogous fashion to that proposed by Lowenbein[15] for 2,2-diphenylchromene.

Another possible pathway (Scheme 3) invokes ring opening as in

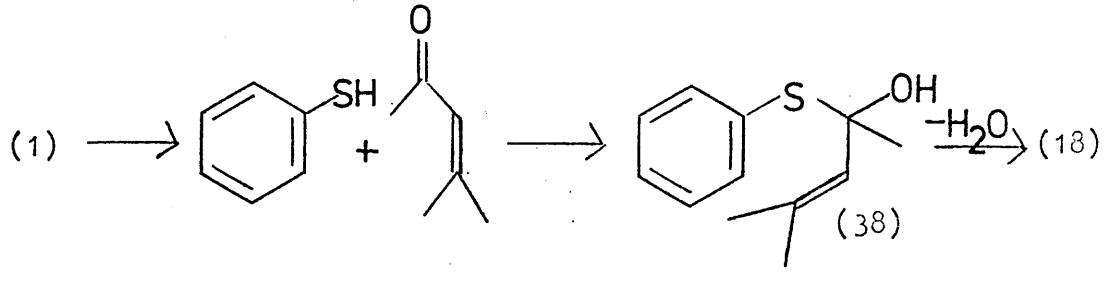


Scheme 3.

the first step of a thia-Claisen rearrangement; the bicyclic skeleton is re-established by attack at C-3, with the intermediate formed undergoing ready proton loss on the way to the condensed thiophene (13).

Although the above mechanisms are possible in theory, some appear less favourable - for example, Scheme 3 depends on the early loss of aromaticity by (7), and, similarly, one would expect the reaction not to proceed through an intermediate allene if an easier route were at its disposal. Endeavouring to ascertain the true mechanism by isotopic labelling (carrying out the cyclisation in deutero-PPA) will be severely restricted since benzo(b)thiophene derivatives with alkyl substituents in the 2- and 3- positions have been shown to undergo ready hydrogen exchange in the presence of acid[65].

The formation, in certain instances, of the 4H-thiachromenes can be accounted for if the ketosulphides retro in acid to re-generate the aryl mercaptans and mesityl oxide. Now if, instead of a Michael condensation, nucleophilic attack takes place on the carbonyl group, there will be produced (in the case of (1)) the intermediate (38), which on cyclodehydration gives 2,4,4-trimethyl-



4H- thiachromene. The small proportion of the 4H isomer present in the product mixture from (2) and (3) (Table 1) may be tentatively ascribed to the steric hindrance of the adjacent methyl groups. To investigate the possibility of this mechanism, an equimolar mixture of thiophenol and mesityl oxide was treated with PPA at 100°C; subsequent work-up gave a low yield of a brown oil containing,

apart from much polymeric material, small amounts of the 4H-thiachromene as well as the 2H isomer and the ring-contracted product. Although evidence for any particular mechanism is not readily forthcoming, the formation of all the products can be satisfactorily explained in terms of one or more of the above pathways.

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded on Varian T-60 and HA-100 instruments with $CDCl_3$ as solvent and TMS as internal standard. Ultra-violet and mass spectra were measured on Unicam SP800A and A.E.I.-G.E.C. MS 12 spectrometers respectively. E.p.r. spectra were run on a Decca X3 spectrometer, and infra-red spectra were recorded on Perkin Elmer 225 and Unicam SP1000 instruments. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. G.L.C. measurements were made on a Pye-Argon Chromatograph. T.L.C. was carried out using Kieselgel G (Merck) for analytical purposes and Kieselgel HF_{254} for preparative work. Light petroleum refers to the fraction boiling between 60 and 80°C. Solvents were removed on a rotary evaporator at reduced pressure.

Abbreviations.

b	broad
d	doublet
m	multiplet (in n.m.r.)
	medium intensity absorption (in i.r.)
q	quartet
s	singlet (in n.m.r.)
	strong intensity absorption (in i.r.)
sh	shoulder
t	triplet
w	weak intensity absorption

I. Preparation of Ketosulphides.

4-Methyl-4-phenylthiopentan-2-one, (1).

Thiophenol (119 g, 1.08 mole) was dissolved in dry benzene (1 l) containing a few drops of piperidine; after warming the

solution, freshly-distilled mesityl oxide (128 g, 1.31 mole) was added, and the mixture refluxed overnight under nitrogen. After checking that all the thiol had reacted (by i.r. or n.m.r.), the cooled solution was washed with 5% NaOH solution (3 x 250 ml), then with water (3 x 500 ml) and dried over anhydrous sodium sulphate. Solvent removal left an oil, which on distillation under reduced pressure, gave (1) as a colourless liquid, b.p. 94 - 95°C/ 0.01 mm Hg, 75% (yields are unoptimised), m/e 208 (M^+);

ν_{max} (thin film) 3065 (w), 2980 (m), 2930 (m), 1712 (s), 1580 (w), 1570 (w), 1475 (m), 1440 (s), 1380 (m), 1362 (s), 1122 (s), 760 (s), 712 (s), 702 (s) cm^{-1};

$\tau(CDCl_3)$ 2.3 - 2.9 (5H, m, aromatics), 7.35 (2H, s, $-CH_2-$), 7.90 (3H, s, CH_3CO), 8.63 (6H, s, $C(CH_3)_2$);

(Found : C, 69.26; H, 7.70. $C_{12}H_{16}OS$ requires C, 69.21; H, 7.74%).

The other ketosulphides were prepared by analogous reactions and are summarised below:

4-Methyl-4-(o-tolylthio)pentan-2-one, (2).

o-Thiocresol (26.4 g, 0.21 mole) refluxed for 5 hours with mesityl oxide (25.3 g, 0.26 mole) gave a colourless liquid, (2), b.p. 89 - 91°C/0.01 mm Hg, 54%, m/e 222 (M^+);

ν_{max} (thin film) 3070 (w), 2980 (s), 2936 (m), 1715 (s), 1620 (w), 1590 (w), 1470 (s), 1380 (s), 1362 (s), 1202 (m), 1180 (m), 1122 (s), 1065 (m), 760 (s), 722 (m) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 3.1 (4H, m, aromatics), 7.29 (2H, s, $-CH_2-$),

7.50 (3H, s, ring CH_3),

7.87 (3H, s, CH_3CO),

8.63 (6H, s, $C(CH_3)_2$);

(Found : C, 70.42; H, 8.29. $C_{13}H_{18}OS$ requires C, 70.24; H, 8.16%).

4-Methyl-4-(m-totylthio)pentan-2-one, (3).

m-Thiocresol (80 g, 0.65 mole) refluxed overnight with mesityl oxide (69 g, 0.70 mole) gave a colourless liquid, (3), b.p. 79 - 80°C /0.01 mm Hg, 77%, m/e 222 (M^+);

ν_{max} (thin film) 2978 (m), 2930 (m), 1715 (s), 1592 (m), 1575 (w), 1470 (m), 1380 (m), 1362 (s), 1120 (s), 785 (s), 697 (s) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 3.0 (4H, m, aromatics), 7.35 (2H, s, $-CH_2-$), 7.67 (3H, s, ring CH_3), 7.90 (3H, s, CH_3CO), 8.62 (6H, s, $C(CH_3)_2$);

(Found : C, 70.39; H, 8.20. $C_{13}H_{18}OS$ requires C, 70.24; H, 8.16%).

4-Methyl-4-(p-tolylthio)pentan-2-one, (4).

p-Thiocresol (80 g, 0.65 mole) refluxed for 5 hours with mesityl oxide (70 g, 0.71 mole) gave a colourless liquid, (4), b.p. 91-92°C/0.06 mm Hg, 56%, m/e 222 (M^+);

ν_{max} (thin film) 2975 (m), 2930 (m), 1716 (s), 1600 (w), 1495 (m), 1382 (m), 1364 (s), 1122 (s), 816 (s) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 3.0 (4H, m, aromatics), 7.35 (2H, s, $-CH_2-$),

7.65(3H, s, ring CH_3),

7.88 (3H, s, CH_3CO),

8.63 (6H, s, $C(CH_3)_2$);

(Found : C, 70.17; H, 8.21. $C_{13}H_{18}OS$ requires C, 70.24; H, 8.16%).

4-Methyl-4-(1-naphthylthio)pentan-2-one, (5).

Naphthalene-1-thiol (10 g, 62 mmole) refluxed for 24 hours with mesityl oxide (7 g, 71 mmole) gave a pale yellow liquid, (5), b.p. 135 - 136°C/0·04 mm Hg, 69%, m/e 258 (M^+);

ν_{max} (thin film) 3060 (m), 2970 (m), 2930 (m), 1718 (s), 1622 (w), 1590 (m), 1502 (s), 1380 (s), 1365 (s), 1120 (s), 805 (s), 775 (s) cm^{-1};

$\tau(CDCl_3)$ 1.9 - 2.7 (7H, m, aromatics), 7.28 (2H, s, $-CH_2-$), 7.91 (3H, s, CH_3CO), 8.60 (6H, s, $C(CH_3)_2$);

(Found : C, 74.37; H,6.88. $C_{16}H_{18}OS$ requires C, 74.39; H, 7.02%).

4-Methyl-4-(2-naphthylthio)pentan-2-one, (6).

Naphthalene-2-thiol (80 g, 0.5 mole) refluxed overnight with mesityl oxide (58.8 g, 0.6 mole) gave a pale yellow liquid, (6), b.p. 146 - 147°C/0.25 mm Hg, 58% (formation of disulphide as by-product proved troublesome in this instance), m/e 258 (M^+);

ν_{max} (thin film) 3055 (m), 2970 (m), 2930 (m), 1715 (s), 1628 (w), 1588 (m), 1500 (m), 1465 (m), 1378 (m), 1360 (s), 1198 (m), 1120 (s), 866 (m), 820 (s), 748 (s) cm^{-1};

$\tau(CDCl_3)$ 1.8 - 2.7 (7H, m, aromatics), 7.28 (2H, s, $-CH_2-$),

7.87 (3H, s, CH_3CO),

8.55 (6H, s, $C(CH_3)_2$);

(Found : C, 74.20; H, 7.04. $C_{16}H_{18}OS$ requires C, 74.39; H, 7.02%).

8-Phenylthio-menthan-3-one, (22).

Thiophenol (50 g, 0.45 mole) refluxed for 4 days with freshly distilled (+)-pulegone (92 g, 0.60 mole) gave a viscous, yellow liquid, (22), b.p. 117 - 122°C/0.01 mm Hg, 71% (some unreacted pulegone came over early in the distillation), m/e 262 (M^+);

ν_{max} (thin film) 3075 (w), 3058 (w), 2950 (s), 2920 (s), 2865 (m), 1708 (s), 1472 (m), 1450 (m), 1436 (m), 1378 (m), 1360 (m), 1116 (m), 750 (s), 706 (m), 694 (s) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 2.9 (5H, m, aromatics), 7.1 - 8.5 (8H, m, $-CH_2-$ and $-CH-$), 8.58 (3H, s, diastereotopic CH_3), 8.62 (3H, s, diastereotopic CH_3), 9.00 and 9.05 (3H combined, 2d - relative weights 3:1, J = 5 Hz for both, CH_3-CH-);

(Found : C, 73.40; H, 8.50. $C_{16}H_{22}OS$ requires C, 73.25; H, 8.45%).

4-Methyl-4-phenylselenopentan-2-one, (21).

Selenophenol (25 g, 0.16 mole) refluxed for 30 hours with mesityl oxide (18.8 g, 0.19 mole) gave a pale yellow liquid, (21), b.p. 100 - 108°C/0.04 mm Hg in high yield, m/e 256 (M^+);

ν_{max} (thin film) 3060 (m), 2965 (m), 2925 (m), 1715 (s), 1620 (w), 1578 (m), 1438 (s), 1380 (m), 1364 (s), 1120 (s), 1022 (m), 744 (s), 696 (s) cm^{-1};

$\tau(CDCl_3)$ 2.2 - 2.9 (5H, m, aromatics),
7.23 (2H, s, $-CH_2-$),
7.90 (3H, s, CH_3CO),
8.50 (6H, s, $C(CH_3)_2$),
8.50 (d, 7.5%, $J_{^{77}Se-^{1}H}$ = 11 Hz);
(Found : C, 56.48; H, 6.40. $C_{12}H_{16}OSe$ requires C, 56.47; H, 6.32%).

II. Reaction of the Ketosulphides with Polyphosphoric Acid.

Polyphosphoric acid was prepared by heating P_2O_5 (80 g) with orthophosphoric acid (50 ml, d = 1.75) at 150°C for 1 hour, precautions being taken to prevent the entry of water vapour. 4-Methyl-4-phenylthiopentan-2-one (1), (20 g) was added in one lot to the PPA at room temperature, and the mixture stirred mechanically (mercury-sealed stirrer) while being maintained at 99 ($\pm$1)°C in a thermostatically controlled bath; the solution became blue, then green, red and finally dark brown. After three hours the viscous product was allowed to cool to room temperature, then poured into iced water (750 ml) and extracted with ether (3 x 500 ml). The combined extracts were washed with saturated sodium bicarbonate solution (1 x 300 ml), followed by water (4 x 400 ml) until pH ~ 7. After drying (Na_2SO_4) the solvent was removed leaving a brown oil which distilled in the range 65 - 114°C/0.02 mm Hg, giving a yellow liquid (4.62 g), equivalent to 23% recovery of material (this figure does not include higher boiling polymeric material), and of composition shown in Table 1.

Identical reactions were carried out with the other ketosulphides, namely (3), (4), (6) and (22), but with (2) and (5) the scale was reduced by a factor of 10; the products from (2) - (6) had boiling point ranges of 63 - 110°/0.06, 38 - 91°/0.04, 71 - 85°/0.03, 70 - 100°/0.005 and 108 - 154°/0.005 mm Hg respectively. The

composition of the various reaction mixtures, together with the overall weights analysed, are set out in Table 1. The distillation of the product from 8-phenylthio-menthan-3-one (22) gave 2 fractions (25% recovery of material) boiling at 48 - 55°C/0.01 mm Hg and 56 - 108°C/0.01 mm Hg; ^{1}H n.m.r. showed the former to be an isomer of pulegone and the latter to be polymeric in nature. A similar reaction with the ketoselenide (21) gave 42% recovery of material, b.p. 74 - 100°C/0.03 mm Hg; ^{1}H n.m.r. revealed the formation of some selenachromene but the majority was again polymeric.

The effect of reaction temperature on the composition of the product derived from ketosulphide (1) is shown in Table 6; as can be seen, increasing the temperature favours the ring-contracted product while lower temperatures favour the thiachromene.

Table 6 . Relative Percentages of Major Products from PPA Treatment of (1).

Temperature (°C).	% Material recovered.	2H-Thia-chromene.	4H-Thia-chromene.	Ring-contracted product.
90	17	55	15	30
100	23	15	15	70
125	21	20	a	80

(a) : present in, at most, trace quantities (< ca 5%)

The ketosulphide (1) (51 mg) was added in one lot to a mixture of methanesulphonic acid (619 mg) and phosphorous pentoxide (56 mg), and stirred for 3 hours at 100°C. Standard work-up gave a brown oil, the ^{1}H n.m.r. spectrum of which gave no peaks which could be assigned to a ring-contracted product. Also, a sample of (1) (3.1 g), satur-

ated with dry, gaseous HCl, did not cyclise to the benzo(b)thiophene (13); after 6 days ^{1}H n.m.r. showed only starting material and a trace of the 2H-thiachromene, the latter increasing as time went on. Work-up after 18 months gave a pale yellow liquid, 0.6 g, b.p 61 - 72°C/0.02 mm Hg; ^{1}H n.m.r. showed this to be impure (7).

III. Construction of Gel Column.

Commercial Sephadex LH-20 (500 g) was subjected to prolonged shaking on British Standard sieves to separate particles of size 53 - 105μ (303 g); under a microscope there was still a variation in particle size with clusters of small particles clinging together. These proved impossible to disperse on shaking but it was feasible to float them off when the gel was steeping in solvent. The gel was split into two batches, each of which was soaked for 24 hours in methylene chloride (1500 ml), purified by a pass through a column of basic alumina, followed by distillation. Modification via the route of Ellingboe and Nystrom[47] was carried out. Boron trifluoride ethyl etherate (37.5 ml, 48% BF_3) was added and the mixture swirled for 15 minutes (N.B. the beads of gel are destroyed if a magnetic stirrer is employed), then portions (100 ml) of a solution of NEDOX* 1114 (900 ml) in methylene chloride (3600 ml) were added, with shaking, over the next 2 hours, the reaction vessel being cooled in an ice bath to prevent uncontrolled refluxing. Having allowed the reaction to proceed for another 20 minutes, the product was filtered on a Buchner funnel and washed successively with chloroform (500 ml), ethanol (500 ml), chloroform-methanol (1:1) (500 ml), and finally with benzene (500 ml). The gel was then refluxed with stirring

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* We thank Ashland Chemical Company, Ohio for the gift of NEDOX 1114.

in chloroform-methanol (3.75 l) for 4 hours, washed with chloroform-methanol and benzene, and refluxed in benzene for 4 hours. The product is carefully washed with benzene and refluxed in benzene for a further 4 hour period. After a final wash with benzene the product is dried under vacuum at room temperature until constant in weight (605 g). The weight increase (302 g) corresponds to a hydroxyalkyl group content of 50% (w/w); this derivative is therefore designated "N1114 - 50%-LH-20". The dried product, unlike the starting material, was hydrophobic and waxy, and it is for this reason that the separation into different particle sizes must be done on the unmodified bead-like gel.

The column was constructed by extending by 1 metre a standard 1 metre "Lab-Crest" chromatographic column of internal diameter 2.5 cms. The gel rested on a porous disc, and the outflow to the collecting vessel was via a Teflon tap and narrow bore Teflon tubing; the top of the column was connected to a reservoir of 2 litre capacity via nylon tubing. The column was calibrated volumetrically before packing so that the bed volume could be measured at any time to allow for variations arising from changes in temperature or flow rate. The gel was allowed to swell in Analar methanol for 48 hours, and, from time to time, any fine particles floating on the surface were decanted. Before packing, the gel slurry was freed from occluded air by immersion for one hour in an ultrasonic bath. The column was fitted with a glass extension and partly filled with methanol; the gel slurry, added in one operation, was allowed to settle under conditions of continuous vibration, a steady solvent flow being maintained. Not all the gel could be accommodated and consequently a bed volume of 950ml sufficed. After 48 hours the bed volume had stabilised and a filter paper was placed on top of the gel to protect the surface from mechanical disturbance. A maximum solvent flow-rate of ~50 ml/hour was

possible but, in practice, a flow rate not exceeding half this value was employed. At first, samples eluted from the column were contaminated by the "bleeding" of small gel particles, but these were easily removed on grade C, glass fibre filter paper.

IV. Isolation of Thiachromenes.

As described earlier, utilisation of this column permitted the isolation of thiachromenes (7),(9),(10),(12),(19) and (20), while (11) crystallised from the distillate of the reaction product on standing; the u.v. and n.m.r. data of these compounds appear in Tables 3 and 4 respectively.

2,2,4-Trimethyl-2H-thiachromene, (7).

Short path distillation of the column eluate gave a colourless liquid (7), b.p. 40°C/0.02 mm Hg; m/e 190 (M^+), base peak at m/e 175 corresponding to methyl loss;

ν_{max} (thin film) 3078 (w), 3050 (w), 3010 (w), 2970 (s), 2922 (m), 1585 (w), 1469 (s), 1431 (s), 1359 (m), 1129 (m), 812 (m), 755 (s), 732 (s) cm^{-1};

(Found : C, 75.94; H, 7.46. $C_{12}H_{14}S$ requires C, 75.76; H, 7.42%).

2,2,4,7-Tetramethyl-2H-thiachromene, (9).

Similarly isolated as a colourless liquid, b.p. 74 - 75°C/0.025 mm Hg; m/e 204 (M^+), base peak at m/e 189;

ν_{max} (thin film) 3070 (w), 3020 (w), 2978 (s), 2930 (s), 1602 (m), 1488 (s), 1462 (m), 1440 (m), 1385 (m), 1362 (m), 1140 (m), 825 (s) cm^{-1};

(Found : C, 76.55; H, 7.92. $C_{13}H_{16}S$ requires C, 76.44; H, 7.90%).

2,2,4,6-Tetramethyl-2H-thiachromene, (10).

Similarly isolated as a colourless liquid, b.p. 70°C/0.01 mm Hg; m/e 204 (M^+), base peak at m/e 189;

ν_{max} (thin film) 3070 (w), 3030 (w), 2960 (s), 2918 (s), 1465 (s), 1435 (w), 1375 (m), 1358 (s), 1132 (s), 810 (s), 609 (m) cm^{-1};

(Found : C, 76.57; H, 7.90. $C_{13}H_{16}S$ requires C, 76.44; H, 7.90%).

2,2,4-Trimethyl-7,8-benzo-2H-thiachromene, (11).

The distillate of the product from (5) became a yellow, waxy solid on standing; sublimation of this material (70°C/0.01 mm Hg) gave a liquid which slowly crystallised. Recrystallisation from light petroleum (75% recovery) produced white prisms, m.p. 104 - 106°C; m/e 240 (M^+), base peak at m/e 225;

ν_{max} (KBr disc) 3048 (w), 2975 (m), 2964 (w), 1502 (m), 1378 (m), 1360 (m), 1336 (m), 1132 (m), 828 (s), 760 (sh), 756 (s) cm^{-1};

(Found : C, 79.96; H, 6.84. $C_{16}H_{16}S$ requires C, 79.97; H, 6.71%).

2,2,4-Trimethyl-5,6-benzo-2H-thiachromene, (12).

Eluted from the gel column as a white solid (approx. S.E.V. 350); recrystallisation from light petroleum (53% recovery) gave large, white crystals, m.p. 73 - 74°C; m/e 240 (M^+), base peak at m/e 225;

ν_{max} (KBr disc) 3044 (w), 2978 (s), 2962 (w), 1612 (w), 1584 (m), 1502 (m), 1374 (w), 1355 (s),

1158 (m), 1124 (s), 812 (s), 779 (s), 748 (s) cm^{-1};

(Found : C, 79.92; H, 6.84. $C_{16}H_{16}S$ requires C, 79.97; H, 6.71%).

2,4,4-Trimethyl-4H-thiachromene, (19).

Short path distillation of the column eluate gave a pale yellow oil, b.p. 50°C/0.03 mm Hg; never obtained completely free of minor impurities;

m.s. peaks at m/e 175 (base peak), 190 and 192 in the ratio 100:15:30;

ν_{max} (thin film) 3058 (w), 2960 (s), 2920 (m), 1588 (w), 1470 (s), 1430 (m), 1382 (w), 1365 (w), 1358 (w), 1126 (m), 752 (s), 732 (s) cm^{-1};

(Found : C, 75.60; H, 7.62. $C_{12}H_{14}S$ requires C, 75.76; H, 7.42%).

2,4,4,6-Tetramethyl-4H-thiachromene, (20).

Similarly isolated as a pale yellow oil, b.p. 70°C/0.05 mm Hg; never obtained free of minor impurities;

m.s. peaks at m/e 189 (base peak), 204 and 206, the ratio of the latter two being 1:3;

ν_{max} (thin film) 3035 (w), 3000 (w), 2950 (s), 2908 (s), 1718 (sh), 1705 (s), 1478 (sh), 1460 (s), 1380 (m), 1362 (m), 1118 (m), 805 (s) cm^{-1};

(Found : C, 76.15; H, 8.10; $C_{13}H_{16}S$ requires C, 76.44; H, 7.90%).

V. Reaction of Thiachromenes (7),(9),(11) and (12) with PPA.

Polyphosphoric acid was prepared by heating P_2O_5 (800 mg) with orthophophoric acid (0.5 ml) at 150°C for 1 hour; 2,2,4-

trimethyl-5,6-benzo-2H-thiachromene (12) (203 mg) was added at room temperature giving a bright red solution, this colour still persisting after stirring for 3 hours at 100°C. On cooling, the mixture was poured into iced water (10 ml), and extracted with ether (3 x 10 ml). The extracts were washed with saturated sodium bicarbonate solution (1 x 10 ml), and with water (3 x 15 ml), then dried over anhydrous sodium sulphate. Solvent evaporation left a clear brown oil (198 mg), comprising mainly the ring-contracted product (18), together with some unreacted starting material, as revealed by ^{1}H n.m.r.. Sublimation of this sample (68°C/0.01 mm Hg) yielded a damp solid, which, on recrystallisation from light petroleum, gave white crystals, identical in every respect to unambiguously prepared (18).

Similar small-scale reactions were performed on thiachromenes (7),(9) and (11), except that in the case of (11), both the weight of polyphosphoric acid and the reaction time were increased, in view of the low percentage of (17) formed during the PPA treatment of the ketosulphide (5). On mixing with PPA, each of these thiachromenes gave a bright persistent colour viz. blue, violet and green for (7), (9) and (11) respectively; also, almost quantitative recoveries were achieved, the only compounds present being the starting thiachromenes and the ring-contracted analogues. The percentage rearrangement was calculated in each case from the ^{1}H n.m.r. spectrum of the products (Table 5).

VI. Reaction of Mesityl Oxide and Thiophenol with PPA.

Polyphosphoric acid was prepared in the usual way from phosphorous pentoxide (8 g) and orthophosphoric acid (5 ml); when cooled to room temperature, there was added simultaneously thiophenol (1.08 g, 9.8 mmole) and mesityl oxide (0.96 g, 9.8 mmole) giving a

brown/green solution which became a black viscous mixture after 3 hours stirring at 100°C. The product was poured into iced water (50 ml), giving an orange solution which was extracted with ether (3 x 50 ml). The extracts were washed with 5M NaOH (1 x 25 ml) to remove unreacted thiophenol, then washed with water (3 x 75 ml) until pH~7. After drying (Na_2SO_4), solvent evaporation gave a dark brown oil (0.20 g); distillation yielded a yellow liquid, boiling range 66 - 98°C/0.06 mm Hg, 0.16 g, equivalent to 8% recovery of material. ^1H n.m.r. exposed several compounds, prominent among which are the 2H-thiachromene (7) and the benzo(b)thiophene (13) as well as the hoped for 2,4,4-trimethyl-4H-thiachromene (19); the approximate ratio of (7):(13):(19) is 1 : 1.25 : 2.

VII. Unambiguous Synthesis of 2-Isopropyl-3-methyl-benzo(b)-thiophene, (13).

3-Bromo-4-methylpentan-2-one was prepared according to Cardwell and Kilner[66], using the route to halogenated ketones established by Jones et al.[67]. Careful distillation gave a high yield of a colourless liquid, b.p. 53 - 55°C/12 mm Hg;

m.s.	bromine isotope pattern revealed by peaks at m/e 178 and 180 (M^+);
ν_{max} (thin film)	2980 (m), 2945 (w), 2880 (w), 1711 (s), 1368 (w), 1358 (m), 1222 (w) cm^{-1};
$\tau(CDCl_3)$	5.98 (1H, d, J = 8 Hz, -CHBr-), 7.66 (3H, s, CH_3CO), 7.5 - 8.0 (1H, m, -CH-), 8.95 (6H, t, J = 6 Hz, $C(CH_3)_2$);

(Found : Br, 44.37. $C_6H_{11}OBr$ requires Br, 44.62%).

Clean sodium (4.5 g, 196 mmole) was dissolved in dry methanol (150 ml) under a stream of nitrogen; thiophenol (21.5 g, 196 mmole)

was poured in and the solution boiled for 5 minutes, then allowed to cool. The above bromoketone (35 g, 195 mmole) was added dropwise with the immediate formation of a pale yellow precipitate; the mixture was refluxed for thirty minutes then stirred overnight at room temperature. After filtration of the sodium bromide, the solvent was evaporated giving a brown oil; two distillations gave 3-phenylthio-4-methylpentan-2-one (27) as a colourless liquid, b.p. 68 - 70°C/0.02 mm Hg;

m.s. m/e 208 (M^+), other prominent peaks at m/e 165, 123, 109;

ν_{max} (thin film) 3060 (w), 2965 (s), 2936 (w), 1705 (s), 1584 (m), 1482 (m), 1468 (m), 1440 (s), 1370 (w), 1355 (s), 1222 (m), 750 (sh), 740 (s), 692 (s) cm^{-1};

τ($CDCl_3$) 2.5 - 2.9 (5H, m, aromatics), 6.65 (1H, d, J = 9 Hz, $(CH_3)_2\underline{CH}$-), 7.81 (3H, s, CH_3CO), ca. 7.90 (1H, m, S-CH-), 8.80 and 9.00 (each 3H, 2d, J = 6 Hz for both, $C(CH_3)_2$);

(Found : C, 69.38; H, 7.78. $C_{12}H_{16}OS$ requires C, 69.21; H, 7.74%).

(27) was cyclised with polyphosphoric acid (3 hours at 100°C, and work-up as before) giving (13) as a colourless liquid, b.p. 147°C/12 mm Hg, 72%;

m.s. m/e 190 (M^+), other prominent peaks at m/e 175, 147, 115.

ν_{max} (thin film) 3060 (w), 2965 (s), 2928 (m), 1462 (s), 1436 (s), 1385 (m), 1364 (m), 1312 (m), 1201 (m), 752 (s), 728 (s), 714 (m) cm^{-1};

λ_{max} (EtOH) 233 ($\log \varepsilon$ 4.54), 268 (3.78), 290 (3.43), 299(3.27)nm;

(Found : C, 75.89; H, 7.50. $C_{12}H_{14}S$ requires C, 75.76; H, 7.42%).

VIII. Unambiguous Synthesis of 2-Isopropyl-3-methylnaphtho-(1,2-b)thiophene, (17).

Repeating the above route using naphthalene-1-thiol instead of benzenethiol gives 3-(1-naphthylthio)-4-methylpentan-2-one as a brown solid (74%). Sublimation (ca. 40°C/0.02 mm Hg) and recrystallisation (light petroleum) gives white needles, m.p. 41 - 43°C;

m.s. m/e 258 (M^+), other prominent peaks at m/e 215, 173, 159, 115;

ν_{max} (KBr disc) 3060 (w), 2962 (m), 1696 (s), 1504 (m), 1370 (w), 1355 (m), 1230 (m), 805 (s), 770 (s), 738 (m) cm^{-1};

$\tau(CDCl_3)$ 1.4 - 1.6 (1H, m, aromatic proton), 2.0 - 2.8 (6H, m, other aromatics), 6.54 (1H, d; J = 9 Hz, $(CH_3)_2C\underline{H}$ -), ca. 7.8 (1H, m, S-CH-), 7.85 (3H, s, CH_3CO), 8.67 and 9.00 (each 3H, 2d, J = 6 Hz, $C(CH_3)_2$);

(Found : C, 74.60; H, 7.13. $C_{16}H_{18}OS$ requires C, 74.39; H, 7.02%).

Cyclisation of this ketosulphide with PPA (3 hours at 100°C) gives a brick-red solid (86%) which on recrystallisation (light petroleum) yields white crystals of (17), m.p. 72 - 73°C;

m.s. m/e 240 (M^+), other prominent peaks at m/e 225, 210, 165;

ν_{max} (KBr disc) 3040 (w), 2955 (m), 1462 (m), 1378 (m), 1310 (m), 1252 (m), 1205 (m), 855 (m), 805 (s), 745 (sh), 742 (s) cm^{-1};

λ_{max} (EtOH) 230 (logε 4.21), 240 (4.19), 249 (4.27), 272 (4.56), 331 (2.91), 347 (2.81) nm;

(Found : C, 79.81; H, 6.89. $C_{16}H_{16}S$ requires C, 79.97; H, 6.71%).

IX. Unambiguous Synthesis of 1-Methyl-2-isopropylnaphtho(2,1-b)-thiophene, (18).

Similarly employing naphthalene-2-thiol yields 3-(2-naphthylthio)-4-methylpentan-2-one as a yellow viscous liquid, b.p. 134 - 136°C/0.05 mm Hg, 47%;

m.s. m/e 258 (M^+), other prominent peaks at m/e 215, 159, 115;

ν_{max} (thin film) 3055 (m), 2962 (s), 2930 (m), 1702 (s), 1502 (m), 1370 (m), 1355 (s), 1225 (m), 852 (m), 815 (s), 745 (s), 475 (s) cm^{-1};

τ ($CDCl_3$) 2.1 - 2.8 (7H, m, aromatics), 6.53 (1H, d, J = 9 Hz, $(CH_3)_2\underline{CH}$-), 7.81 (3H, s, CH_3CO), ca. 7.9 (1H, m, S-CH-), 8.77 and 8.99 (each 3H, 2d, J = 6 Hz for both, $C(CH_3)_2$);

(Found : C, 74.50; H, 7.08. $C_{16}H_{18}OS$ requires C, 74.39; H, 7.02%).

Cyclisation of this ketosulphide with PPA (3 hours at 100°C) produces a pale yellow solid (87%) which on two recrystallisations (light petroleum) gives (18) as white crystals, m.p. 72 - 74°C;

m.s. m/e 240 (M^+), other prominent peaks at m/e 225, 210, 165;

ν_{max} (KBr disc) 3050 (w), 2962 (m), 2920 (w), 1508 (w), 1455 (m), 1371 (m), 1360 (m), 1318 (m), 900 (m), 802 (s), 780 (s), 748 (s), 742 (s), 684 (m) cm^{-1};

λ_{max} (EtOH) 232 (logε 4.56), 243 (4.58), 2.57 (4.45), 302 (4.15), 334 (3.19) nm;

(Found : C, 80.10; H, 6.66. $C_{16}H_{16}S$ requires C, 79.97; H, 6.71%).

^{1}H n.m.r. parameters for (13), (17) and (18) were identical

to those found from corresponding materials obtained by rearrangement and are listed in Table 4. Mixtures of samples from the two sources also gave identical ^{1}H n.m.r. spectra, and mixed melting points for (17) and (18) were found to be undepressed.

REFERENCES

1. E. Campaigne, D.R. Knapp, E.S. Neiss and T.R. Bosin, Adv. Drug Res., 1970, 5, 1.
2. T.R. Bosin, R.P. Maickel, A. Dinner, A. Snell and E. Campaigne, J. Heterocyclic Chem., 1972, 9, 1265.
3. T.R. Bosin, E. Campaigne and R.P. Maickel, Life Sci., 1972, 11, Part 1, 685.
4. E. Campaigne and R.B. Rogers, J. Heterocyclic Chem., 1973, 10, 297.
5. K. Kikugawa and M. Ichino, Chem. and Pharm. Bull. (Japan), 1973, 21, 1151.
6. J.G. Lombardino and E.H. Wiseman, J. Medicin. Chem., 1970, 13, 206.
7. J.R. Kilsheimer, H.A. Kaufman, H.M. Foster, P.R. Driscoll, L.A. Glick and R.P. Napier, J. Agric. Food Chem., 1969, 17, 91.
8. R.R. Grenshaw, A.T. Jeffries, G.M. Luke, L.C. Cheney and G. Bialy, J. Medicin. Chem., 1971, 14, 1185.
9. V. Erspamer, Progr. Drug Res., 1961, 3, 151.
10. N.B. Chapman, R.M. Scrowston and R. Westwood, J. Chem. Soc. (C), 1969, 1855.
11. R.M. Pinder, D.M. Green and P.B.J. Thompson, J. Medicin. Chem., 1971, 14, 626.
12. E. Campaigne, R.B. Rogers, A. Donelson and T.R. Bosin, J. Heterocyclic Chem., 1973, 10, 979.
13. N.B. Chapman, K. Clarke, A.J. Humphries and S.U-D. Saraf, J. Chem. Soc. (C), 1969, 1612.
14. N.B. Chapman, K. Clarke, B.A. Gore and K.S. Sharma, J. Chem. Soc. (C), 1971, 915.
15. A. Lowenbein, Ber., 1924, 57, 1517.

16. R. Wizinger and H. Wenning, Helv. Chim. Acta, 1940, 23, 247.

17. R.A. Archer and B.S. Kitchell, J. Amer. Chem. Soc., 1966, 88, 3462.

18. R.B. Morin, D.O. Spry and R.A. Mueller, Tetrahedron Letters, 1969, 849.

19. R.B. Morin and D.O. Spry, Chem. Comm., 1970, 335.

20. I.W.J. Still and M.T. Thomas, Tetrahedron Letters, 1970, 4225.

21. H. Hofmann and G. Salbeck, Angew. Chem. Internat. Edn., 1969, 8, 456.

22. F. Krollpfeiffer, H. Schultze, E. Schlumbohm and E. Sommermeyer, Ber., 1925, 58, 1654.

23. W.D. Cotterill, C.J. France and R. Livingstone, and (in part) J.R. Atkinson and J. Cottam, J.C.S. Perkin I, 1972, 787.

24. A.G. Schultz and R.H. Schlessinger, Tetrahedron Letters, 1973, 4787.

25. A.G. Schultz and R.H. Schlessinger, Tetrahedron Letters, 1973, 4791.

26. A. Ruwet, J. Meessen and M. Renson, Bull. Soc. chim. belges, 1969, 78, 459.

27. N. Bellinger, D. Cagniant and P. Cagniant, Tetrahedron Letters, 1971, 49.

28. E. Fischer and A. Steche, Annalen, 1887, 242, 353.

29. W.E. Parham, C.G. Fritz, R.W. Soeder and R.M. Dodson, J. Org. Chem., 1963, 28, 577.

30. D.G. Hawthorne and Q.N. Porter, Austral. J. Chem., 1966, 19, 1751.

31. D. Sullivan and R. Pettit, Tetrahedron Letters, 1963, 401.

32. B. Iddon and R.M. Scrowston, Adv. Heterocyclic Chem., 1970, 11, 177.

33. W.E. Parham and R. Koncos, J. Amer. Chem. Soc., 1961, 83, 4034.

34. S.H. Groen, J. Org. Chem., 1968, 33, 2218.

35. D.C. Neckers and J. DeZwaan, Chem. Comm., 1969, 813.

36. K. Undheim and R. Lie, Acta Chem. Scand., 1973, 27, 595.

37. B.D. Tilak and V.M. Vaidya, Tetrahedron Letters, 1963, 487.

38. M.M. Dhingra, G. Govil, C.L. Khetrapal and V.M. Vaidya, Tetrahedron Letters, 1963, 497.

39. B.D. Tilak, H.S. Desai, C.V. Deshpande, S.K. Jain and V.M. Vaidya, Tetrahedron, 1966, 22, 7.

40. B.D. Tilak, T. Ravindranathan and K.N. Subbaswami, Tetrahedron Letters, 1966, 1959.

41. B.D. Tilak and Z. Muljiani, Tetrahedron, 1968, 24, 949.

42. B.D. Tilak, R.B. Mitra and Z. Muljiani, Tetrahedron, 1969, 25, 1939.

43. P.E. Eaton and R.H. Mueller, J. Amer. Chem. Soc., 1972, 94, 1014.

44. J. Porath and P. Flodin, Nature, 1959, 183, 1657.

45. C.J.W. Brooks and R.A.B. Keates, J. Chromatog., 1969, 44, 509.

46. J. Ellingboe, E. Nystrom and J. Sjovall, Biochim. Biophys. Acta, 1968, 152, 803.

47. J. Ellingboe, E. Nystrom and J. Sjovall, J. Lipid Res., 1970, 11, 266.

48. E. Kovats, Helv. Chim. Acta, 1958, 41, 1915.

49. E. Kovats and A. Wehrli, Helv. Chim. Acta, 1959, 42, 2709.

50. R.A.B. Keates and C.J.W. Brooks, Biochem. J., 1969, 114, 16P.

51. K.D. Bartle, D.W. Jones and R.S. Mattews, Tetrahedron, 1971, 127, 5177.

52. E. Campaigne and R.E. Cline, J. Org. Chem., 1956, 21, 39.

53. E.G.C. Werner, Rec. Trav. chim., 1949, 68, 509.

54. H.M.E. Cardwell and A.E.H. Kilner, J. Chem. Soc., 1951, 2430.

55. R.P. Dickinson and B. Iddon, J. Chem. Soc.(C), 1968, 2733.

56. O. Dann and M. Kokorudz, Chem. Ber., 1958, 91, 172.

57. A.G. Schultz and M.B. DeTar, J. Amer. Chem. Soc., 1974, 96, 296.

58. K. Clarke, D.N. Gregory and R.M. Scrowston, J.C.S. Perkin I, 1973, 2956.

59. L.J. Pandya and B.D. Tilak, J. Sci. Ind. Res., India, 1959, 18B, 371.

60. R. Zahradnik and C. Parkanyi, Coll. Czech. Chem. Comm., 1965, 30, 3016.

61. R. Zahradnik and C. Parkanyi, Coll. Czech. Chem. Comm., 1965, 30, 195.

62. W. Carruthers and J.R. Crowder, J. Chem. Soc., 1957, 1932.

63. E.R. de Waard, W.J. Vloon and H.O. Huisman, Chem. Comm., 1970, 841.

64. W.H. Mueller, Angew. Chem. Internat. Edn., 1969, 8, 482.

65. C. Eaborn and G.J. Wright, J. Chem. Soc. (B), 1971, 2262.

66. H.M.E. Cardwell and A.E.H. Kilner, J. Chem. Soc., 1951, 2430.

67. J.R. Catch, D.F. Elliott, D.H. Hey and E.R.H. Jones, J. Chem. Soc., 1948, 272.

68. A. Chatterjee and B.K. Sen, Chem. Comm., 1974, 626.

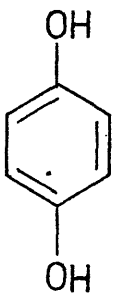
Section 2

Design and Synthesis of Clathrate Hosts.

INTRODUCTION

I. Clathrates[1] - what are they?

For about a century chemists speculated that certain compounds might enclose other species of suitable size and geometry, but it was not until the late 1940's, however, that this form of molecular architecture was actually shown to exist. The first reported instance of clathrate formation was in 1849, when Wöhler[2] prepared two compounds $4C_6H_4(OH)_2 \cdot H_2S$ and $3C_6H_4(OH)_2 \cdot H_2S$; shortly afterwards while attempting to synthesise hydroquinone (I) by sulphur dioxide



(I)

reduction of an aqueous solution of benzoquinone, Clemm[3] stumbled upon a compound of composition $3C_6H_4(OH)_2 \cdot SO_2$. Under normal conditions these crystals are perfectly stable and have no smell of the occluded gas, but if ground in a mortar, dissolved or melted, then a smell characteristic of the gas evolved, is detected; this observation was perhaps the first contribution to an understanding of the nature of these compounds since the volatile component could not be held by conventional chemical bonds. At that time chemical theory naturally suggested expressing their composition by the ratio of hydroquinone molecules to a single gas molecule, a practice which probably played a part in misdirecting thought and discouraging further attention. Clearly they did not obey some of the rules as then understood, and could not be formulated in a chemically acceptable way.

In 1886 Mylius[4] came near an explanation while investigating several interesting and intriguing features of the complex compounds formed by hydroquinone with certain volatile substances; he suggested that no ordinary combination occurred between the molecules which formed the complexes, and that somehow the molecules of hydroquinone were able to lock the second component into position, but without chemical bonding. To him it seemed probable that a complex resulted from the complete enclosure of one molecule by two or more molecules of another component in such a manner as to prevent escape of the enclosed molecule, unless the strong forces which hold together the enclosing molecules could be broken.

Interest in these compounds lay dormant until the 1940's when the classical X-ray work of Powell[5] demonstrated that hydroquinone molecules link together through hydrogen bonds to form infinite, three dimensional complexes, and that these giant molecules do, indeed, enclose a second component. Together with his coworkers, he noted the firmness with which the components were held together, even though no strong attractive forces appeared to be acting between them. Powell[6], therefore, proposed that the apt term "clathrate", from the Latin clathratus meaning "enclosed by the crossbars of a grating", be used to describe this class of molecular compounds having a regular cage structure in which one component (the host) physically encloses the other component (the guest).

The best-known clathrates are those in which hydroquinone forms the host component; in addition to the sulphur dioxide and hydrogen sulphide clathrates previously mentioned, it forms a series of molecular compounds with for example HCN, HCl, HBr, MeCN, HCO_2H, CO_2 and the noble gases. Powell was first to undertake a comprehensive X-ray study of the crystalline nature of hydroquinone, beginning with its sulphur dioxide clathrate[7]. The linking of hydroquinone molecules can be seen in Figure 1; the circles represent

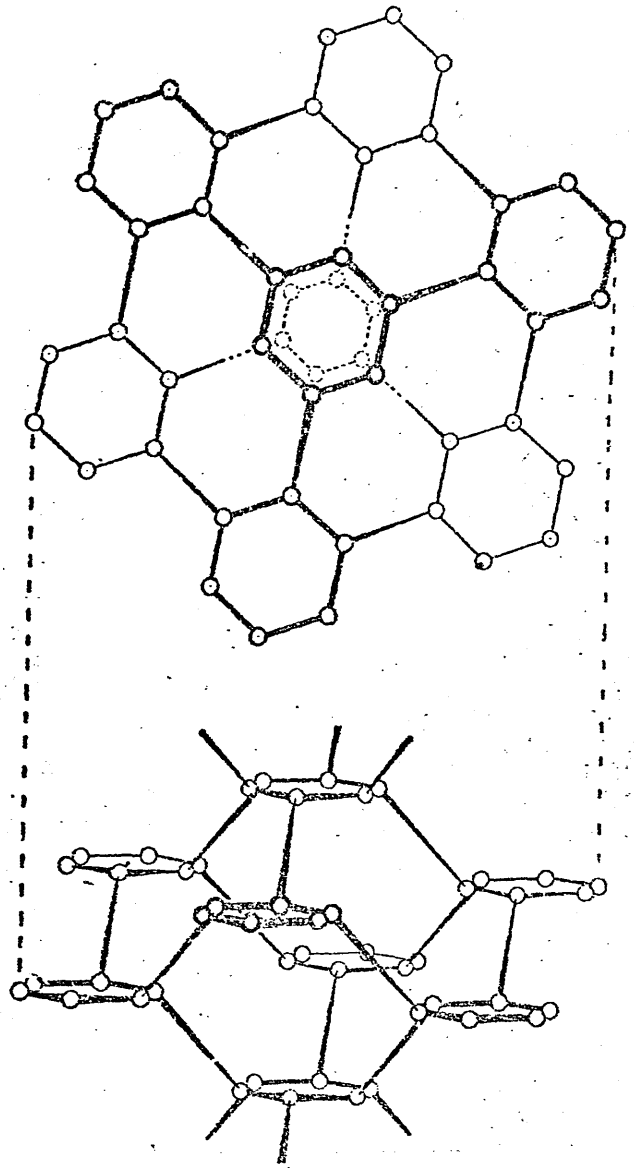


Figure 1. Manner of hydrogen bonding of hydroquinone molecules.

Above : Each regular hexagon denotes six hydrogen bonds between oxygen atoms. Hexagons at different levels are denoted by different line thickness. The tapered lines, representing the O - O axis of a hydroquinone molecule, show the method of linking to form an infinite three dimensional cagework. Each taper points downwards from the observer.

Below : Perspective drawing corresponding to the above. The hexagons denote the hydrogen bonds; the longer lines connecting different hexagons denote the O - O axis of the hydroquinone molecule.

(D.E. Palin & H.M. Powell, J.Chem.Soc., 1947, 208.)

oxygen atoms of the hydroxyl groups linked by hydrogen bonds to form approximately plane hexagons of side 2.7 A°. The central lines of six hydroquinone molecules extend alternately up and down from these oxygen atoms, thus forming an infinite cage in three dimensions. Although the hexagon is a satisfactory hydrogen bond arrangement, the molecular grouping is very ineffective as regards space filling; the gaps left are so large that it is possible to insert a second, identical, framework, displaced vertically halfway between the top and bottom hexagons, and the holes of the structure are such that the two cageworks are able to interpenetrate each other without closer contact than that usual for unlinked atoms.

Although the two frameworks approach to give normal van der Waals distances, there remain between the two cageworks cavities, of sufficient size to contain a small molecule, at normal unlinked distances from the surrounding atoms (Figure 2). These spaces are bounded by the oxygen hexagons of the two different equivalent frameworks on the top and bottom of the cavity, and by the aromatic rings on the sides; it is in these nearly spherical cavities, about 5 A° in diameter, that the trapped molecules are located. A particular cage, therefore, contains only guests which fall within a definite range of size and shape; the lower size limit is determined by the openings in the cage walls through which escape can occur - for example, the helium clathrate of hydroquinone cannot be prepared.

The above hydroquinone compounds are described as β-hydroquinone clathrates because the above structure does not readily form in the absence of clathratable material. Hydroquinone crystallised under normal conditions from solvents that cannot be trapped in the β-hydroquinone cavities has a different structure known as α-hydroquinone; a third variant is γ-hydroquinone, obtained by sublimation.

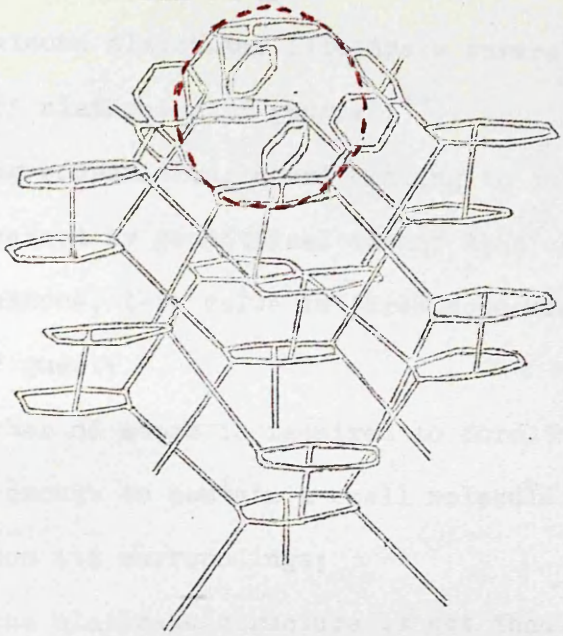


Figure 2. Representation of the interpenetration of two similar hydrogen-bonded cageworks, each identical with that shown in Figure 1. Benzene rings are shown by small hexagons in the upper part of the figure but are omitted elsewhere for clarity. The larger hexagons represent hydrogen bonds. The roughly spherical space between the two cageworks is outlined in red.

(D.E. Palin & H.M. Powell, J.Chem.Soc., 1947, 208.)

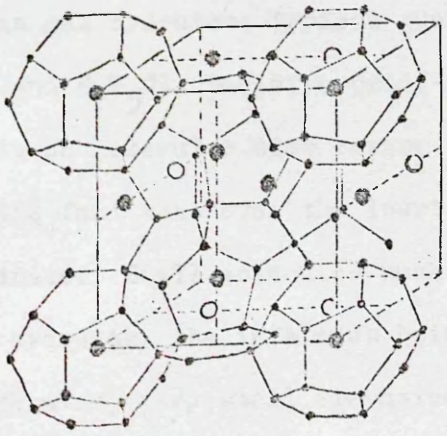


Figure 3. Structure of gas hydrates. Large circles, gas molecules; small circles, water molecules.

(M. von Stackelberg & H.R. Müller, Z. Electrochem., 1954, 58, 25.)

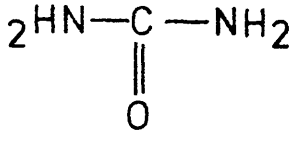
The hydroquinone clathrates illustrate several features characteristic of clathrates in general:

1. the limiting composition, corresponding to occupancy of every cage is governed by geometrical rather than chemical factors; for hydroquinone, this value is three molecules of host to one molecule of guest;
2. a large number of atoms is required to form the walls of a cage large enough to contain a small molecule at van der Waals distance from its surroundings;
3. sometimes the clathrate structure is not that normally given by the host when it is crystallised alone;
4. chemical reactivity between possible host and guest components precludes clathrate formation.

Many substances contain "water of crystallisation" when isolated from aqueous solutions; called hydrates, most of these compounds are not clathrates but contain water molecules attached by the usual chemical bonds. The substances with which water does form true clathrates are largely gases or low-boiling liquids, and the complexes are known as gas hydrates; typical guests are Cl_2, Br_2, SO_2, H_2S, C_2H_6, CH_3I and C_2H_5Cl. Decisive proof that clathrate formation is dependent on molecular size rather than on chemical bonding arises from the fact that even the inert gases are capable of forming stable hydrates. Small molecules such as hydrogen, however, do not give hydrates, the inference being that, as with the hydroquinone clathrates, very small dimensions are unfavourable, since an imprisoning action depends on a sufficient size of trapped molecule in relation to possible escape holes in the surrounding cage structure. X-ray studies of these gas hydrates have shown that five water molecules are linked together, through hydrogen bonds, to form rings, the rings then joining up to produce dodecahedra

(Figure 3). The packing of these structures is such that space cannot be completely filled and it is in the interstices that the guest molecules reside.

A different type of structure has been found in the crystalline inclusion compounds formed by urea (II) and thiourea (III) where the cavities of the host crystal consist of long cylindrical spaces in which the guest molecules lie end to end. Urea has long been known



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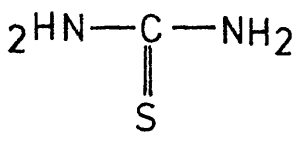


(III)

to form stable adducts[8], but interest was only reawakened by the accidental discovery, in 1940, by Bengen[9] that it complexed almost exclusively with straight chain hydrocarbons and their derivatives, while simultaneously rejecting branched and cyclic paraffins. The interconnected urea molecules, held together by hydrogen bonds between nitrogen and oxygen atoms, are arranged in a similar fashion to the wax in a honeycomb, leaving long tubular cavities of 5 A^{o} diameter. This size is ideal for the accommodation of linear hydrocarbons, and any such substance having a chain length of more than six carbon atoms will complex with urea at room temperature.

Thiourea has a similar crystal structure but the channel diameter is increased from five to seven angstroms because of the greater size of the sulphur atom. This small, but meaningful, change has important consequences since too much of the cavity would be left unfilled by an n-alkane, and any possible complex would simply collapse. Conversely, the channel is ideally suited to the trapping of bulky guest molecules, such as branched paraffins and small cyclic hydrocarbons - one of the largest compounds to form a thiourea adduct is 2,6,9,13,16-pentamethylheptadecane which has a

length of approximately 22 A°. The urea and thiourea complexes resemble the hydroquinone clathrates in that the presence of the guest induces the host to adopt configurations different from those of their normal structures, but they differ from the clathrates since they produce channel rather than cage structures.

Channels of a similar type to those formed by the ureas can be found among the inclusion compounds of cyclodextrin; here, however, the cavity is not in the lattice but in a single molecule and, consequently, the complex is not disintegrated by dissolving the crystal, the hole existing even in solution. Extensive studies by Cramer[10] have proved that these crystalline compounds are rigid, doughnut-shaped molecules formed by joining glucose units together in rings, and are thus the cyclic analogues of amylose, which contains the same units linked together in long chains. Three cyclodextrins are known (α, β and γ), containing six, seven and eight glucose units, and having internal diameters of about six, eight and ten A° respectively (Figure 4); they form a true homologous series, so that in any problem, the correct host can be found for a prospective guest. As expected, as the diameter of the void increases, the size of the molecules clathrated likewise increases. For example, bromobenzene is too wide to fit in α-cyclodextrin whereas β- and γ-cyclodextrins form clathrates with bromobenzene quite readily. The behaviour with halogens is likewise typical; Cl_2, Br_2 and I_2 are clathrated by α-cyclodextrin while β-cyclodextrin includes only Br_2 and I_2 since Cl_2 is too small. γ-Cyclodextrin combines only very loosely with I_2.

The remarkable ability of deoxycholic acid (IV) to form inclusion compounds with a capricious range of solvents was first observed by Wieland and Sorge[11]. An arched architecture is conferred on this molecule on account of the cis fusion of its A/B rings, and two of these sickle-shaped structures are held together by hydrogen bonding,

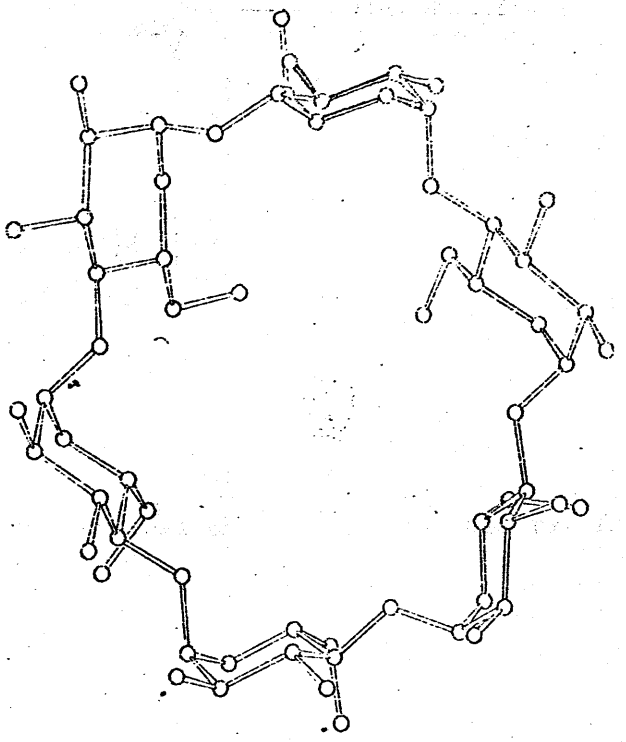
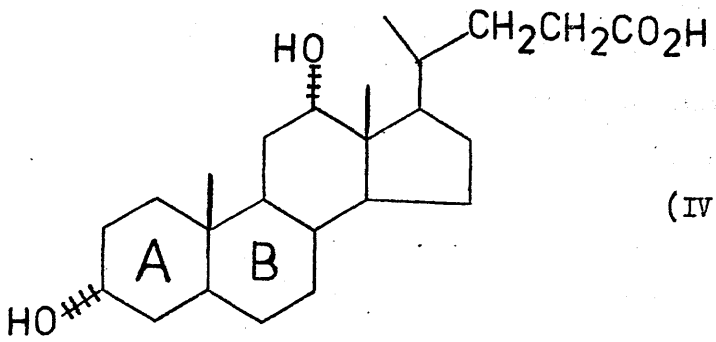


Figure 4. The torus shaped cavity of α-cyclodextrin.

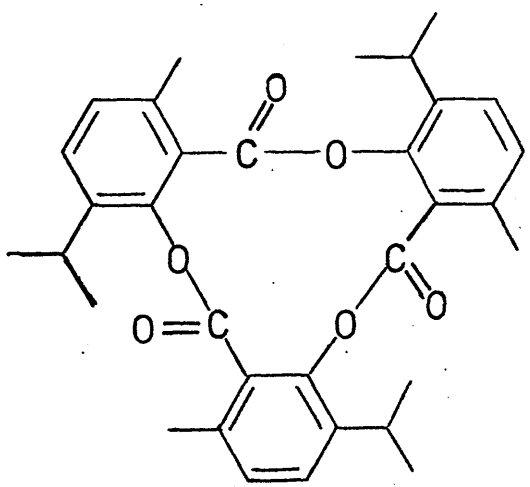
(P.C. Manor & W. Saenger, Nature, 1972, 237, 392.)



(IV)

leaving free, oval-shaped channels in the centre. In this case, straight-chain as well as highly-branched molecules may be included, for instance fatty acids, xylene, naphthalene, benzaldehyde and camphor.

The molecular compounds formed by tri-o-thymotide (V) provide a fascinating example of how the structure adopted by the host can be



(V)

modified by the presence of a guest. Urea and β-hydroquinone do not form inclusion compounds with molecules which have some dimension

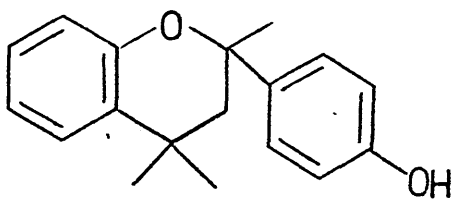
incompatible with the space available. With (V) similar critical dimension are found[12], but molecules are not divided by these limits into those which do and those which do not form molecular compounds; rather, the dimensions determine which of several structurally different types of molecular compound is formed. If the guests do not differ much from the "straight"-chain type, the resulting structure belongs to one of two classes; a clathrate type, $2C_{33}H_{36}O_6.M$, is formed when the guest, M, has a length less than 9.5 A^{o}. Longer guests are enclosed in a different channel-type structure of composition $C_{33}H_{36}O_6.xM$, where x, which need not be rational, diminishes with increasing length of the guest. Molecules capable of being accommodated in the cavity include methylene iodide, and ethanol while, for example, n-pentyl iodide and diethyl mercury require the channel structure[13].

The foregoing examples do not constitute a comprehensive survey of all the inclusion compounds encountered in organic chemistry, but serve only to illustrate the spectacular manner in which clathrates have risen from being curiosities to take a place of increasing importance on the chemical scene.

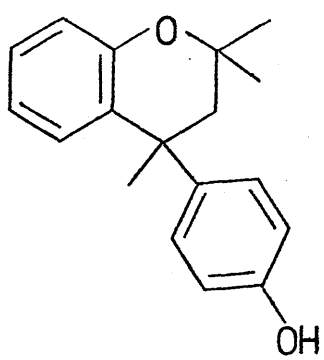
II. Dianin's Compound and its Sulphur Analogue.

In 1914 the Russian chemist Dianin[14] was studying the reaction of various ketones with phenol, and observed that a mixture of phenol (2 moles) and mesityl oxide (1 mole), saturated with gaseous HCl, thickened to a solid crystalline mass during the period of a month. After removal of the excess phenol with boiling water, the crude product was recrystallised yielding needle-like crystals, always containing a fixed amount of the several solvents from which it was deposited; crystalline adducts were formed with ethanol, acetone,

acetic acid, chloroform and ether. Desolvated material, obtained by melting the crystals, analysed satisfactorily for $C_{18}H_{20}O_2$; treatment with potassium hydroxide gave o-hydroxybenzoic acid while the action of chromic acid on its methyl ether produced p-methoxybenzoic acid. Distillation gave phenol and an olefin, $C_{12}H_{14}O$, which recombined with phenol to yield $C_{18}H_{20}O_2$ when treated with hydrogen chloride. On the evidence available Dianin proposed that the isolated product was the monohydric phenol (VI).



(VI)



(VII)

No further work was done on the subject until Baker and McOmie were prompted to reinvestigate the reported behaviour in the light of Powell's recent work on inclusion compounds. Treating the alleged product with potassium permanganate gave a solid, $C_{13}H_{16}O_3$, which was shown to be 2,2,4-trimethylchroman-4-carboxylic acid, thus proving that Dianin's compound was (VII), a structure previously rejected on somewhat obscure grounds. Similarly, the derived olefin was shown by its synthesis from 4-methylcoumarin to be essentially 2,2,4-trimethyl-2H-chromene. In addition to the previous examples, the authors demonstrated that (VII) formed stable inclusion complexes with SO_2, Ar, I_2 and with a wide variety of organic solvents.

In an accompanying publication Powell and Wetters[16] gave details of crystallographic examinations of these compounds; several adducts as well as the desolvated material were found to have

similar crystalline forms, and all gave the same unit cell dimensions, namely $\underline{a}$ = 27.0 and $\underline{c}$ = 11.1 A°, referred to hexagonal axes. The authors continued by speculating on whether the guests are located in channels or in cages, eventually coming out in favour of the latter. The structure has space group $R\bar{3}$ and thus any atom is one of a group of six equivalents related by a rotation inversion axis $\bar{3}$; the OH groups could link by hydrogen bonds in a hexagon of side about 2.8 A°, similar to that found in hydroquinone clathrates which have the same space group symmetry, but in this instance there is no second OH group to continue the pattern. Model structures showed that in the space of the unit cell three complexes of six hydrogen-bonded molecules could be arranged with satisfactory intermolecular contacts. The complex of six molecules has a form roughly resembling an hour-glass, the top and bottom of which are comprised of hexagons of hydrogen-bonded hydroxyl groups with alternate molecules pointing up and down to confer the cup-like geometry. (Figures 5 and 6) In the crystal these complexes are piled directly above each other with their symmetry axis parallel to the $\underline{c}$-axis; the distance between successive OH hexagons in the $\underline{c}$-direction is 11.1 A°, approximately twice that found in hydroquinone, thus indicating the great potential of this clathrate.

Conclusive proof that Dianin's compound was in reality (VII) came in 1956 with the repetition of some of the previously reported transformations together with speculation as to how the condensation took place[17]. Furthermore, crystalline adducts were found to form with no less than fifty organic solvents tried, as well as with SO_2, I_2 and ammonia; the majority of these give a ratio of 6:1 for Dianin's compound:guest, i.e. each cage, constructed from six molecules of host as proposed by Powell and Wetters[16], contains one molecule of solvent. With small molecules, such as ethanol and acetone, the ratio is 3:1, indicating double occupancy of the cavities,

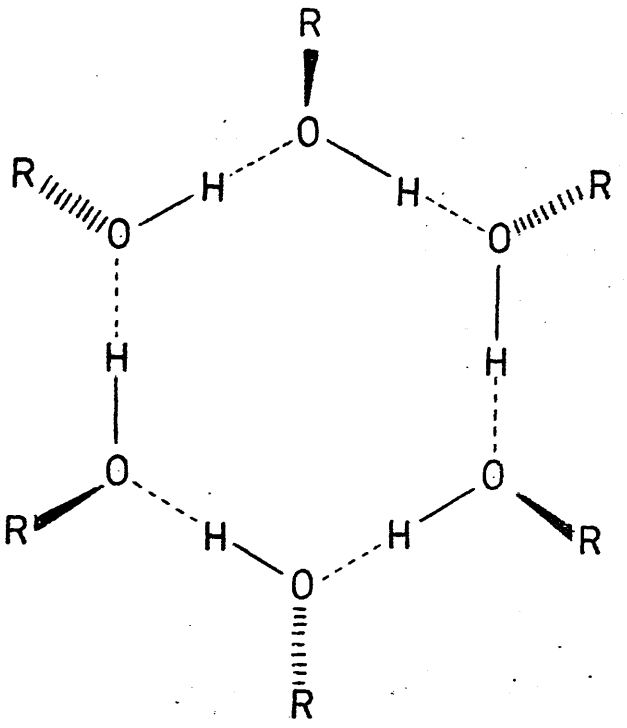


Figure 5. Hexagons of hydrogen bonded hydroxyl groups form the floor and ceiling of the cavities. R = $C_{18}H_{19}O$.

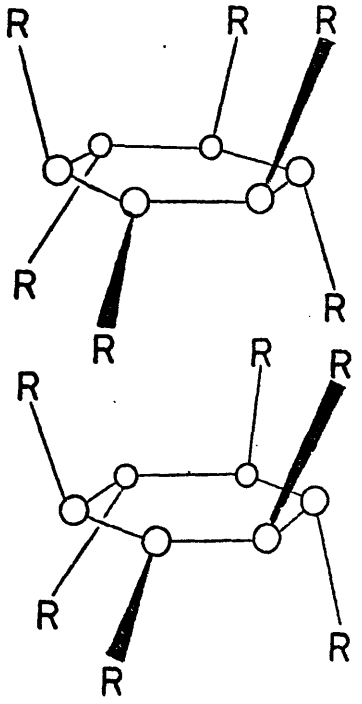
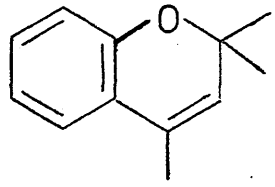


Figure 6. Alternate R groups point up and down from the hexagons to confer the cup-like geometry on the cavity. R = $C_{18}H_{19}O$.

while higher ratios are observed with larger guests, for example 8:1 with 1-methylnaphthalene, corresponding to some cages being left unfilled. An attempt to prepare derivatives of Dianin's compound substituted in the phenolic nucleus was made by condensing substituted phenols with 2,2,4-trimethylchromene (VIII); with m- and p-cresol



(VIII)

the chromene yielded non-phenolic resins, probably cresol ethers, but o-cresol gave a phenolic crystalline homologue of Dianin's compound, which formed no complexes with solvents. 1,2-Dihydroxybenzene also combined with the chromene, but the product could not be crystallised and it gave no adducts. The structure of Dianin's compound was confirmed as 4-p-hydroxyphenyl-2,2,4-trimethylchroman, (VII), by an unambiguous synthesis described in a subsequent communication[18].

The first indication of the compound's potential use came in 1960 with the preparation[19] and patenting[20] of the sulphur hexafluoride clathrate; obtained by recrystallisation at a high pressure of SF_6, the material was found to contain about 13% by weight of the gas, equivalent to a host : guest ratio of 6 : 1.7. The clathrate, therefore, constitutes a convenient means of storage and controlled release of this gas, which has been found to be of considerable use in the electrical industry on account of its low dielectric constant. Examination of the i.r. spectra revealed that chemical interactions between the SF_6 and the enclosing cages are slight, since the additional peak at 938 cm^{-1} from the clathrated species corresponds to one of the fundamental vibration frequencies of the free gas, reported

as[19] 940 and 932 cm^{-1}. The stability of the clathrate was studied for various temperatures and pressures; after three years at room temperature and atmospheric pressure less than 0.5% decomposition had occurred. Evidence that the guest-free form of Dianin's compound also possessed the clathrate structure was derived from density measurements. A futher application of Dianin's compound has been reported[21]; the diethylamine clathrate can be employed as a developer in the production of heat-sensitive copying sheets.

Since the early 20th. century it has been known that phenol and some of its derivatives can form inclusion compounds; these together with Dianin's compound have been reviewed by Bhatnagar[22]. The inclusion of several carbohydrates in Dianin's compound and in β-cyclodextrin has been investigated[23] with the aim of ascertaining whether clathration affects their reactivity. It was found, for example, that glycerol included in Dianin's compound was protected from oxidation by hydrogen peroxide and lead tetraacetate, but not from attack by periodic acid. Cyclodextrin with its more open structure offered less shelter, there being no essential difference between oxidation of included and free carbohydrates.

No systematic X-ray analysis of Dianin's compound was attempted until 1970 when Flippen, Karle and Karle[24] established the crystal structures of the ethanol and chloroform clathrates. Their results, in agreement with the preliminary work of Powell, reveal that six molecules are held together by hydrogen bonding between their hydroxyl groups (OH ....O = 2.85 A^{o}) to form a large complex in which alternate molecules point up and down; the complexes are stacked directly above each other, with their symmetry axis parallel to the c-axis, to form long columns. A cage is produced when two of these complexes line up together, with one hexagon of hydrogen-bonded oxygens forming the floor of the cage, and the next hexagon of hydrogen-bonded oxygens, one unit cell away in c, forming the ceiling

of the cage. The hour-glass shape is conferred on the cavity by the gem-dimethyl groups protruding into the void, giving rise to a waist at Z ~0.5; the cage is much larger than that of the hydroquinone clathrates, being about 11 A° in length, and 6.2 A° wide at its point of maximum extension at Z ~0.3 and Z ~ 0.7. This cage structure apparently persists regardless of the type of molecule clathrated, although slight expansion can occur to accommodate larger guests as exemplified by the slightly larger cell dimensions found for the chloroform adduct - this is analogous to the cavity lengthening observed in the acetonitrile clathrate of hydroquinone. Further evidence of slight cage distortion comes from an X-ray analysis of the n-heptanol clathrate[25]. A consideration of the van der Waals radii suggest that this guest is able to fit through the waist, but appears to be too long to be accommodated within the cage; Flippen and Karle demonstrated that both ends of this normally extended molecule adopt a gauche configuration in order to be included.

It should be noted[44] that detailed structural information about the guest molecule will only be obtained by X-ray analysis directly when a) the molecular symmetry of the guest is compatible with the symmetry of the cavity, namely C_{3i}, and b) the van der Waals model of the guest is the approximate shape and volume of the empty cavity. If criterion a) is not met the guest will be disordered within the cavity, and if b) is not satisfied the subsequent motion of the guest within the cavity may render it unresolvable by X-ray methods at room temperature. An analysis of desolvated Dianin's compound has shown that the molecule has a crystal structure similar to that of its clathrates, the hour-glass shaped cavity being preserved with only minor alterations in its dimensions[26] (Figure 7).

The stability of clathrates, coupled with only a small degree of interaction between host and guest molecules, has enabled a

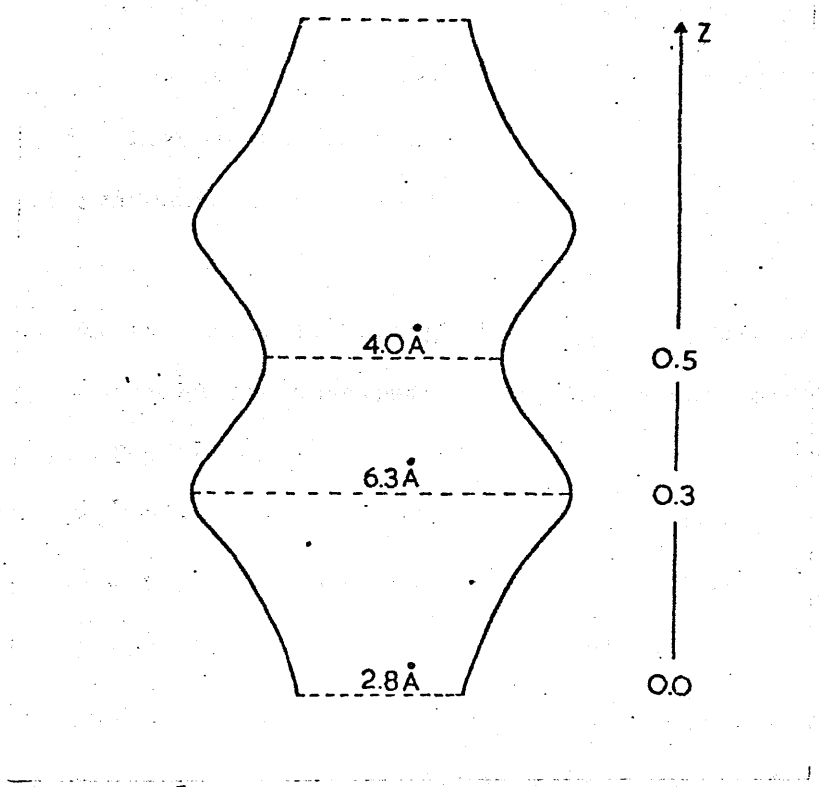


Figure 7. A section through the van der Waals surface of the cavity present in desolvated Dianin's compound. The length of the cage is 10.9 A°.

(F.B. Wilson, Ph.D. thesis, University of Glasgow, 1971.)

wide range of thermodynamic and other physical studies to be carried out on the nature of the rattling and rotational motions of the trapped species. One serious disadvantage of clathrate hosts, as compared for instance to noble gas matrices, is the absorption of the host material which is usually extensive and, on occasion, may completely obscure that of the guest molecules. This area of clathrate potential is the subject of a recent review[27]. Davies and Child[28] have looked at the infra-red spectra of various clathrates of hydroquinone and of Dianin's compound. The latter host proves awkward since the guest absorptions are either weak or non-observable, the exception being the carbonyl stretching bands of carboxylic acids; the spectrum of the acetic acid clathrate revealed two peaks of approximately equal strength, suggesting that a significant fraction of the guest is not dimerised in the doubly occupied cavities. However, later relaxation studies by Davies and Williams[29] showed that the guest was completely dimerised; the appearance of the i.r. absorptions was interpreted as being due to appreciable distortion of the normally symmetrical dimer. Gregoire and Meinnel[30] have recorded proton magnetic resonance spectra to evaluate the enthalpies of activation of movement of toluene, bromobenzene and bromodurene enclathrated in Dianin's compound.

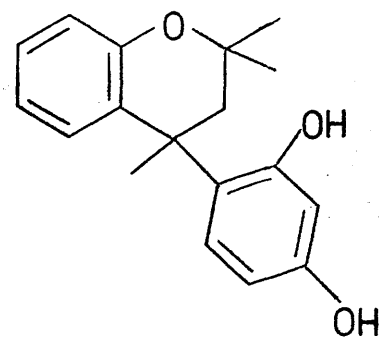
Electron paramagnetic resonance has also been employed to characterise the motion of guest molecules and to estimate the magnitudes of the energy barriers which hinder these motions. A clathrate is formed between Dianin's compound and di-t-butyl nitroxide, the odd electron of this guest providing a useful probe of its behaviour inside the host lattice[31]; a subsequent e.p.r. investigation of the same guest employed thiourea as the host material[32]. That a clathrate host lattice can serve as a convenient means of stabilising a free radical is illustrated by the observation of the Br_2^- radical, formed on irradiation of the clathrate of

Dianin's compound with 1,2-dibromo-1,1-difluoroethane[33].

Molecular compounds have excited interest as selective agents capable of effecting separations difficult or impossible by conventional methods; an early patent decribed the isolation of n-heptane from mixtures of C-7 hydrocarbons by allowing the samples to come into contact with Dianin's compound[34]. Other separations accomplished included cyclohexane/benzene and toluene/benzene. An extension of this work has appeared[35] and it is interesting to consider the selectivity exhibited by Dianin's compound in the light of the X-ray work of Flippen, Karle and Karle. The most noticeable feature of the results is that the linear paraffins C_5 - C_7 are readily included, whereas hydrocarbons containing one or more methyl groups at C-3 are almost totally rejected since inclusion would invoke steric repulsion around the waist of the cavity. The selectivity pattern for olefins is again dominated by molecular shape, cis- and trans-hept-3-enes being most readily included on account of their small cross-sectional area mid-way along the carbon backbone. Many hydrocarbons with similar boiling points are difficult to separate by distillation and, since they contain no useful functional group, the preparation of derivatives is impossible. Such cases are obvious candidates for separation by clathration; a particularly attractive example is an equimolar mixture of 2-methylhexane (b.p. 90.05°C) and 2,3-dimethylpentane (b.p. 89.78°C), from which 99% of the former can be recovered in a single clathration with Dianin's compound.

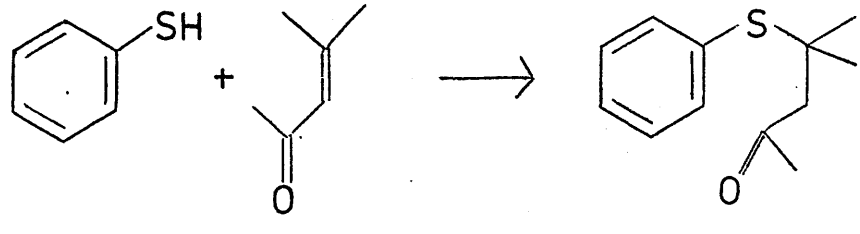
The $(CF_3SO_2)_2CH_2$ clathrate of Dianin's compound has been used as a latent curing catalyst in cationic polymerisations[36] while Johnson[37] has patented various amine complexes of (VII) and (IX) as polymerising agents in the preparation of epoxy and urethane resins; (IX) is a hitherto unknown clathrate host and is prepared by reaction of 2,2,4-trimethylchromene (VIII) with 1,3-dihydroxy-

(IX)

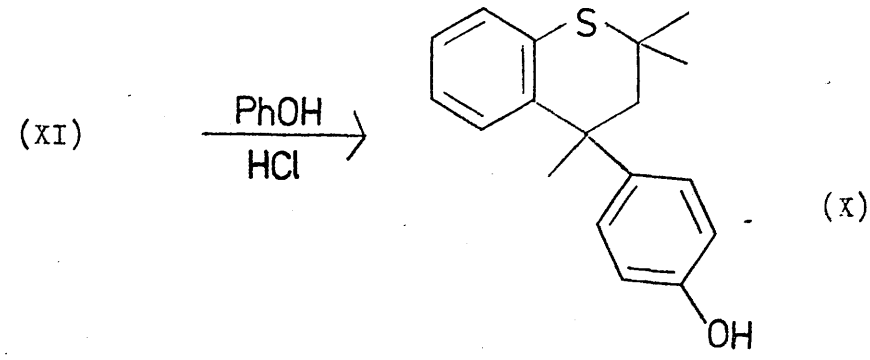


benzene in the presence of an acid catalyst. A new cyclising agent has been reported for the preparation of Dianin's compound itself, namely $H_3PO_4.BF_3$, containing 37% BF_3[38]; this gives the product in 50% yield after only 5 days at room temperature. Dianin's compound has been suggested as a suitable host for the observation of transitions between two rotational sublevels of the same vibrational state in small organic molecules, for example chloroform[39]. Crystallogenesis of the bromobenzene clathrate of Dianin's compound has shown that the crystals grow along the c-axis of the rhombohedral system[40].

As will be recalled, the early attempts of Baker and coworkers to prepare new clathrate hosts structurally related to Dianin's compound were unsuccessful. A significant advance in this direction came in 1969 with the synthesis of the thia analogue of Dianin's compound, 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman, (X)[41]; the ketosulphide (XI), prepared by the method of Tilak et al.[42], was



(XI)



cyclised in the presence of phenol, with anhydrous HCl as catalyst. The thiachroman (X) forms clathrates with all the organic solvents tried, the host to guest ratio being dependent on the size of the guest molecule; for fairly small molecules, such as ethanol and acetone, the ratio is 3:1, whereas for larger molecules, such as toluene and p-xylene, the ratio is 6:1. Subsequent X-ray analysis showed crystals of the ethanol clathrate to be isomorphous with the guest-free form of (X), and with the clathrates of Dianin's compound[43]; the basic feature of the structure is again the linking of the hydroxyl groups of six molecules by a network of hydrogen bonds such that the oxygen atoms form a distorted hexagon of side 2.9 A^{o}. The walls of each cage are formed by six molecules; three are of one configuration and are involved in hydrogen bonding at the lower end of the cage, and the remaining three of the other configuration are involved in hydrogen bonding at the upper end of the cage.

MacNicol and Wilson[44] have successfully used this host in the first unambiguous determination of the orientation, conformation and dimensions of a guest molecule within the cavity of an organic clathrate; bearing in mind the dimensions of the hour-glass shaped void, the guest chosen was 2,5,5-trimethylhex-3-yn-2-ol (XII). The acetylenic unit was found to be collinear with the c-axis, the triple bond fitting neatly into the cavity waist, leaving a tetrahedral unit in the upper and lower halves of the cage (Figure 8). The staggered conformation imposed on (XII) by the van der Waals

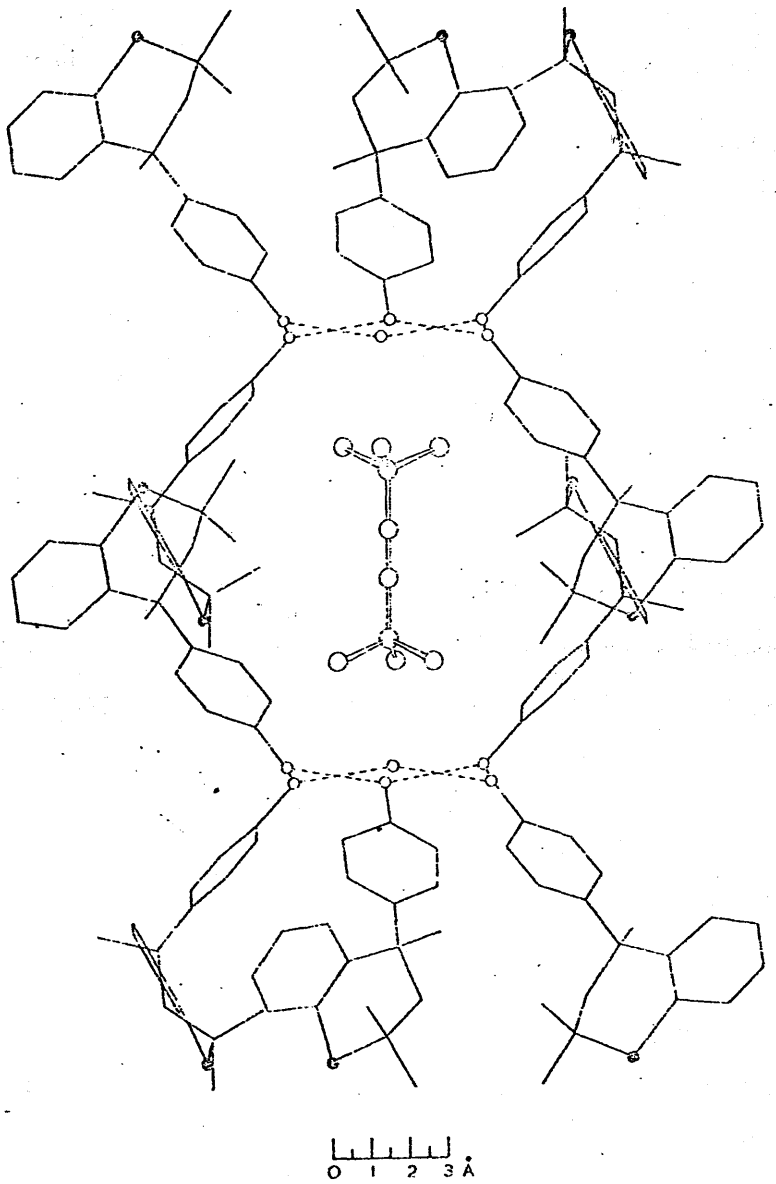
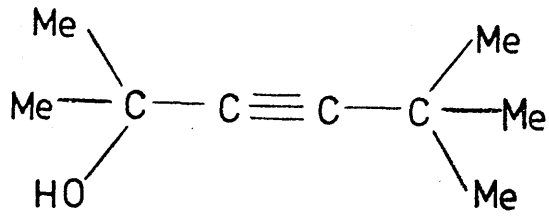


Figure 8. The structure of (X) projected along the a-axis, showing the guest molecule (XII) within the cavity. Two molecules of (X), which lie directly above and below the cavity as viewed in this direction, have been excluded apart from their hydroxyl oxygen atoms.

(D.D. MacNicol & F.B. Wilson, Chem.Comm., 1971, 786.)



(XII)

surface of the cavity may be taken as an example of a "lock and key" type interaction in which the conformation of the guest molecule is governed by the host.

The internal rotation of the formyl group of benzaldehyde clathrated in this host has been studied by MacNicol[45]; the measured barrier height is greater than that found for the molecule in the vapour phase suggesting increased double bond character in the bond linking the aldehyde group to the benzene ring. This corresponds to increased π-electron delocalisation in clathrated benzaldehyde, arising from interaction with the host molecules comprising the cage wall. Additionally, the similarity between clathrate and liquid phase barriers is significant since an individual molecule in a host lattice approximates to many theoretical models of solution.

III. The Practical Uses of Clathrates.

The recognition of clathrates as a distinct class of inclusion compounds has awakened great scientific interest from both theoretical and practical standpoints. The early work of Bengen[9] soon led to numerous patents describing practical uses of urea and thiourea complexes, the majority of these concerning the separation of molecules on the basis of shape. Although the guest molecules in a cavity are protected from attack by external reagents[23], they remain capable of reacting with each other; if this happens unusual products can arise since the enclosing walls impose severe restrict-

ions on the ways in which the reacting molecules can approach each other. For example vinyl chloride and butadiene monomers have been polymerised in their urea hosts giving highly crystalline, stereo-specific products in sharp contrast with normal polymers obtainable by irradiation of the liquid monomers[46].

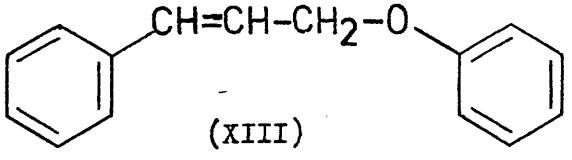
The potential use of clathrates in difficult separations has been demonstrated by Goldup and Smith[35], as discussed previously. An important extension of this is the resolution of racemic mixtures; when the host structure consists of an arrangement of atoms which is not superimposable on its mirror image, the cavities will be optically active and, consequently, may be able to trap one form of a guest molecule while rejecting, or disfavouring the inclusion of, its enantiomer. The size of the molecules to be resolved should be the only limiting factor in this method of resolution, while its chief advantage lies in the fact that no chemical reaction occurs and no change of configuration is possible.

Clathration has been suggested as a means of inert gas storage; if the argon present in the complex of composition $3C_6H_4(OH)_2 \cdot Ar$ were to occupy the same volume when free of its hydroquinone cage at 15°C, it would have to be kept under a pressure of 91 atmospheres. One of the most ingenious uses to which clathrates have been put is the storage of the radioactive Kr^{85}; clathrating the latter in a hydroquinone lattice gives a safe, easy-to-handle source of beta radiation[47]. The authors devised an air pollution monitor operating on the principle that if the material to be detected (for example SO_2, O_3) can oxidise the clathrate cage, and thereby destroy it, the released Kr^{85} can be measured by means of conventional radiation detectors.

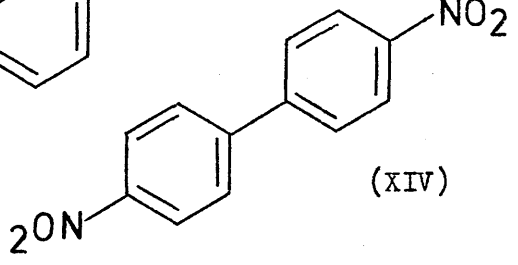
A recent review[27] has shown that a clathrate host lattice can serve as a convenient means of stabilising free radicals, permitting the study of new radicals, potential barrier effects and orientation.

While many examples are known where reactions of molecules are inhibited by embedding them in rigid glasses or crystals, little use seems to have been made of clathrates in this direction. Breslow and Campbell[48] have demonstrated that the presence of cyclodextrin alters the product array obtained on HOCl treatment of anisole; the 60:40 p:o product ratio from reaction with free substrate changes to 100% p-chloroanisole with appropriate cyclodextrin concentrations, as a consequence of the ortho- and meta-positions being well shielded within the torus shaped cavity of the carbohydrate. Furthermore, not only was the selectivity of this aromatic substitution markedly changed, but the substrate was even more reactive in the complex than it was in free solution, so the cyclodextrin was playing a catalytic role and not simply acting as a geometric blocking agent.

The Claisen rearrangement of cinnamyl phenyl ether (XIII) has been studied of late[49]; as well as noting the effect of various



(XIII)



(XIV)

solvents the authors employed the 4,4'-dinitrobiphenyl (XIV) clathrate[50] of the substrate. The strong restraint imposed by the channels of this host was found to produce a thousand-fold decrease in the rate of rearrangement.

Over the past few years several chemists have looked for methods of simulating the activities of enzymes and, in particular, their fascinating specificity. The role of inclusion compounds in this speculation has been firmly established by, for example, the

this speculation has been firmly established by, for example, the

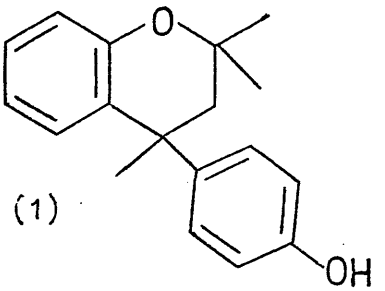
observation of the esterolytic properties of the cyclodextrins[51]. A recent article has discussed the original "lock and key" theory of enzymatic specificity proposed by Emil Fischer in terms of the host - guest chemistry exhibited by the crown ethers. The paper[52] concludes: "Molecular evolution provides chlorophyll, haemoglobin, and vitamin B_{12} as instructive examples of complexes composed of metal ions and an array of ligands and counterions structured into cages by covalent bonds. Although the chemist lacks the time-span of nature to produce equally interesting substances, he has certain advantages. He has nature's example. He is not limited to functional groups which are stable to water. He can perform experiments at a variety of temperatures. He might know in advance what specific task his compounds are designed to perform."

RESULTS AND DISCUSSION

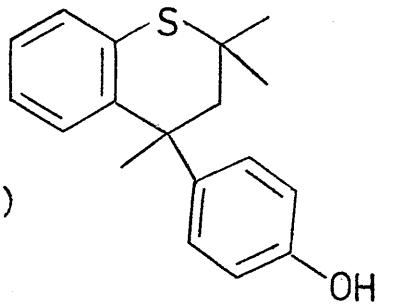
The importance of clathrates has been demonstrated with reference to their role in selective separations and in the storage of difficult reagents. The possibilty that "lock and key" interactions may occur in the living cell arose from the observation that not all compounds with the same functional groups underwent similar reactions in biological systems. Evidently a factor in addition to the nature of the functional groups was involved, and all indications pointed to this being the overall shape of the molecule. In accounting for biochemical dependence on molecular shape it seems reasonable to postulate that some form of host-guest relationship is operating and support for this hypothesis will grow with the discovery and understanding of novel inclusion compounds.

Any application proposed for a known clathrate host must of necessity recognise the importance of the dimension and geometry of the cavity; these parameters are all-important in deciding which guest will be admitted and which will be rejected outright - ample illustration of this comes from the studies of Dianin's compound by Goldup and Smith[35]. Since one can decide, empirically at least, which separations are feasible with a given host, would it be possible to attempt the converse, namely, being faced with a given problem, to construct a specific "tailor-made" host by effecting a deliberate variation in cavity topography? In 1955 Powell[53] attempted to define the characteristics required of a compound in order that it should exhibit inclusion behaviour, a task which he found to be well-nigh impossible. Probably the basic essential is poor packing of the molecules; in the special case of the cyclodextrins, there is empty space in the middle of rigid molecules, while in hydroquinone the cavities result from the directional properties of the intermolecular hydrogen bonds. Voids

suitable for accommodating guests may arise directly from the straightforward poor packing of hosts, the dimensions and rigidity of which are such that it is impossible to fill space efficiently - Dianin's compound (1) is such an example of this. The hour-glass



(1)



(2)

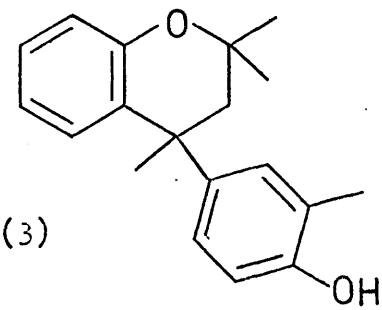
geometry of this host's cavity will impose restrictions on its possible ways of stacking, whereas a complex with the outline of a single cup could pack one inside the other.

The object of the present study was to ascertain whether it is possible to make small structural alterations to a known clathrate host, while at the same time, preserving its ability to trap various guest species. Optimally, the molecules included by any new host should be markedly different from those favoured by existing hosts, thus reflecting a significant variation of cavity topography. It should be noted that most recent clathrate work has concentrated on the applications of known hosts, and there have been very few reports of systematic searches for new enclosing structures. Which host should be chosen for modification? As the hydroquinone lattice has no space for additional functional groups, the ideal compound must have larger cavities where minor substitution would not disrupt the network of hydrogen bonds. Ideal candidates are Dianin's compound (1) and its sulphur analogue (2), a notable feature of these hosts being their ability to retain the cavity structure in the absence of any guest[26]; this demonstration of host lattice stability suggests that some of their simple derivatives should also be capable of forming clathrates.

The crystal structure of the thiachroman (2)[43] reveals an hour-

glass shaped cavity (Figure 1); the basic feature of the structure is the linking of the hydroxyl groups of six molecules by a network of hydrogen bonds such that the oxygen atoms (shown in red in Figure 1) form a distorted hexagon of radius 2.9 A^{o}. Such hexagons, 10.9 A^{o} apart, comprise the floor and ceiling of the cage, while the walls are formed by six molecules, three of which are of one configuration and are involved in hydrogen bonding at the lower end of the cage, the remaining three being of the other configuration are involved in hydrogen bonding at the upper end of the cage. The other interesting feature of the cage is that the gem-dimethyl groups of the six molecules point into the cavity to produce a waist at about Z = 0.5; six of these methyl groups, one from each molecule, form a distorted hexagon of carbon atoms at the waist with a radius of 4.16 A^{o}. In Figure 1 the carbon atoms of the gem-dimethyl groups are coloured purple.

As will be recalled, an earlier attempt by Baker et al.[17] to modify the structure of Dianin's compound by adding substituted phenols to 2,2,4-trimethylchromene met with little success; only o-cresol gave a crystalline product (3) but this did not form complexes with solvents. Catechol combined with the chromene but the



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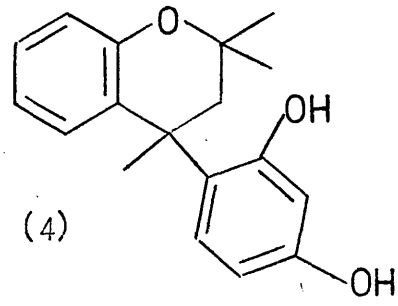


(4)

compound could not be crystallised, while m- and p-cresols gave only non-phenolic resins. More recently, however, Johnson[37] condensed the above chromene with resocinol in an inert solvent containing some mineral or Lewis acid as catalyst to produce the new host (4). Substitution of the phenolic ring could have a marked effect on the

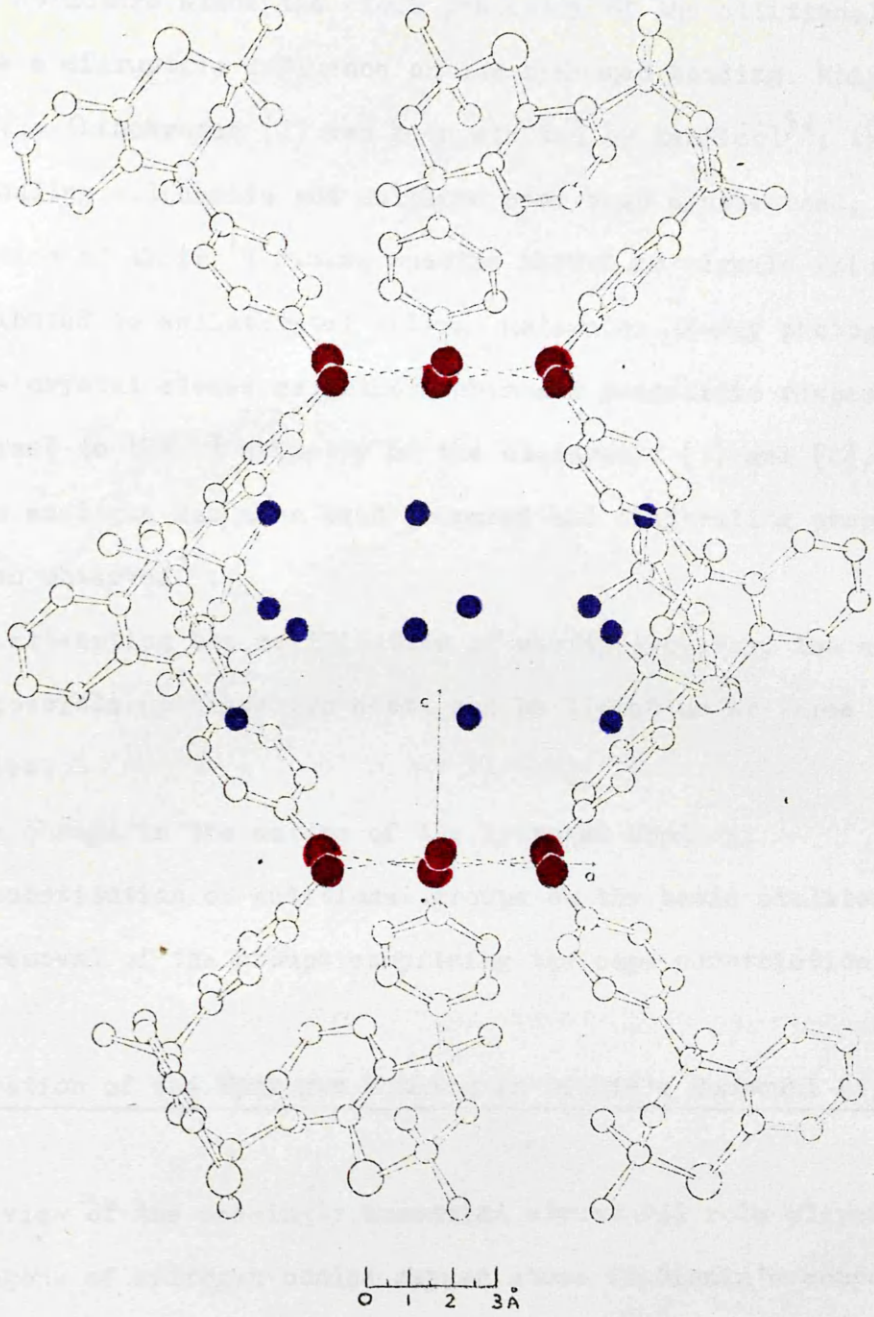


Figure 1. 4-p-Hydroxyphenyl-2,2,4-trimethylthiachroman from ethanol. The packing of the molecules as projected on (010). Two host molecules, which lie directly above and below the cavity as viewed in this direction, have been excluded apart from their hydroxyl oxygen and gem-dimethyl carbon atoms.

(F.B. Wilson, Ph.D. Thesis, University of Glasgow, 1971)

crystal structure since the close proximity of the additional groups may have a disruptive influence on the hydrogen bonding. Modification of the thiachroman (2) has been started by MacNicol[54]; the corresponding sulphoxide and sulphone have been synthesised, but examination of their ^{1}H n.m.r. spectra showed no signals which could be attributed to enclathrated solvent molecules. X-ray photographs gave the crystal clsses as orthorhombic and monoclinic respectively, in contrast to the $R\bar{3}$ symmetry of the clathrates (1) and (2). The selenium analogue has also been prepared and clathrating properties have been observed[54].

In attempting the modification of cavity geometry, the alterations possible on these two hosts can be listed under three main categories:

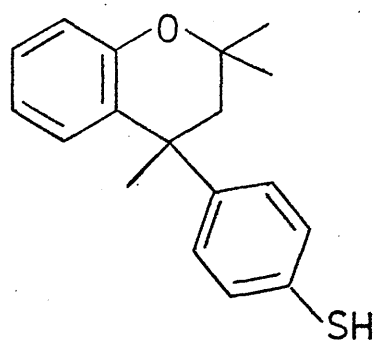
a) a change in the nature of the hydrogen bonding;

b) substitution of additional groups on the basic skeleton;

c) removal of the groups comprising the cage constriction.

I. Alteration of the Hydrogen Bonding in Dianin's Compound (1).

In view of the seemingly essential structural role played by the hexagons of hydrogen-bonded oxygen atoms in Dianin's compound[24], it should be instructive to discover whether a modification of a hydroxyl group is reflected in the clathrating properties of the host. The methyl ether of Dianin's compound, 4-p-methoxyphenyl-2,2,4-trimethylchroman has already been synthesised and shown to lack clathrating properties[18]. A less drastic change, not involving the total destruction of hydrogen bonding, would be more satisfying and, consequently, the mercapto analogue, 4-p-mercaptophenyl-2,2,4-trimethylchroman (5) was prepared. Newman and Karnes[55] have described a general method for the conversion of phenols to thiophenols via dialkylthiocarbamates; phenols are readily converted into the corres-



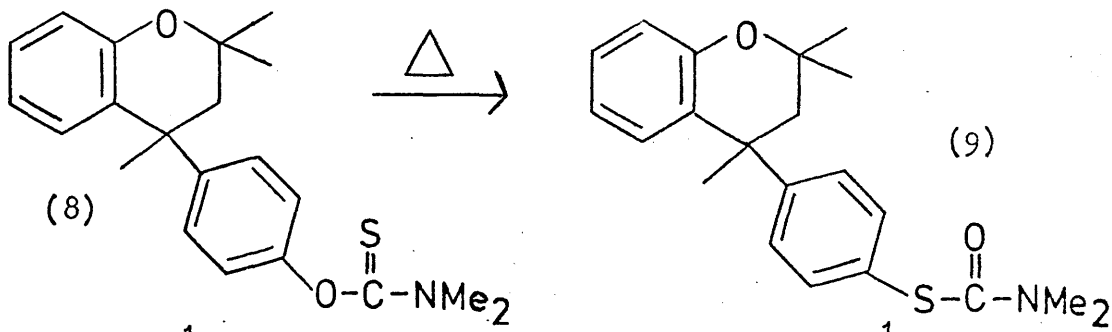
(5)

ponding O-aryl dialkylthiocarbamates (6) in high yield by treatment with dialkylthiocarbamoyl chlorides. Pyrolysis affords the S-aryl

$$ArOH \longrightarrow \underset{(6)}{ArOC(S)NR_2} \xrightarrow{\Delta} \underset{(7)}{ArSC(O)NR_2} \longrightarrow ArSH$$

dialkylthiocarbamates (7) which can be hydrolysed to the corresponding aryl mercaptans.

The ethanol clathrate of Dianin's compound, prepared by the method of Baker et al.[17], was converted to its sodium salt and then heated with dimethylthiocarbamoyl chloride to give (8) in high yield. The i.r. spectrum of (8) did not have the broad hydroxyl band

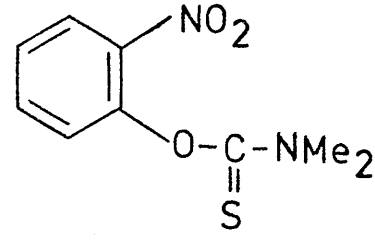


(8) (9)

at 3300 cm^{-1} characteristic of Dianin's compound; its ^1H n.m.r. spectrum showed three sharp singlets from the methyl protons and an AB quartet from the methylene protons while the two singlets from the N-methyl groups occurred at 6.56 and 6.68τ ($CDCl_3$). This position is not in agreement with Newman and Karnes'[55] observation that the N-methyl groups of the O-aryl compounds gave two signals in the region 7.3 - 7.5τ, while the S-aryl compounds showed sharp singlets at 7.0 - 7.1τ - however, they do not quote the solvent employed.

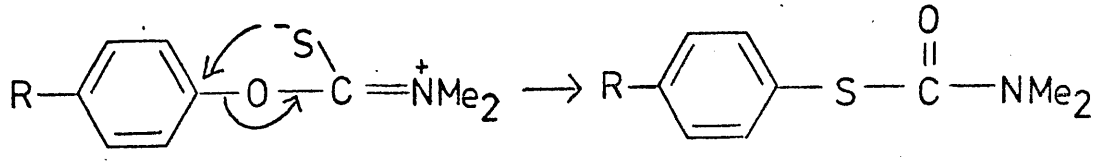
With a view to clarifying the position the reaction was repeated with 2-nitrophenol, one of the compounds listed in the authors' paper; The ^{1}H n.m.r. of this product (10) gave the two singlets at

(10)



6.56 and 6.62 τ, while Lemire and Thompson have found that the N-methyl groups of $CH_3OC(S)NMe_2$ appear as two peaks at 6.66 and 6.89 τ when the ^{1}H n.m.r. spectrum is recorded with CCl_4 as solvent. A further discrepancy was found with the O-(2-nitrophenyl)dimethylthiocarbamate, namely its melting point which was some twelve degrees higher than the value of 112 - 113°C claimed by Newman and Karnes[55].

The authors' conditions for the rearrangement of (10) were checked by heating to 170°C a nitrobenzene solution of (8) in the probe of a Varian H.A.-100 n.m.r. spectrometer; by 110°C the signal from the N-methyl groups had collapsed to a singlet, which disappeared as the temperature was increased, to be replaced by a singlet further upfield. The reaction appeared to be complete after 20 minutes at 170°C. Newman and Karnes[55] suggested that the rearrangement involves nucleophilic attack of the sulphur at the carbon bearing the oxygen, the desired polarisation being assisted by the dialkylamino group (Scheme 1). The conditions required for the conversion of (8) to (9)



Scheme 1.

were investigated by heating samples (60 mg) of (8) at various temperatures for varying times, the reactant being in pyrex tubes sealed at atmospheric pressure. Three methods of observing the degree of conversion were available: in ^{1}H n.m.r. spectra the peaks at 6.56 and 6.68 τ were replaced by a singlet at 6.95 τ, while t.l.c. indicated the formation of a less polar species, R_f = 0.7 ($CHCl_3$); on infrared analysis the bands at 1530 and 1170 cm^{-1}, characteristic of (8)[55], were seen to disappear with the simultaneous arrival of new bands at 1665 cm^{-1} (tertiary amide) and 685 cm^{-1} (C-S stretch).

Using a temperature of 270°C and a reaction time of 1.5 hours, the rearrangement was found to proceed smoothly. A t.l.c. of the crude product indicated four components, all of which were eventually identified; in addition to the major desired product there were trace amounts of Dianin's compound, unrearranged material and, suprisingly, the thiol (5). In attempting to purify the glass-like product vacuum sublimation was tried over a range of temperatures up to 100°C with a pressure of 0.05 mm Hg; this proved unsuccessful as did recrystallisation. In view of the reasonably sharp melting point and lack of any foreign peaks in its ^{1}H n.m.r. spectrum, the purity of the pyrolysis product must be high. Consequently it was decided to use this unpurified material for the hydrolysis to the thiol.

The hydrolysis required a five molar excess of base and an overnight reflux, the reaction being followed on t.l.c. by the appearance of a relatively non-polar species, R_f = 0.9 ($CHCl_3$). The ^{1}H n.m.r. spectrum of the product showed a singlet at 6.70 τ, about the position expected for the proton of a SH group, while its i.r. gave a sharp peak at 2540 cm^{-1} (nujol mull). The corresponding absorption of β-thionaphthol occurred at 2560 cm^{-1} when run under the same conditions. This proved encouraging since the lowering by 20 cm^{-1} of the S-H stretching frequency may be wholly or partly due to hydrogen bonding - the hydrogen bonding which must be present

to maintain the clathrate structure. Recrystallisation of the thiol from various solvents, namely benzene, ether, ethanol and methanol, was attempted, but with little success; the best crystals, those grown in acetone, were small and could not be used for space group determination. The ^{1}H n.m.r. spectra of these recrystallised samples showed no signals which could be assigned to enclathrated molecules and, in addition, microanalysis data corresponded exactly to the theoretical values required for $C_{18}H_{20}OS$. Later work, however, has shown that the thiol forms a complex with carbon tetrachloride; a sample recrystallised from this solvent gave colourless prisms having a Cl content of 14%, this value corresponding to a host to guest ratio of 3:1. However, the crystals decompose with loss of CCl_4 to a white powder over a few days - under vacuum this transformation occurs in a matter of hours.

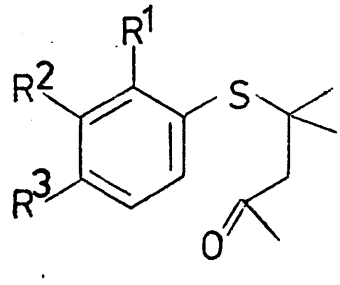
The apparent lack of general clathrating properties on the part of the thiol (5) highlights the importance of hydrogen bonding in these hosts. The OH.....O hydrogen bonding system is relatively strong, worth on average 4.0 - 4.5 Kcals/mole, while the sulphur analogue is considerably weaker, so weak that for many years it was thought not to exist. Pogorelyi and Gragerov[57] have described the investigation by proton magnetic resonance of the thermodynamics of hydrogen bond formation between acetone and a series of thiophenols, and give the strength of the hydrogen bond between acetone and p-thiocresol as 2.9 Kcals/mole. The difference in hydrogen bond strengths between analogous oxygen and sulphur systems is brought out in i.r. spectra where the value of the O-H stretching frequency is used as a test for, and a measure of the strength of, hydrogen bonds - the stronger the hydrogen bond the lower the vibration frequency and the broader the absorption band. The S-H stretching frequency is weaker and much less affected by hydrogen bonding; on examining spectra in the liquid state and in dilute solutions, only

a small shift of the S-H absorption due to association is observed.

It would appear then that the strength of the hydrogen bonds formed between SH groups is not sufficient to hold the molecules together to form a cage, but other factors cannot be rigorously excluded. It is perhaps significant that while hydroquinone readily forms clathrates with many small molecules, the similar compounds benzene-1,4-dithiol and 4-mercaptophenol do not possess such an ability. A further modification of the hydrogen bonding in Dianin's compound was achieved by reacting its ethanol clathrate with methyl isocyanate to form the corresponding urethane; however, the isolated product, a fine white powder, did not exhibit any inclusion behaviour. Since the presence of hydrogen bonding through hydroxyl groups seems essential for clathrate formation in structures of the normal Dianin's family, further modification of the skeleton must take place at a distant site or not interfere with the hydrogen bonding capability.

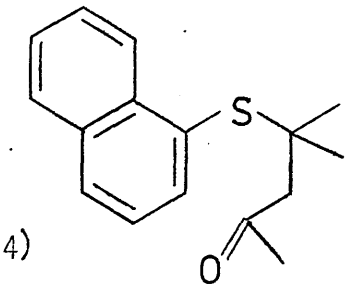
II. Substitution of the Thiachroman Host (2).

An inspection of Figure 1 suggests that sufficient space may be available in the crystal structure of (2) to allow substitution of the aromatic nucleus without destroying the column packing necessary for the continued presence of cavities. Consequently, each

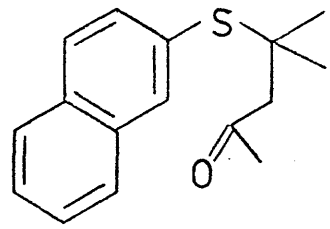


(11) R^1 = Me, R^2 = R^3 = H
(12) R^1 = R^3 = H, R^2 = Me
(13) R^1 = R^2 = H, R^3 = Me

of the ketosulphides (11) - (15), prepared by piperidine-catalysed Michael addition of the appropriate aryl mercaptan to mesityl oxide (see Section 1), was cyclised in the presence of phenol with anhydrous hydrogen chloride as catalyst. After a period of time at room temp-

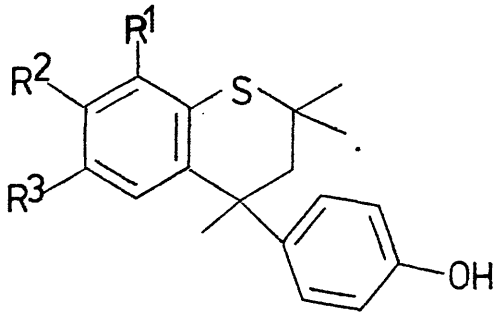


(14)



(15)

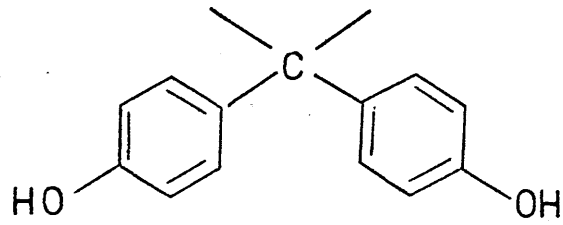
erature the reactants had become dark-red viscous liquids, except in the instance of (14) where a pale brown solid was formed. Work-up involved extracting the unreacted phenol with boiling water, then adding a small volume of a suitable solvent to effect crystallisation; with compounds (1) and (2) this was readily accomplished with ethanol but it soon became apparent that compounds (16) - (18) would prove



(16) R^1 = Me, R^2 = R^3 = H
(17) R^1 = R^3 = H, R^2 = Me
(18) R^1 = R^2 = H, R^3 = Me

more troublesome. The clear pale-brown glass obtained from (13) defied all attempts at crystallisation. Its ^{1}H n.m.r. spectrum confirmed that (18) had been produced in the reaction but there were additional peaks present, notably a sharp singlet at 8.38τ together with a D_2O-exchangeable signal and extra aromatic resonances. Separation by distillation led to the decomposition of (18), probably catalysed by residual traces of acid but, more promisingly, t.l.c. revealed two well-separated components having R_f values of about 0.3 (the region expected for (18)) and 0.8 ($CHCl_3$ as solvent). However, hopes were dashed with the decomposition of (18) when purification on an alumina column was attempted; among the products was 2,2,4,6-tetramethyl-2H-thiachromene showing that the active sites of alumina could cleave the phenol from the desired product. On silicic acid, however, separation of the two components was possible; first to be

eluted was the impurity as white needles having a molecular weight of 228. Infrared analysis showed a broad hydroxyl absorption at 3350 cm^{-1} and a strong band at 828 cm^{-1} indicative of a para disubstituted benzene ring, thus enabling the impurity to be identified as 2,2-di-(p-hydroxyphenyl)propane, more commonly known as "bisphenol A". This compound, observed in the original preparation



Bisphenol A

of Dianin's compound[14], is produced when the carbon-carbon double bond of mesityl oxide is hydrated, leading to the formation of acetone, which can then combine with two molecules of phenol. Biphenol A comprised about 30% of the crude product from (13) and on a subsequent run partially crystallised out during work-up.

The second component eluted from the silicic acid column was a pale yellow glass, which from its ^{1}H n.m.r. spectrum, appeared to be pure (18). However, its trace impurites defeated the countless attempts at crystallisation and resort had to be made to gel chromatography. Final purification was achieved by methanol elution from a 200 x 2.5 cm column of Sephadex LH-20 modified with NEDOX 1114 (see Section 1) to yield a colourless brittle glass which was found to be extremely soluble in most organic solvents. Consequently crystallisation proved difficult, the only successful method being to suddenly cool a sample dissolved in the minimum volume of hot petrol with simultaneous scratching, whereupon fine white crystals were deposited. Enclathrating behaviour with a host to guest ratio of 6:1, is exhibited by (18) on recrystallisation from n-pentane, cyclopentane and cyclohexane, as revealed by ^{1}H n.m.r. spectroscopy;

attempts to include other solvents were frustrated by the high solubility of the host which tended to come back out of solution as an oil. The cyclopentane clathrate has a crystal structure of space group $R\bar{3}$ and lattice constants, referred to a hexagonal unit cell, of $\underline{a}$ = 29.22 and $\underline{c}$ = 10.82 A^{o}, these values being very similar to the corresponding lattice parameters found for clathrates formed by the parent host (2), for example $\underline{a}$ = 27.81 and $\underline{c}$ = 10.90 A^{o} for its ethanol clathrate, so implying fairly similar cage structures for (2) and (18). The infrared spectrum of the cyclopentane clathrate of (18) shows the O-H stretching as a broad symmetrical band (Figure 2), similar to that found for (2); the frequency of absorption is 3410 cm^{-1} compared with the value of 3430 cm^{-1} for the 2,2,5,5-tetramethyl-3-hexyne clathrate of (2).

A similar work-up of the product from (12) gave a clear pale-brown glass, but in this instance the proportion of bisphenol A impurity was noticeably less (ca. 5%). Nevertheless, chromatography on silicic acid and on modified Sephadex LH-20 was required before a solid product could be isolated. Cyclisation of (12) can occur in two ways but, as a result of steric factors, condensation is unlikely to be effected between the thioether and methyl groups, a conclusion which appeared to be borne out in practice. Samples of (17) crystallise unsolvated from cyclopentane, cyclohexane, methylcyclohexane and benzene, showing that moving the methyl substituent only onto an adjacent ring carbon completely eliminates any clathrate forming properties. The unsolvated material from cyclopentane and cyclohexane was self-resolving, being found to crystallise in the enantiomorphous space group $P2_12_12_1$, with lattice constants of $\underline{a}$ = 11.8, $\underline{b}$ = 16.5 and $\underline{c}$ = 8.5 A^{o}. Long chains of molecules parallel to the $\underline{y}$-axis are held together by O-H....S hydrogen bonding with the angle OHS about 160°, this decrease of 20° from the normal values indicating the weak nature of the hydrogen bonds. An i.r. spectrum reveals that the O-H

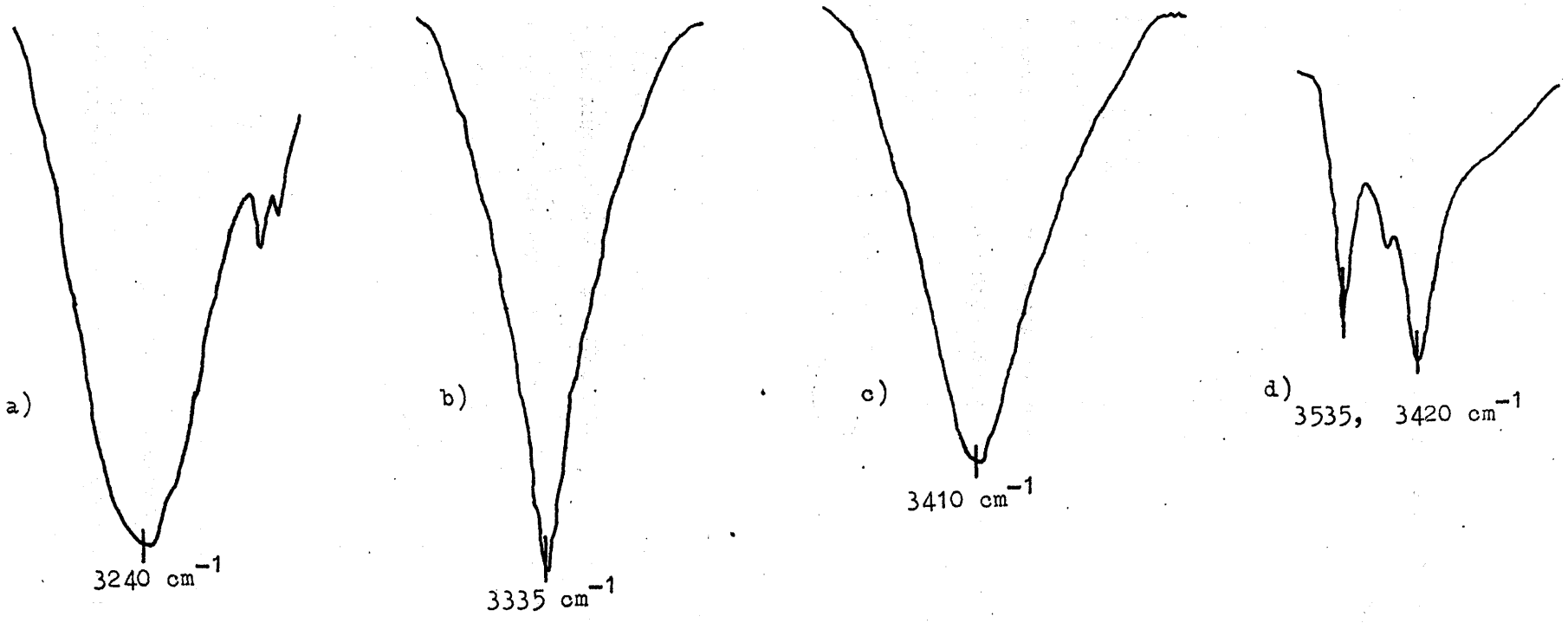


Figure 2. Infrared O-H stretching frequencies for compounds a) (16), b) (17), c) (18), d) (19). (16), (17) and (18) recrystallised from cyclopentane, (19) from benzene.

stretch of (17), occurring at 3335 cm^{-1}, is a sharper absorption than those observed previously (Figure 2). At this point it is interesting to recall the spontaneous optical resolution of solvated tri-o-thymotide discovered by Newman and Powell[58]; crystal structure examination showed that this compound crystallised as a racemate but that resolution took place on formation of its adduct with n-hexane, benzene or chloroform.

Ketosulphide (11) cyclised in the presence of phenol gave a number of products among which were (16) and bisphenol A. However, their separation proved relatively easy and one pass through a column of silicic acid was sufficient for the isolation of a solid sample of (16). This material was found to form clathrates with many of the solvents tried (Table 1) while it proved too soluble in others (for example ethanol and tetrahydrofuran) and was deposited as an oil; crystals grown from nitromethane were unsolvated. Notable among the guests is cyclopropane (boiling point -33°C) which forms a clathrate with a host to guest ratio of 6:1, so providing a convenient means of handling this gas for certain applications. The inclusion of the relatively large cyclooctane molecule immediately suggests a different cavity geometry from that of the parent host (2) which, on recrystallisation from this solvent, gives a host to guest ratio of 14:1. This disfavouring of cyclooctane by (2) is also refelcted in its i.r. spectrum (Figure 3) where the O-H stretching absorption is sharper and at lower frequency than the corresponding band in its 2,2,5,5-tetramethyl-3-hexyne clathrate.

The cyclocctane clathrate of (16) was found to crystallise with an $R\bar{3}$ space group, as was found for (2) and (18); however, a significant shortening of the c dimension, referred to a hexagonal system of axes, to 8.23 A°, together with a lengthening to about 33 A° for the a dimension, implies that this particular structural modification has been effective in bringing about a fundamental

Table 1. Solvents Capable of Clathrate Formation with (16).

Guest.	Mole ratio of host to guest[(a)].	Analysis method.
Benzene	5:1	b
Carbon Tetrachloride	6:1	c
Cyclopropane	6:1	b
Cyclopentane	6:1	b
Cyclohexane	6:1	b
Cycloheptane	4:1	b
Cyclooctane	4:1	b
Cyclodecane	25:1	b
Toluene	4:1	b

(a) The ratio is given as n:1 where n is the nearest integer.

(b) Examined by integration of the 100 MHz ^{1}H n.m.r. spectrum, several runs being averaged. In the case of the cyclopropane clathrate the spectrum was recorded at $-40^{\circ}C$.

(c) Examined by microanalysis for chlorine.

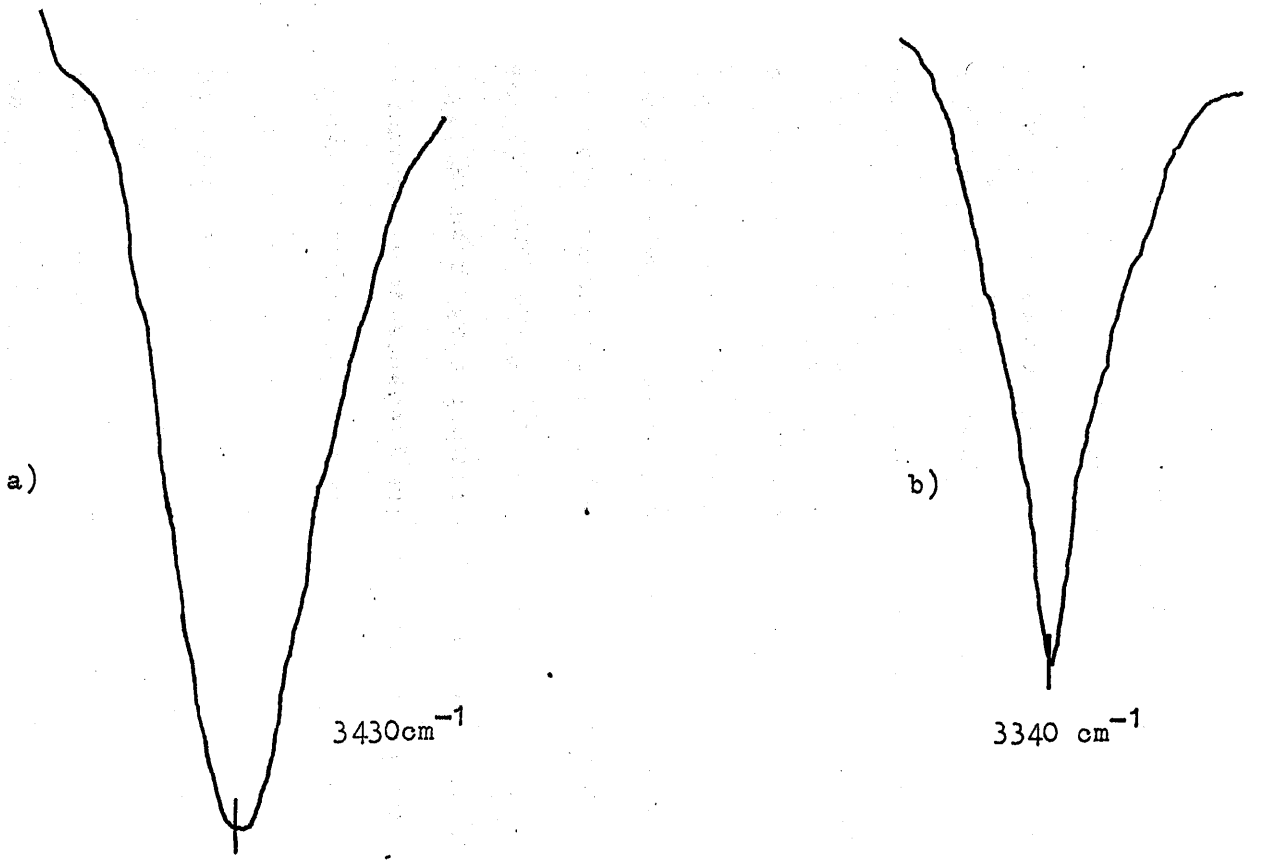


Figure 3. Infrared O-H stretching frequencies for 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman recrystallised from a) 2,2,5,5-tetramethyl-3-hexyne and b) cyclooctane.

change in the size and shape of the cavity. From the ratios in Table 1 it is apparent that more than one of the larger cycloalkanes must be accommodated in some of the cages, suggesting that a marked bulging in the two halves of the cavity has occurred. Whether or not a waist still persists is open to speculation until a full X-ray analysis is completed. If this constriction were absent then a molecule such as tetramethylsilane should be included; recrystallisation of (16) from this solvent proved unsuccessful, the potential host being deposited as an oil. The solubility of (16) in but-2-yne, a molecule whose length corresponds to that of the cavity, was too high, while the opposite problem, namely insolubility, was encountered with perfluorobut-2-yne, even in the presence of a cosolvent. The O-H stretching frequencies of the various clathrates of (16) are listed in Table 2. Values at the top end of the range are observed when bulkier molecules are included, this indicating that some distortion of the hydrogen-bonded hexagons is taking place, so lengthening the O-O bond distance. The lower frequencies found for (16) imply that the hydrogen bonds are stronger than those in the crystal structure of (18)[59].

Work-up of the solid obtained from the cyclisation of phenol and the ketosulphide (14) yielded a glass which on standing transformed to a yellow crystalline mass; several recrystallisations from benzene gave pure, unsolvated 4-p-hydroxyphenyl-2,2,4-trimethyl-7,8-benzothiachroman (19). These crystals were orthorhombic, having a space group of Fmm2 or Pnn2. Samples of (19) grown from numerous solvents, for example acetone, ethanol and n-pentane, revealed no enclathrated species when their ^{1}H n.m.r. spectra were recorded. The aromatic region of the 220 MHz ^{1}H n.m.r. spectrum of (19) showed the expected AB quartet from H_5 and H_6, so providing unequivocal evidence that cyclisation had occurred in the manner predicted (Figure 4). Also notable is the low position of the H_{10} resonance, this

Table 2. Influence of Guest on O-H Stretching Frequency of (16).

Guest.	ν(O-H) cm^{-1} (KBr disc).
Benzene	3260
Carbon Tetrachloride	3265
Cyclopropane	3250
Cyclopentane (a)	3240
Cyclohexane	3260
Cycloheptane	3265
Cyclooctane	3275
Toluene	3275

(a) The clathrate of this solvent with (18) shows ν(O-H) at 3410 cm^{-1} while unsolvated (17) shows ν(O-H) at 3335 cm^{-1}.

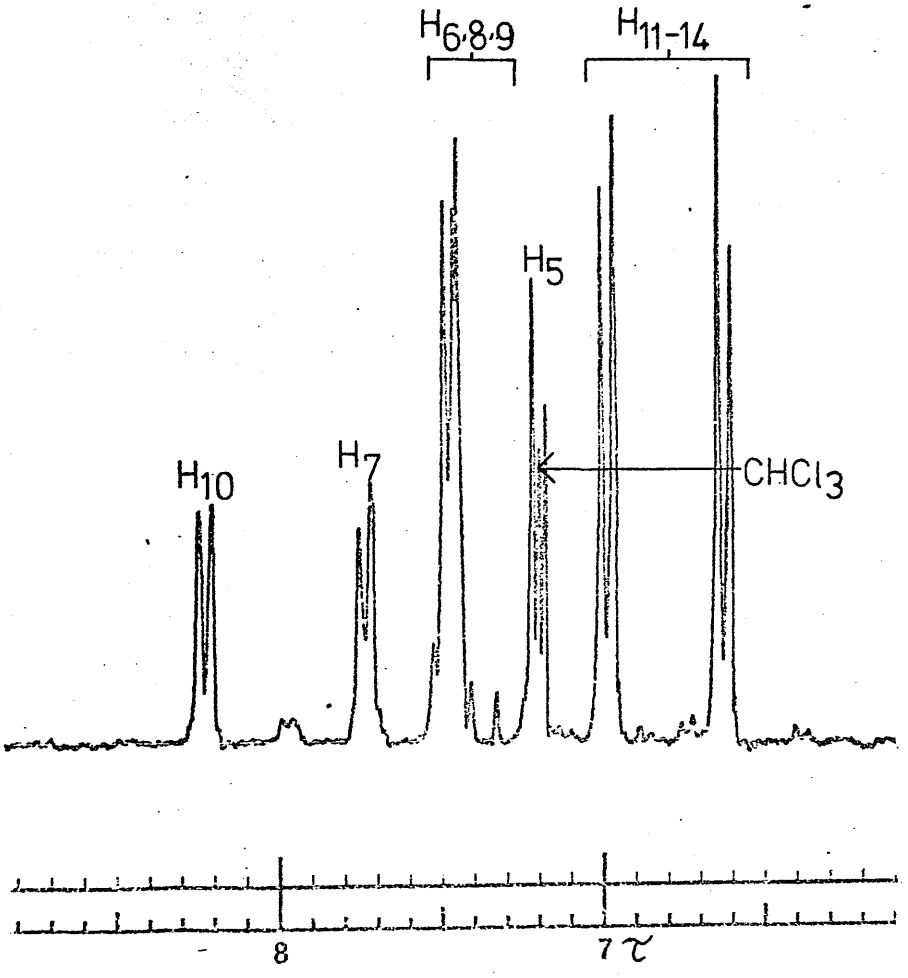
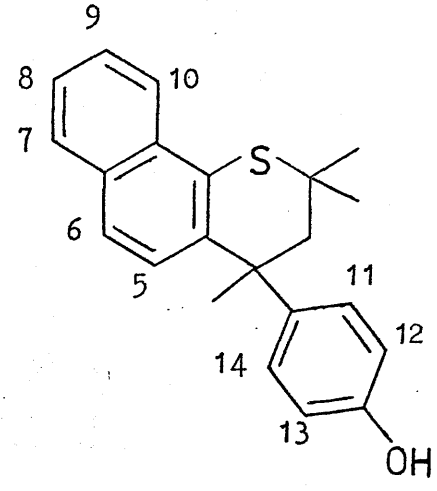
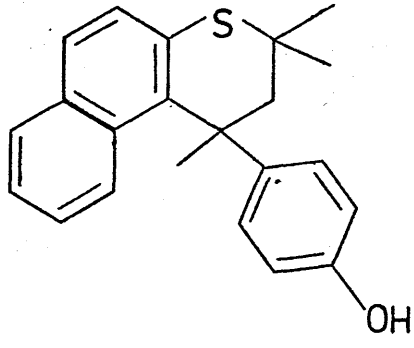


Figure 4. Aromatic region of 220 MHz ^{1}H n.m.r. spectrum of (19).

being attributed to the deshielding influence of sulphur.

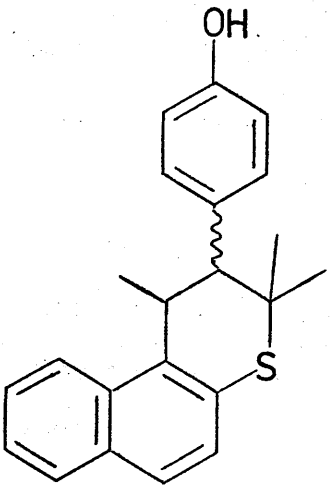


(19)



(20)

At least seven components were detected by t.l.c. in the product mixture obtained from the ketosulphide (15); silicic acid and gel chromatography permitted their partial separation but none of the compounds isolated had spectral parameters consistent with the expected structure (20). However, an off-white solid (molecular weight 334), which was never completely freed of impurities, did have a R_f value comparable to that of (19); also, its ^1H n.m.r. spectrum (solvent $CDCl_3$) contained an AB quartet and a D_2O exchangeable singlet characteristic of a p-hydroxyphenyl substituent, but at higher field, instead of the expected AB quartet and three singlets, there were two singlets at 8.65 and 8.81τ, a doublet (J = 6 Hz) at 8.79τ and a multiplet at ca. 6.3τ. Integration of the peak areas implied a proton ratio



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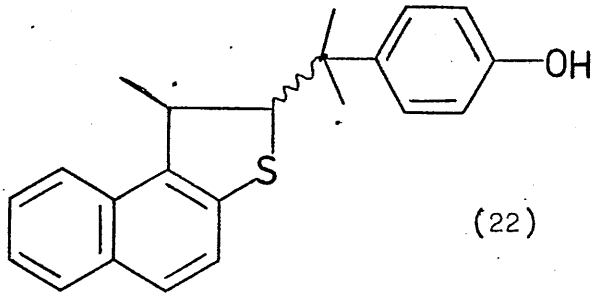


(22)

of 10:1:3:3:3:2. The two tertiary and one secondary methyl groups which this information suggests, can be accounted for in terms of structure (21), this being formed by ring closure of (15) to give 2,2,4-trimethyl-5,6-benzo-2H-thiachromene, followed by phenol addition at C-3, instead of at the expected C-4 position.

A sample of this thiachromene when treated with phenol in the presence of gaseous HCl, gave a solid, the ^{1}H n.m.r. spectrum of which corresponded exactly to that of the above material. It appears then that phenol addition is being prevented at C-4, presumably for steric reasons. Also, it is known (see Section 1) that 2,2,4-trimethyl-5,6-benzo-2H-thiachromene readily undergoes

acid-catalysed ring contraction to a benzo(b)thiophene derivative, and, if this were to happen here, phenol could attach itself at one of three possible sites. However, the observed ^1H n.m.r. data permits only the isomer with phenol on the C-2 side chain, namely structure (22). The mass spectrum of the solid has a molecular ion at m/e 334 and a very intense base peak at M - 105 (m/e 199), a loss which is not seen in the spectrum of (19) and may be explained by (22) losing $C(CH_3)_2.C_6H_4OH$ from position 2. The isolated product which could be either (21) or (22), the latter being strongly favoured on mass spectral evidence, did not show any clathrating properties.

An explanation of which substitutions are allowable while still maintaining the ability to form stable inclusion compounds can be obtained by an examination of a model of the crystal structure of the thiachroman host (2) (Figure 5). Considering one molecule of the twelve shown, for example that in the top right-hand corner, it would appear that a substituent introduced ortho or para to sulphur should not be too awkward, whereas a group in the meta position would markedly interfere with the column packing, resulting in the molecules adopting a different crystal structure.

III. Selectivity of Clathrate Hosts (2), (16) and (18).

Selectivity experiments have been shown to yield valuable information about cavity geometry[35] and have excited interest in separations which would be extremely difficult by more established methods. In view of its liking for cycloalkanes (Table 1) it was thought appropriate to recrystallise a sample of (16) from a mixture of these hydrocarbons and to compare the relative ratios of the included species with those exhibited by the other hosts, (2) and (18). Wiberg and Nist[60] have shown that cycloheptane and cyclooctane give the same chemical shift when their ^1H n.m.r. spectra

Figure 5. Crystal structure of 4-p-hydroxyphenyl-2,2,4-trimethyl-thiachroman.

black	- carbon	red	- oxygen
white	- hydrogen	yellow	- sulphur

are recorded as 15% solutions in carbon tetrachloride; consequently, to facilitate product analysis, an equimolar mixture of only cyclopentane, cyclohexane and cycloheptane was employed. Samples of (2), (16) and (18), along with a few ml of the solvent mixture, were placed in separate sealed tubes at atmosphereic pressure and heated to 120°C, then allowed to cool to room temperature in a draught-free environment over a period of several hours. After careful vacuum drying, 100 MHz ^{1}H n.m.r. spectra were recorded on the crystalline products, using $CDCl_3$ as solvent. This, however, proved unsuitable since the resonance positions of 8.48, 8.50 and 8.57 τ for cycloheptane, cyclopentane and cyclohexane respectively did not permit accurate integration of the two low field signals. Better separation was achieved with C_6D_6 or C_6H_6, solvents which gave singlets at 8.50, 8.55 and 8.60 respectively.

A dramatic difference in the selective clathration properties of (2) and (16) was found; the parent host (2) exhibits a very strong preference for cyclopentane (Figure 6), the relative percentages for cyclopentane, cyclohexane and cycloheptane being 85%, 10% and 5% whereas (16) shows a relatively increased tendency to include the larger cycloalkanes (Figure 7), the corresponding values 20%, 50% and 30% reflecting the altered cavity shape reported earlier. That more smaller guests, for example cyclopropane, are not included by (16) is consistent with the idea that the larger cycloalkanes lend some stabilising influence to the crystal structure. Nevertheless, a large alteration in cavity geometry as found for (16) may not be required to effect marked changes in selective clathration behaviour, since ratios of 12%, 57% and 31% (Figure 8) were found for (18), the cavity shape of which is probably not greatly different from that of (2) according to X-ray evidence. However, the infrared spectrum of (18) shows the O-H stretching frequency as 3410 cm^{-1}, some 170 cm^{-1} higher than that observed for (16), implying a lengthening of the

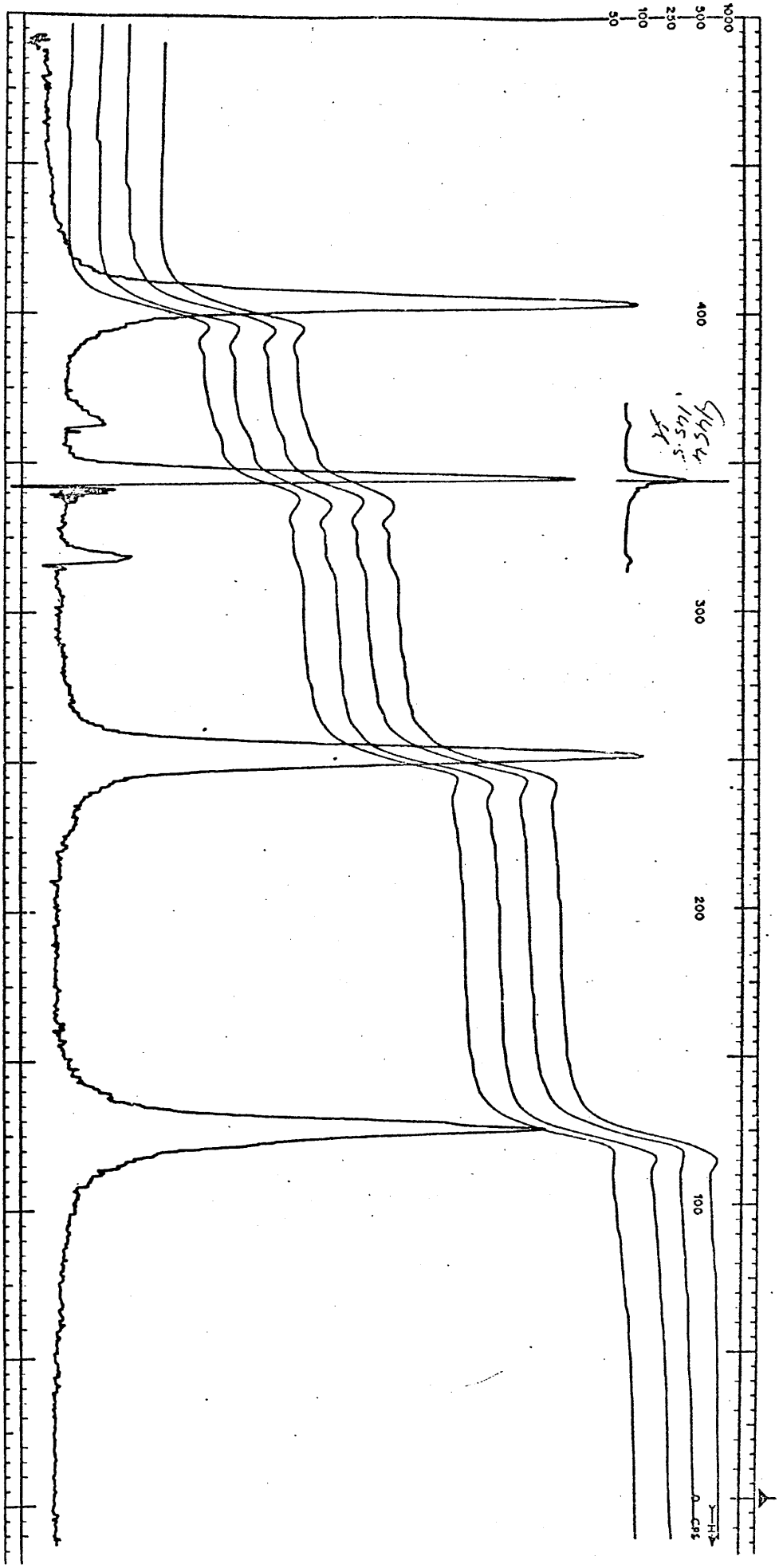


Figure 6. 100 MHz ^{1}H n.m.r. spectrum of (2) recrystallised from an equimolar mixture of cyclopentane, cyclohexane and cycloheptane.

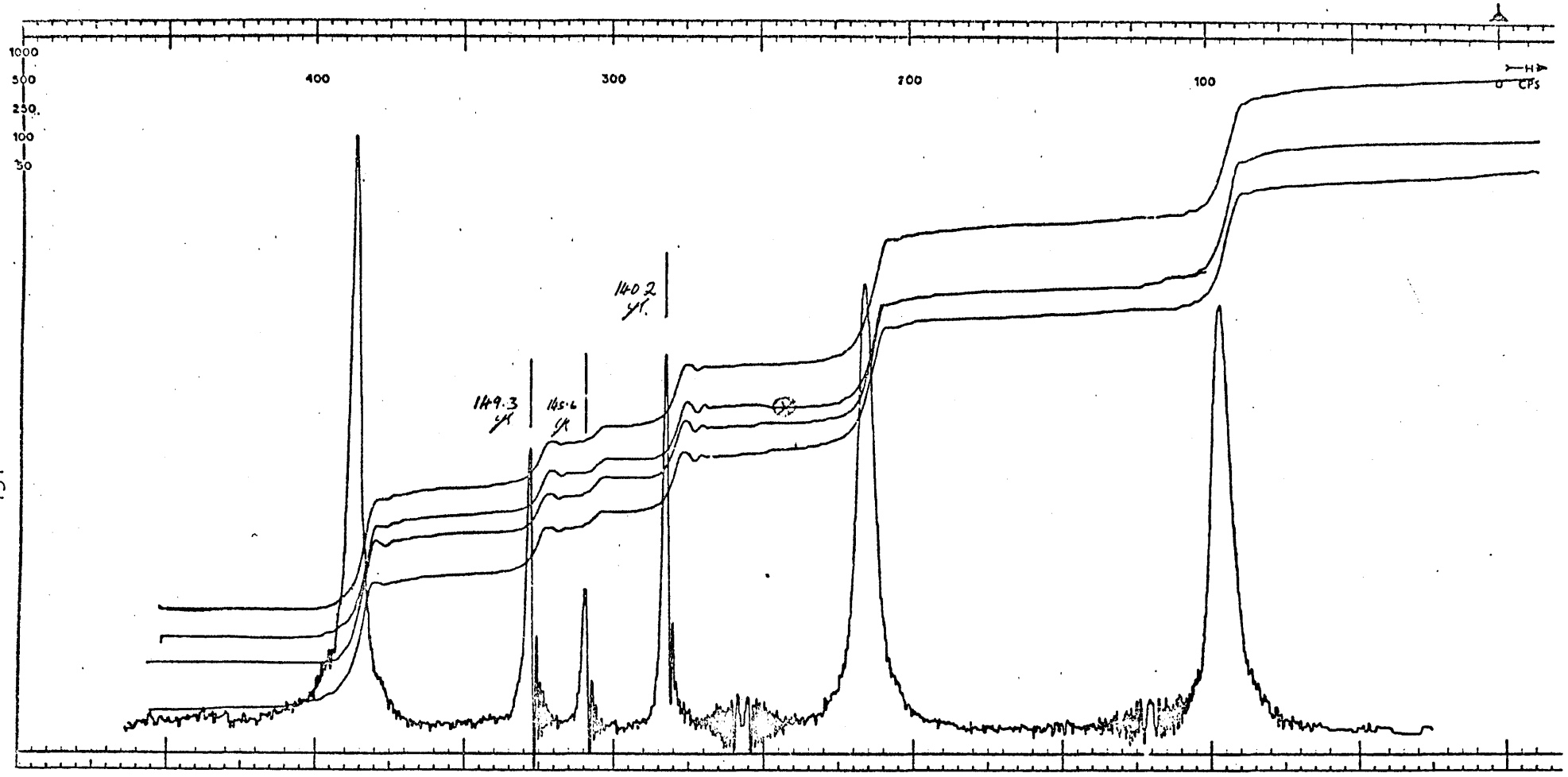


Figure 7. 100 MHz ^{1}H n.m.r. spectrum of (16) recrystallised from an equimolar mixture of cyclopentane, cyclohexane and cycloheptane.

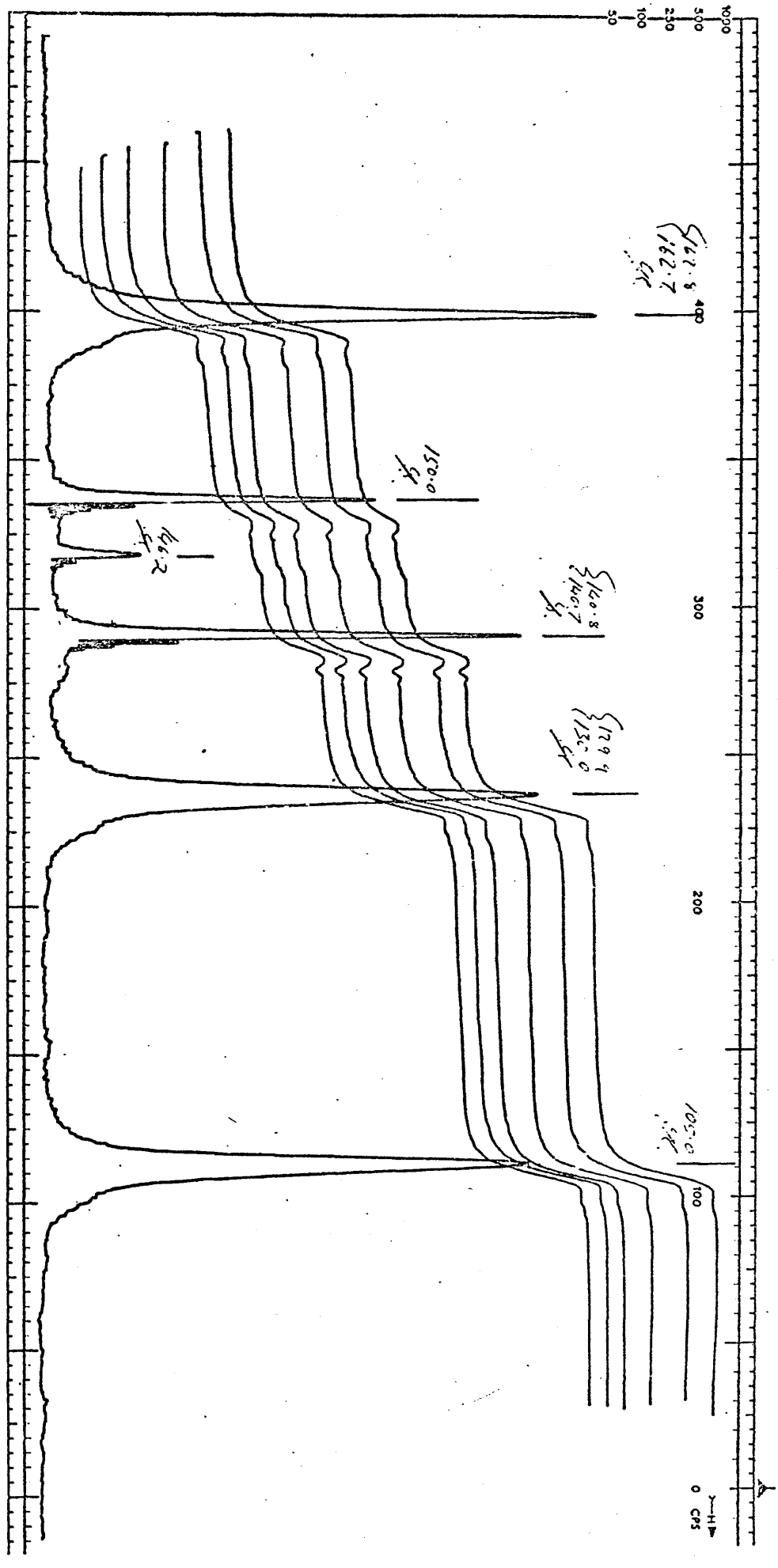
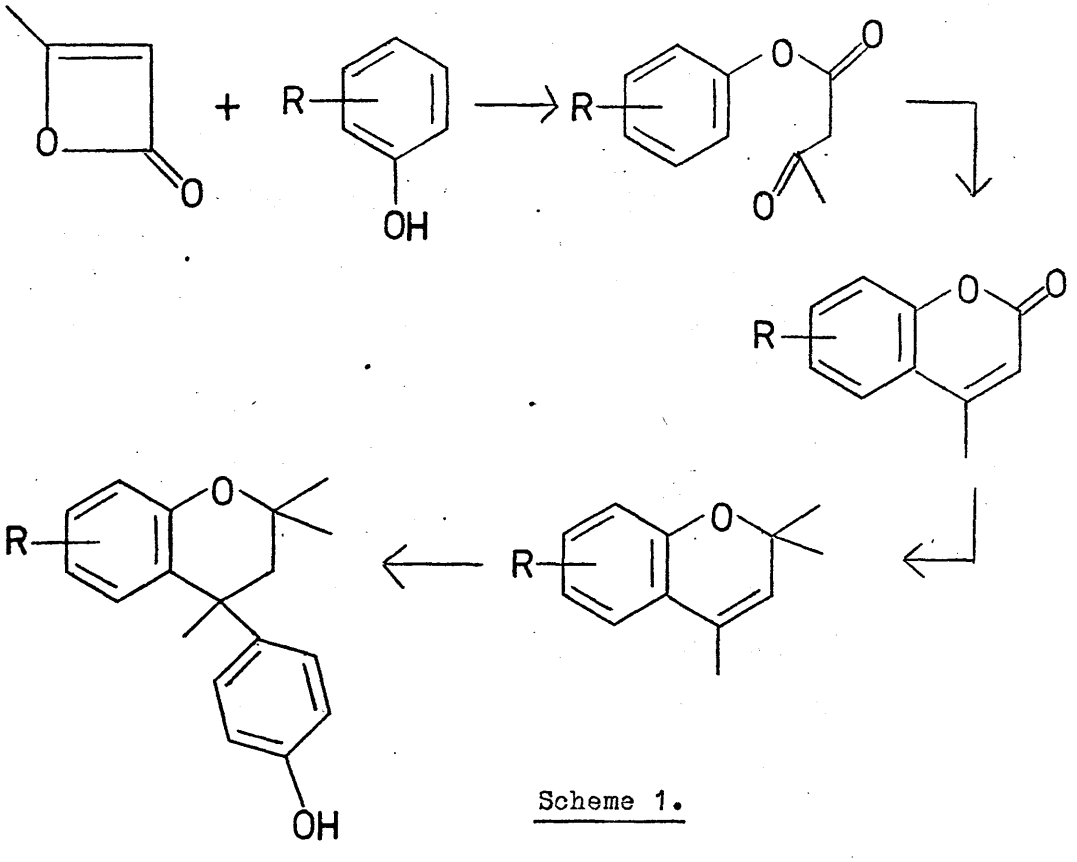


Figure 8. 100 MHz ^{1}H n.m.r. spectrum of (18) recrystallised from an equimolar mixture of cyclopentane, cyclohexane and cycloheptane.

O-O bond. This distortion at the top of the cage may account for the similar selectivities of (16) and (18).

IV. Substitution of Dianin's Compound (1).

Having discovered two new clathrate hosts by substitution of the thiachroman (2), it appeared desirable to prepare the oxygen analogues. The route used (Scheme 1) involved the base catalysed

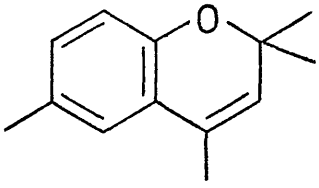


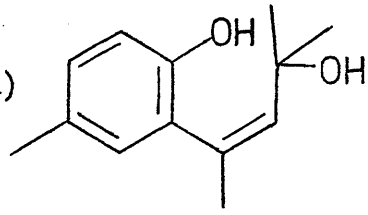
Scheme 1.

addition of a phenol to diketene, then cyclisation of the resulting aryl acetoacetate to give the corresponding coumarin. A Grignard reaction should produce a chromene derivative to which phenol can be added by the method of Baker et al.[17].

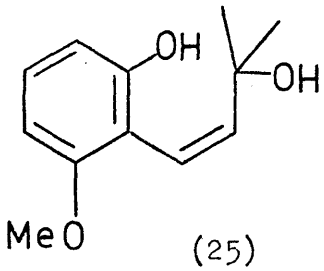
p-Tolylacetoacetate was prepared by adding freshly-distilled diketene to a warm mixture of p-cresol and triethylamine according to Lacey[61]. Cyclisation of the ester was accomplished smoothly using concentrated sulphuric acid giving 4,6-dimethylcoumarin. Reacting

this with methylmagnesium iodide by the method of Shriner and Sharp[62] produced a white solid, the spectral properties of which were not consistent with the predicted chromene (23) - the mass spectrum did,

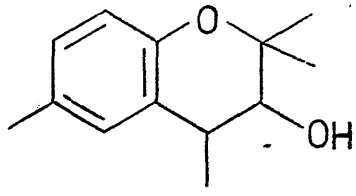
(23) 

(24) 

however, show a molecular ion at m/e 188. An infrared spectrum (KBr disc) confirmed the absence of any unreacted coumarin, but its principal feature was a sharp peak at 3350 cm^{-1} accompanied by a broad absorption over the range 2500 - 3500 cm^{-1}, immediately suggesting the presence of a hydrogen-bonded hydroxyl group. A carbon analysis gave a value markedly lower than expected, but most significantly, attempts to remove trace impurities from the product by chromatography on silicic acid resulted in the isolation of a different compound. This colourless oil had a similar ^1H n.m.r. spectrum to that obtained from the white solid, but the olefinic resonance had moved upfield from 4.23 to 4.63 τ ($CDCl_3$) while a singlet, previously at 8.78 τ, appeared further downfield at 8.63 τ. No O-H stretch was seen in the i.r. spectrum and the mass spectrum was identical to that recorded from the earlier product. In short the spectral parameters of this latter material were in agreement with structure (23), further evidence being the similarities in ultra-violet absorption between this compound and 2,2,4-trimethyl-2H-chromene isolated by Baker *et al.*[17]. Considerable attention has been devoted to the reactions of coumarins with Grignard reagents, the various products being discussed by Smith and Ruoff[63]. This together with the above spectral information allows identification of the original reaction product as the unsaturated diol (24). Hepworth and Livingstone[64] have isolated the analogous solid (25) during the



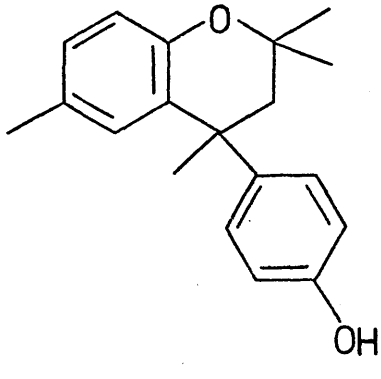
(25)



(26)

preparation of 5-methoxy-2,2-dimethylchromene (a colourless liquid) by methylmagnesium iodide treatment of 5-methoxycoumarin. Distillation or refluxing in acetic acid brings about ready diol cyclisation; presumably this loss of water also occurred on attempting to record the mass spectrum of (24). It is just conceivable that 2,2,4,6-tetramethylchromene (23) was formed in the reaction, only to be hydrated to (26) when the excess Grignard reagent was destroyed with ammonium chloride solution. Pure (23) was unchanged after a three hour reflux with 22% NH_4Cl solution in the presence of magnesium ions, thus eliminating this possibility.

The diol (24) and phenol were saturated with gaseous HCl and kept at ~45°C for 6 days, using a method similar to that of Baker et al.[17]. The gum formed after removal of excess phenol solidified on

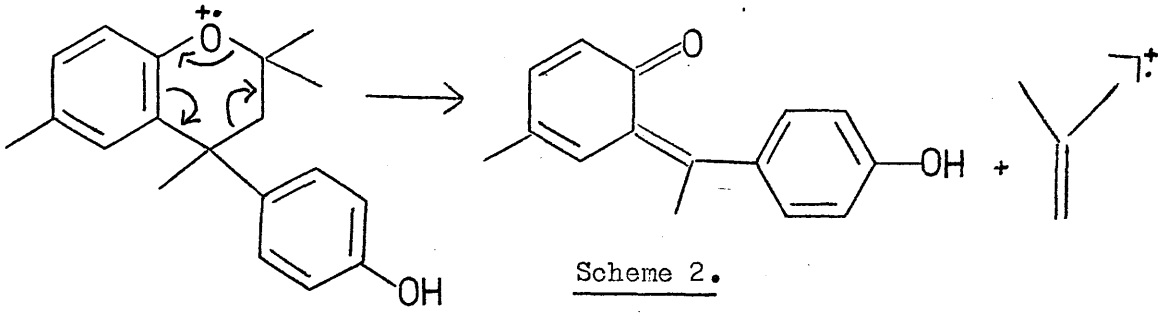


(27)

adding ethanol to give (27). Unlike its sulphur analogue, this compound readily crystallises from a wide range of solvents, for example methanol, carbon tetrachloride and toluene, but unfortunately no clathrating properties were observed. The mass spectrum of

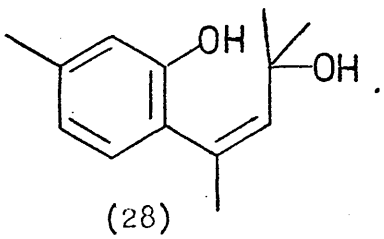
(27) and Dianin's compound are similar, both exhibiting intense peaks at M - 15 due to the loss of a methyl radical (Figure 9); this, followed by elimination of ethylene accounts for the M - 43 signals, while a retro Diels-Alder reaction explains the peaks at M - 57 (shown for (27) in Scheme 2).

Repeating the reaction sequence with m-cresol allows the

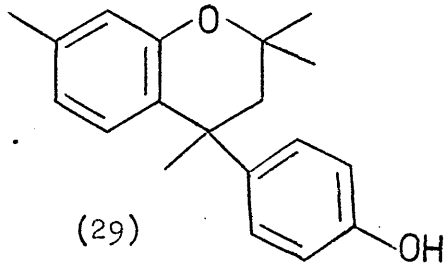


Scheme 2.

isolation of the analogous diol (28); refluxing this for 2 hours



(28)



(29)

with 5N sodium hydroxide produces a colourless oil with ^{1}H n.m.r. spectrum revealing a (2:1) mixture of 2,2,4,7-tetramethylchromene and (28). Work-up of the cyclisation product of the diol (28) with phenol gives a solid (29); however, repeated recrystallisations from different solvents leave a persistent grey colour, requiring sublimation for its complete removal. ^{1}H n.m.r. spectra of (29) grown from cyclopentane, ethanol and toluene did not show any signals which could be assigned to trapped species.

Attempts to prepare the isomer with methyl substituted ortho to oxygen were less fruitful. Lacey[61] claimed to have obtained o-tolyl-acetoacetate (30) as an oil which on cyclisation gave the appropriate coumarin in just under 20% yield, this being substantially lower than for the other two isomers. However, purification of (30) by distillation proved impossible as simultaneous decomposition appeared to be

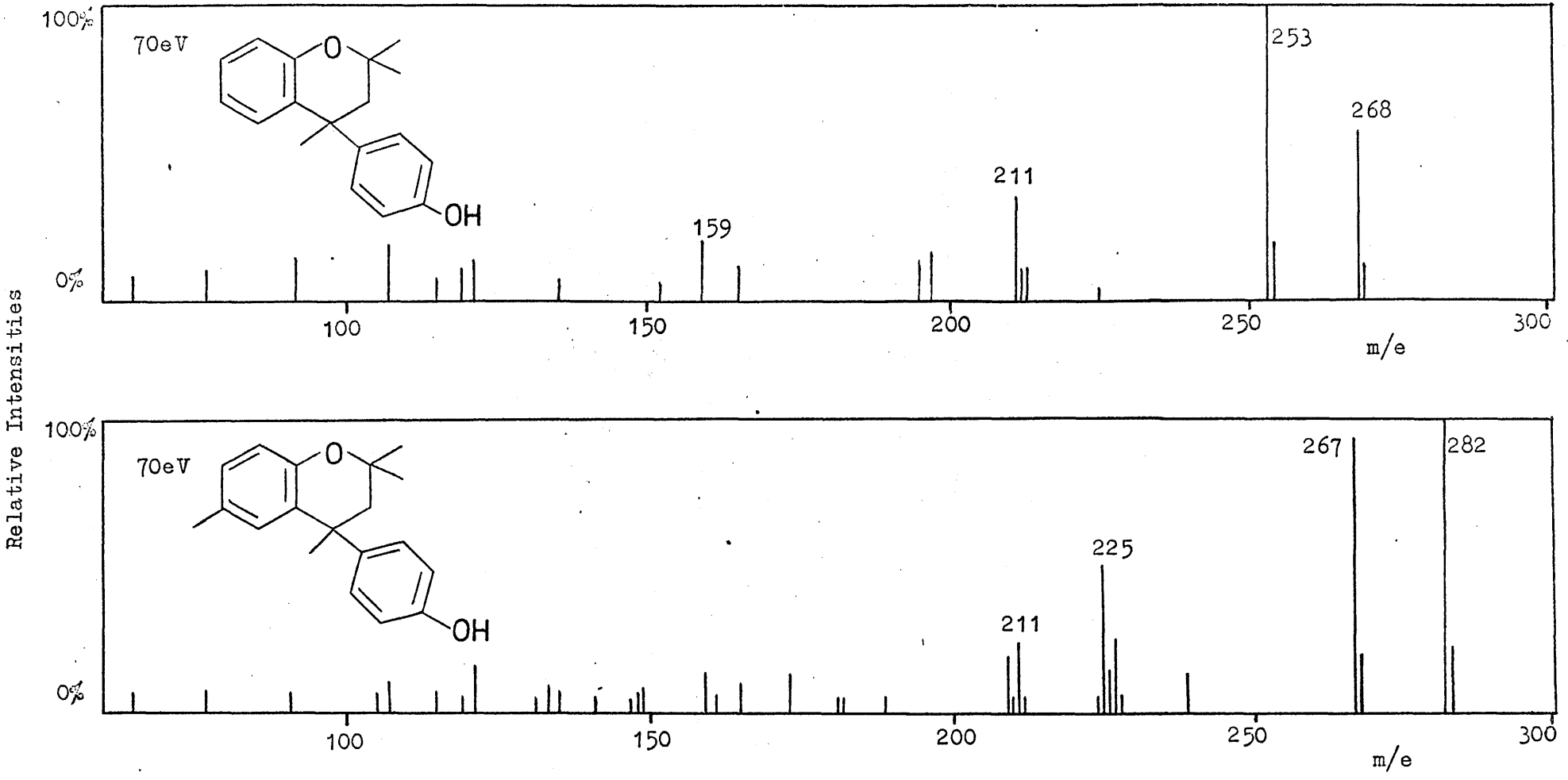
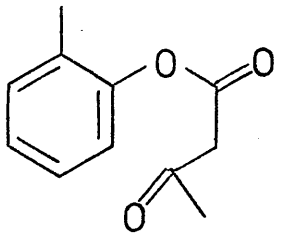
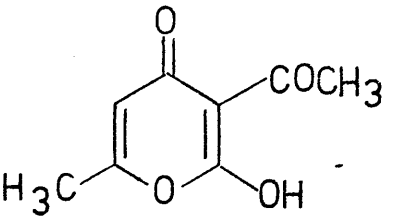


Figure 9. Mass spectra of top) Dianin's compound and bottom) 4-p-hydroxyphenyl-2,2,4,6-tetramethylchroman.



(30)



(31)

taking place giving rise to fine, white needles. A ^{1}H n.m.r. spectrum of the latter showed three singlets at ca.-6.6, 7.33 and 7.73 τ and an ill-resolved quartet at 4.08 τ ($CDCl_3$) with a proton ratio of 1:3:3:1. Two carbonyl and one hydroxyl absorptions were observed in the i.r. spectrum, thus permitting the solid's identity to be established as dehydracetic acid (31), formed by (30) undergoing a retro reaction, followed by self condensation of acetoacetic acid. Lacey's alleged 4,8-dimethylcoumarin had a melting point of 112 - 113°C and did not give a precipitate with bromine in acetic acid; the sample of dehydracetic acid also gave a negative test and melted at 110 - 111°C.

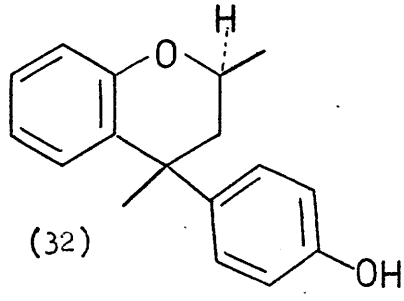
Following the failure to isolate (30), cyclisation of the crude mixture was attempted, but in every instance a dark-red, polymeric resin resulted. An alternative route explored was an adaptation of Woodruff's[65] preparation of 4-methylcoumarin; aluminium trichloride dissolved in nitrobenzene was added to a solution of o-cresol in ethyl acetoacetate and heated to 130°C for 3 hours. No coumarin was observed on work-up, the condensation presumably having failed on steric grounds.

V. Modification of the Cage Waist in Dianin's Compound (1).

Flippen, Karle and Karle[24] have described the hour-glass shaped cavity of Dianin's compound, their X-ray analysis revealing how the gem-dimethyl groups of the six molecules comprising a cage

form a constriction in the cavity at about Z = 0.5. Obviously, if this waist could be removed without collapse of the entire framework then the enclathrating ability of this host should be vastly improved. The possible 50% increase in the cross-section of the cage at its mid-point would be particularly useful in storage applications, and this modification could be considered as the first important step towards the synthesis of hosts "tailor-made" for specific tasks.

Methyl vinyl ketone and 3-penten-2-one were each condensed with phenol at 0°C by saturating the mixture with a stream of dry hydrogen chloride gas. Work-up of the former gave a black glass which was still acidic after prolonged extraction with boiling water. T.l.c. in various solvent systems highlighted a fierce concoction, suggesting that extensive polymerisation had occurred and consequently no further purification was attempted. Chromatography on silicic acid of the product from 3-penten-2-one yielded a black oil which solidified on the addition of ethanol. Recrystallisation from benzene gave brown prisms requiring a sublimation for their decolourisation. A ^{1}H n.m.r. spectrum showed the large hexagonal crystals isolated to be a mixture of Dianin's compound and the expected product (32); attempts to bring about their separation by high pressure liquid chromatography



(32)

failed but success was ultimately achieved by using gel chromatography.

Information about the stereochemistry of (32) comes from a comparison of its ^{1}H n.m.r. spectrum with that of Dianin's compound, the latter showing a characteristic high field singlet above 9 τ which arises from the shielding effect of the underlying phenol ring.

Most significantly, this methyl is one of the six comprising the waist of the cavity, and the absence of its peak in the spectrum of (32) indicates the successful removal of the cage constriction. Also, the phenol would be expected to attach itself on the opposite side of the molecule to that bearing the C-2 methyl substituent, resulting in (32) having the two methyl groups cis to each other.

The mass spectrum of (32) shows a fragmentation pattern similar to that of the parent host (1) with peaks at M - 15, M - 43, M - 57 and M - 109. Inclusion behaviour has been observed when (32) is grown from cyclohexane and carbon tetrachloride with host to guest ratios of 5:1 and 6:1 respectively, as compared with ratios of 7:1[35] and 3:1 when Dianin's compound is recrystallised from these solvents. The infrared spectrum of the carbon tetrachloride clathrate shows the C-Cl stretch at 785 cm^{-1} while the O-H absorption appears as a broad symmetrical band at 3275 cm^{-1}. The apparent change in the size of the cavity from that present in Dianin's compound provides a promising host for future investigation.

VI. Storage by the Formation of Clathrates.

Organometallic compounds are of considerable importance in many fields and especially in chemical synthesis but often their usefulness is limited by the extreme difficulties encountered when handling them in their free state. Packaging such compounds in the form of clathrates can mitigate properties such as volatility, toxicity, reactivity or instability since:

a) toxic materials are secured in a lattice thus avoiding the danger consequent on using the free materials;

b) reactive materials, particularly those exhibiting instability due to reaction or spontaneous ignition in air, are protected from the environment by their retaining lattice;

c) volatile materials may be more easily handled and accurately weighed as crystalline inclusion compounds despite their normal physical properties.

An additional advantage is that the release of a guest compound from a clathrate may readily be achieved in a controlled manner, when desired; the available techniques are melting, distillation, sublimation or dissolution in a suitable organic solvent, conveniently one appropriate to the mixture of guest and host as well as to the use to which the resulting solution of guest is to be put. Choice of the clathrate host material is governed by considerations such as cavity size and lack of any reaction between host and guest. An investigation of the possible applications of Dianin's compound (1) and its sulphur analogue (2) commenced by attempting to include mercury dialkyls and, in particular, the volatile and extremely toxic dimethylmercury, a compound which has recently received popular attention in connection with environmental pollution studies. Although diethylmercury and longer chain mercury dialkyls have been reported[66] to form inclusion compounds with urea and dimethylmercury has been included in the tri-o-thymotide channel structure[12], there have been no previous reports of a successful preparation of a stable clathrate containing dimethylmercury.

The thiachoman host (2), chosen because of its better solubility than (1), was desolvated by the method of Baker et al.[17] and then recrystallised from neat dimethylmercury to give a highly crystalline product containing 10.42% mercury. Its ^{1}H n.m.r. spectrum (Figure 10) shows the resonance of the methyl groups at 9.72 τ along with satellite peaks from $^{1}H - ^{199}Hg$ coupling (J = 102 Hz); integration gives a host to guest ratio of 6:1, corresponding to single occupancy of the clathrate cages. The crystals suffer no detectable loss of guest (n.m.r. analysis) even when pumped for several days under vacuum. Release of the dimethylmercury occurs when the host lattice

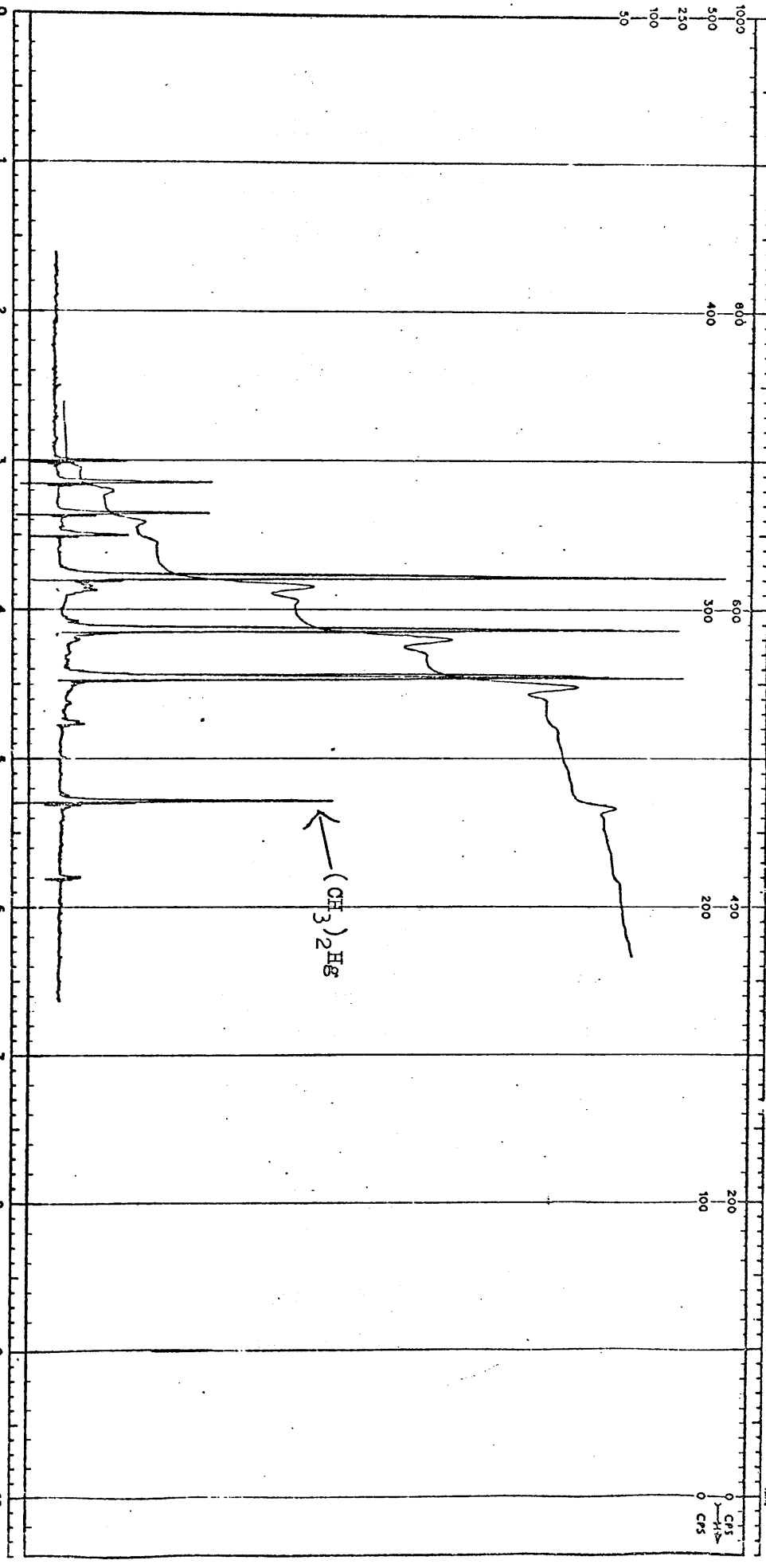


Figure 10. 100 MHz ^{1}H n.m.r. spectrum of 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman recrystallised from dimethylmercury.

is physically destroyed; thus grinding the crystals liberates sufficient guest to be detectable by mass spectrometry. When crystals of the adduct in an evacuated flask attached to the inlet of a mass spectrometer are finely ground by using a magnet to agitate a small steel ball in the flask, the mass spectrum of dimethylmercury is observed. The minimal interference found from the spectum of the host makes this an attractive method for obtaining the mass spectra of guest molecules in clathrates. Diethylmercury should also be capable of being accommodated in the cage of the thiachroman (2) but the ^{1}H n.m.r. spectrum of a sample recrystallised from this solvent showed no signals in the reported region[67], there being instead a few small peaks at lower field. Unlike the dimethylmercury clathrate the material was not sharp melting while microanalysis gave a mercury content of 14.9%. A mass spectrum of the guest did not show any peaks with the characteristic mercury isotope pattern around m/e 260, the molecular weight of diethylmercury but, as well as the host's spectrum, peaks with the sulphur isotope pattern were seen at m/e 297 and m/e 312, while mercury-containing species appeared at m/e 327, m/e 341 and m/e 356. It is suggested that the former imply the ethylation of (2) whereas the latter arise from the scavaging of EtHgI, a possible precursor during the preparation of Et_2Hg, followed by loss of methyl and ethyl radicals on bombardment; positive identification, however, has not proved possible. Similar scavaging appears to take place on recrystallising (2) from tetramethylsilane since, although this solvent is not included, the elemental analysis is not consistent with unsolvated material.

Trimethylphosphine is an example of a class of compounds whose use is severely restricted by their high reactivity, and appears to be of suitable size and shape for enclathration. Inflammability in air and a low boiling point (ca. 40°C) dictate that a vacuum line should be employed for its manipulation. A 100 MHz ^{1}H n.m.r. spectrum

of freshly-distilled trimethlphosphine showed a doublet at 8.99τ ($J_{^{31}P - ^{1}H}$ = 1.8 Hz) with $CDCl_3$ as solvent, and at 9.05τ ($J_{^{31}P - ^{1}H}$ = 1.2 Hz) when run in d_6 - acetone; the distillation residue which gave a spectrum comprising of a doublet at 8.46τ ($CDCl_3$) with a coupling constant of 12.5 Hz was an oxidation product, namely trimethylphosphine oxide, $(CH_3)_3P{=}O$. Recrystallisation of (2) from trimethylphosphine was carried out in an "h"-shaped pressure vessel equipped with a "Rotaflow" tap and side-arm for attaching to a vacuum line. To record the ^{1}H n.m.r. spectrum of the crystalline product the following procedure was adopted: a) pipette excess solvent (here $CDCl_3$) into sample tube and fit serum cap; b) degas solvent via needle through serum cap; c) fill tube with nitrogen to minimise guest oxidation; d) introduce solid at the top of the tube and degas; e) dissolve solid and record spectrum.

Apart from the host's absorption, the spectrum showed the anticipated doublet from $(CH_3)_3P$ together with very small multiplets from some minor impurity at 6.26 and 8.14τ; the doublet which had now moved downfield by 2 Hz, also appeared asymmetric with the lower field signal markedly more intense, an observation confirmed by scale expansions. As the presence of thiachroman (2) is the only additional factor since recording the spectrum of unclathrated $(CH_3)_3P$, hydrogen bonding between the latter and the hydroxyl group of (2) must be responsible for the difference in its chemical shift - introducing phenol to the earlier sample of $(CH_3)_3P$ also caused a shift in the doublet's position. However, using d_6 - acetone as solvent gave a symmetrical doublet at 9.05τ ($J_{^{31}P - ^{1}H}$ = 2.4 Hz) from included trimethylphosphine while integration and microanalysis allowed the host guest ratio to be calculated as 4:1.

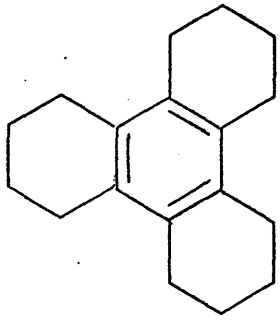
The mass spectrum of the guest was recorded by grinding crystals of the clathrate in an evacuated flask attached to the inlet of a

mass spectrometer, but despite repeated attempts the reported[68] fragmentation pattern of a molecular ion at m/e 76 and base peak at m/e 61 from trimethylphosphine was not observed. Instead two peaks of equal intensity were seen at m/e 72 and m/e 71 with the base peak at m/e 42, and after some time it was realised that this pattern was in complete agreement with that described by Smakman and de Boer[69] for tetrahydrofuran, an impurity which would explain the additional peaks observed in the ^1H n.m.r. spectrum of the clathrate; failure to identify trimethylphosphine by mass spectrometry is probably a result of its very low boiling point, this being some 25°C lower than that of THF. However, a neat method of demonstrating its presence is to allow the clathrate to react with bisbenzonitrile-palladium-dichloride, $(PhCN)_2PdCl_2$, to give $(Me_3P)_2PdCl_2$. A ^1H n.m.r. spectrum of the product shows no trace of the doublet from free $(CH_3)_3P$, but a new triplet at 8.56 τ (solvent $CDCl_3$) is consistent with the reported[70] resonance position of trans-$(Me_3P)_2PdCl_2$. Clathration therefore provides a valuable addition to the methods of handling trimethylphosphine evaluated by Goodfellow[71] et al..

The ethanol complex of Dianin's compound was recrystallised from phenylphosphine, a material which spontaneously ignites on contact with air; its high boiling point (160-1°C), however, enables certain procedures to be carried out in a countercurrent of nitrogen rather than under vacuum. The method employed was to introduce desolvated Dianin's compound and phenylphosphine to one leg of a Schlenk tube, then pass the resulting solution through a sintered glass disc and allow crystallisation to take place under nitrogen (or vacuum) in the other limb. A ^1H n.m.r. spectrum (solvent $CDCl_3$) of the product showed only negligible inclusion of phenylphosphine by the appearance of a doublet at 6.07 τ ($J_{^{31}P - ^1H}$ = 200 Hz).

In an attempt to find a better host for these larger organometallics, attention was focussed on trans-anti-trans-anti-trans-

perhydrotriphenylene (34) which has been reported[72] to form inclusion



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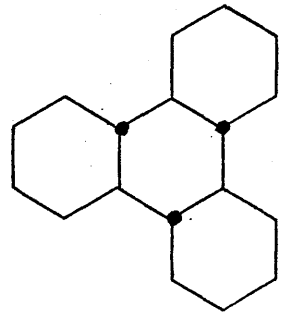

(34)

compounds with a wide range of compounds including macromolecules; the adducts have a channel-like structure and the many different crystal modifications observed[73] depend on the nature of the guest molecule. This host was prepared by a drastic catalytic hydrogenation* (10 days, 300°C, 250 atmospheres) of dodecahydrotriphenylene (33), the reaction giving (34) in high yield minimising the concomitant isomer formation which troubled Farina[74]. Recrystallisation from tetramethylsilane and hexamethyldisilane gave some incorporation as revealed by ^{1}H n.m.r. analysis, but drying the crystals under vacuum led to their crumbling with simultaneous guest leakage.

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* We thank Dr. Knox, University of Strathclyde for his assistance with this hydrogenation.

EXPERIMENTAL

The introductory remarks to Section 1, Experimental also apply here.

X-ray studies were carried out by Dr. A.D.U. Hardy, University of Glasgow.

O-(p-4-(2,2,4-trimethylchromanyl)phenyl)dimethylthiocarbamate, (8).

The ethanol clathrate of Dianin's compound (11.33 g) was added under nitrogen to clean sodium metal (1.07 g) dissolved in absolute ethanol (40 ml); more ethanol was added until complete dissolution was achieved on heating. A water pump was used to remove the excess solvent, final traces requiring the use of an oil pump. Benzene (10 ml) was introduced then evaporated off leaving a dry, white powder - the sodium salt of Dianin's compound.

Dimethylthiocarbamoyl chloride (8.41 g) in dry dimethylformamide (56 ml) was added to this salt at 10°C and the reaction mixture stirred for 1.5 hrs at 40 - 45°C[55]. On cooling, the product was poured into water (120 ml) and extracted with a 4:1 mixture of benzene and n-hexane (4x100 ml). The combined extracts were washed with water (3x100 ml), 5% sodium hydroxide (3x100 ml) and sodium chloride (3x100 ml), finally being dried over anhydrous magnesium sulphate. Solvent removal left a yellow oil which on two recrystallisations from methanol gave (8) as a white solid, m.p. 139 - 141°C, 91%;

m.s.	m/e 355 (M^+), other prominent peaks at m/e 340, 253, 165;
ν_{max} (nujol mull)	1605 (w), 1575 (w), 1530 (s), 1442 (s), 1285 (s), 1205 (s), 1170 (s), 1130 (s),

1010 (m), 765 (s) cm^{-1};

$\tau(CDCl_3)$ 2.6 - 3.3 (8H, m, aromatics),
6.56 and 6.68 (each 3H, 2s, $N(CH_3)_2$),
7.75 (2H, AB q, J = 14 Hz, $-CH_2-$),
8.27, 8.65 and 9.06 (each 3H, 3s,
ring CH_3 and $C(CH_3)_2$);

(Found : C, 70.77; H, 6.86; N, 3.99. $C_{21}H_{25}O_2NS$ requires
C, 70.96; H, 7.09, N, 3.94%).

O-(2-nitrophenyl)dimethylthiocarbamate, (10).

The same procedure as above was employed; 2-nitrophenol (2.82 g) was added to a solution of clean sodium metal (0.54 g) in absolute ethanol (20 ml) giving a red precipitate which did not dissolve even after the addition of more solvent followed by gentle heating. Removal of excess ethanol left a red powder to which was added dimethylthiocarbamoyl chloride (4.24 g) in dry DMF (28 ml); heating for 1.5 hrs at 40 - 45°C gave an orange solution. Similar work-up left a yellow residue which was recrystallised twice from methanol to yield white crystals, m.p. 125 - 126°C, 87%;

$\tau(CDCl_3)$ 1.9 - 2.9 (4H, m, aromatics),
6.56 amd 6.62 (each 3H, 2s, $N(CH_3)_2$).

S-(p-4-(2,2,4-trimethylchromanyl)phenyl)dimethylthiocarbamate, (9).

After vacuum drying at 50°C for 1 hour, O-(p-4-(2,2,4-trimethylchromanyl)phenyl)dimethylthiocarbamate (4 g) was sealed in a pyrex tube, extreme caution being exercised to prevent the inclusion of any water vapour which causes hydrolysis to Dianin's compound. The tube was immersed in a Wood's metal bath, preheated to 200°C and the temperature raised to 270°C, where it was maintained for 1.5 hours.

On cooling the tube was opened to release a smell of fish and a brown gum which solidified on air exposure to a yellow solid, m.p. 123 - 127°C; minor impurities present were Dianin's compound, unrearranged material and the thiol (5) but attempts at purification by recrystallisation and sublimation were not successful;

ν_{max} (nujol mull) 1665 (s), 1605 (w), 1575 (w), 1250 (m), 1202 (m), 1085 (s), 900 (s), 760 (s) cm^{-1};

τ ($CDCl_3$) 2.5 - 3.3 (8H, m, aromatics), 6.95 (6H, s, $N(CH_3)_2$), 7.76 (2H, AB q, J = 14 Hz, $-CH_2-$), 8.28, 8.66 and 9.06 (each 3H, 3s, ring CH_3 and $C(CH_3)_2$).

4-p-Mercaptophenyl-2,2,4-trimethylchroman, (5).

A five-fold excess (56 ml) of 10% NaOH was added to the pyrolysis product dissolved in methanol (110 ml) and the mixture refluxed overnight under nitrogen; a white precipitate formed on cooling. Water (100 ml) was added and the solution acidified (pH 5 - 6) with dilute hydrochloric acid. The product was extracted into benzene (3x150 ml), washed with water (1x100 ml) and dried over anhydrous magnesium sulphate. Solvent evaporation gave a pale yellow oil which solidified on standing. Recrystallisation from benzene yielded (5) as small white crystals, m.p. 107 - 109°C, 38% (based on O-aryl compound);

m.s. m/e 284 (M^+), other prominent peaks at m/e 269, 228, 195;

ν_{max} (nujol mull) 2540 (s), 1605 (w), 1580 (m), 1195 (s), 1145 (s), 830 (m), 760 (s) cm^{-1};

τ ($CDCl_3$) 2.6 - 3.3 (8H, m, aromatics), 6.70 (1H, s, -SH),

7.83 (2H, AB q, J = 14 Hz, $-CH_2-$),
8.37, 8.70 and 9.10 (each 3H, 3s,
ring CH_3 and $C(CH_3)_2$);

(Found : C, 76.18; H, 7.25. $C_{18}H_{20}OS$ requires C, 76.03; H, 7.09%).

O-(p-4-(2,2,4-trimethylchromanyl)phenyl)methylcarbamate.

Methyl isocyanate (0.62 g) was added to a solution of the ethanol complex of Dianin's compound (1.51 g) in sodium-dried benzene (30 ml). A few drops of triethylamine were introduced and the mixture refluxed for 48 hrs; the reaction was followed on t.l.c. by the appearance of a less polar species - too long a reflux time led to the recovery of starting material. Evaporation of the solvent left the carbamate, contaminated by trace amounts of Dianin's compound which were removed by chromatography on silicic acid.(100:1, eluant 10% ethyl acetate in benzene). Recrystallisation from toluene gave the carbamate as fine white crystals, m.p. 142 - 145°C, 66%;

m.s. m/e 325 (M^+), other prominent peaks at
m/e 310, 253, 225;

ν_{max} (KBr disc) 3360 (s), 2965 (s), 2920 (w), 1710 (s),
1498 (s), 1210 (s), 1170 (s), 1010 (m),
928 (s), 768 (s) cm^{-1};

$\tau(CDCl_3)$ 2.6 - 3.3 (8H, m, aromatics),
ca. 5.1 (1H, broad, -NH-),
7.12 (3H, d, J = 5 Hz, $N-CH_3$),
7.78 (2H, AB q, J = 14 Hz, $-CH_2-$),
8.30, 8.66 and 9.06 (each 3H, 3s,
ring CH_3 and $C(CH_3)_2$);

(Found : C, 74.08; H, 7.24; N, 3.99. $C_{20}H_{23}O_3N$ requires
C, 73.82; H, 7.12; N, 4.30%).

4-p-Hydroxyphenyl-2,2,4,8-tetramethylthiachroman, (16).

A mixture of phenol (7.7 g) and 4-methyl-4-(o-tolylthio)pentan-2-one (9.0 g) prepared from o-thiocresol and mesityl oxide (see Section 1, Experimental) was saturated (4 hours) at 0°C with dry, gaseous HCl. The resulting dark-red, viscous liquid was then set aside in a flask fitted with a drying tube; after 21 months the excess phenol was extracted with boiling water (6x50 ml) leaving a thick yellow gum which, following chromatography on Mallinckrodt silicic acid (ratio 25:1, eluant 10% chloroform in light petroleum), gave on standing a pale yellow solid, (16), 15% based on the ketosulphide. Recrystallisation from some solvents (methanol, ethanol, tetrahydrofuran, but-2-yne, tetramethylsilane) proved unsuccessful, an oil being deposited, while with others (see Table 1) inclusion behaviour was observed; the percentage recoveries from these solvents were 72, 37, 34, 60, 61, 58, 48, 29 and 34% respectively. For example, cyclooctane gave colourless hexagonal crystals, 48%, m.p. 110 - 111°C;

m.s. m/e 298 (M^+), other prominent peaks at m/e 241, 227, 189;

ν_{max} (KBr disc) 3275 (broad), 2960 (s), 2910 (s), 1610 (m), 1598 (m), 1510 (s), 1460 (s), 1440 (s), 1242 (s), 1185 (s), 826 (s), 788 (s) cm^{-1};

$\tau(CDCl_3)$ 2.8 - 3.4 (7H, m, aromatics), 5.38 (1H, s, -OH), 7.70 (3H, s, aromatic ring CH_3), 7.74 (2H, AB q, J = 14 Hz, $-CH_2-$), 8.24, 8.59 and 8.90 (each 3H, 3s, other methyls).

Desolvated (16) was obtainod as a clear glass by melting crystals of the cyclopentane clathrate under vacuum;

(Found : C, 76.70; H, 7.66. $C_{19}H_{22}OS$ requires C, 76.48; H, 7.43%). The melting points of the clathrates vary, for example with benzene and carbon tetrachloride as guests, partial melting takes place about 90 - 94°C, followed by complete melting about 106 - 114°C. Recrystallisation from cyclopropane was achieved by introducing (16) to a sealed tube equipped with a Rotaflo TF6/18 teflon tap and side arm for attaching to a vacuum line. After condensing in the solvent under vacuum, degassing was carried out and the tube sealed. The tube was then placed in a water-bath, heated to 90°C for 1 hour and allowed to cool to room temperature in a draught-free environment. The excess solvent was allowed to escape into the atmosphere and the crystals scraped out and air-dried before subjecting them to ^1H n.m.r. analysis. An identical method was used for an attempted recrystallisation from perfluorobut-2-yne but (16) was found to be insoluble, even after adding perfluorodecalin as cosolvent. With m-nitrobenzotrifluoride as cosolvent two phases formed but, although dissolution was accomplished, the isolated crystals did not contain the acetylene.

4-p-Hydroxyphenyl-2,2,4,7-tetramethylthiachroman, (17).

A mixture of phenol (34.6 g) and 4-methyl-4-(m-tolylthio)pentan-2-one (36.7 g) prepared from m-thiocresol and mesityl oxide (see Section 1, Experimental) was saturated (6 hours) at 0°C with dry, gaseous HCl. The resulting dark-green, viscous liquid was then set aside in a flask fitted with a drying tube - over a few days the colour changed to dark-red; after 4 months, the excess phenol was extracted with boiling water (5x150 ml) leaving a pale brown glass. Chromatography on Mallinckrodt silicic acid (ratio 55:1, eluant 50% ethyl acetate in benzene) gave a pale yellow oil which defied crystallisation. Final purification was achieved by gel chromatography (200 x 2.5 cm column of Sephadex LH-20 modified with NEDOX 1114,

elution with methanol) which gave a colourless oil having a S.E.V. of about 130. Solidification proved extremely difficult, the only successful method being to suddenly cool a sample dissolved in the minimum volume of hot petrol with simultaneous scratching, whereupon fine white crystals of (17) are deposited. Recrystallisation from cyclopentane gave single, colourless prisms m.p. 114 - 115°C, 43%;

m.s. m/e 298 (M^+), other prominent peaks at m/e 283, 255, 241, 227;

ν_{max} (KBr disc) 3335 (broad), 2965 (s), 1611 (m), 1510 (s), 1265 (s), 1205 (s), 1175 (m), 834 (s), 822 (s) cm^{-1};

$\tau(CDCl_3)$ 2.7 - 3.5 (7H, m, aromatics), 5.22 (1H, s, -OH), 7.73 (3H, s, aromatic ring CH_3), 7.75 (2H, AB q, J = 14 Hz, $-CH_2-$), 8.26, 8.59 and 8.92 (each 3H, 3s, other methyls);

(Found : C, 76.28; H, 7.32. $C_{19}H_{22}OS$ requires C, 76.48; H, 7.43%).

4-p-Hydroxyphenyl-2,2,4,6-tetramethylthiachroman, (18).

A mixture of phenol (29.7 g) and 4-methyl-4-(p-tolylthio)pentan-2-one (35.0 g) prepared from p-thiocresol and mesityl oxide (see Section 1, Experimental) was saturated (6 hours) at 0°C with dry, gaseous HCl. The resulting dark-red, viscous liquid was then set aside in a flask fitted with a drying tube; after two months the excess phenol was extracted with boiling water (5x150 ml) leaving a clear yellow glass. A ^1H n.m.r. spectrum showed the product to contain a considerable amount of 2,2-di-(p-hydroxyphenyl)propane, which on a second run could be partially removed by adding benzene and

chilling the solution. However, chromatography on Mallinckrodt silicic acid (ratio 40:1, eluant 10% ethyl acetate in benzene) was necessary in both cases, yielding a pale yellow oil which did not crystallise. Final purification of (18) was again accomplished by gel chromatography (identical column and conditions), the isolated colourless glass being crystallised by suddenly cooling a hot petrol solution as before. Desolvation by sublimation (60°C/0.01 mm Hg) was a limited success since after 3 weeks only 80 mg had condensed. (Found : C, 76.50; H, 7.71. $C_{19}H_{22}OS$ requires C, 76.48; H, 7.43%). Recrystallisation from most solvents tried (for example benzene, ethanol, carbon disulphide, cycloheptane and 2,2,5,5-tetramethyl-hex-3-yne) was unsuccessful on account of the high solubility of (18). However, it exhibited clathrating properties when grown from cyclopentane, cyclohexane and n-pentane; cyclopentane gave colourless prisms, m.p. 64 - 67°C, 74%;

m.s.	m/e 298 (M^+), other prominent peaks at 283, 255, 241, 227;
ν_{max} (KBr disc)	3410 (broad), 2964 (s), 1608 (m), 1592 (w), 1508 (s), 1210 (m), 1199 (s), 1178 (s), 836 (s), 814 (s) cm^{-1};
$\tau(CDCl_3)$	2.8 - 3.4 (7H, m, aromatics), 4.95 (1H, s, -OH), 7.76 (2H, AB q, J = 14 Hz, $-CH_2-$), 7.78 (3H, s, aromatic ring CH_3), 8.26, 8.61 and 8.91 (each 3H, 3s, other methyls).

2,2-Di-(p-hydroxyphenyl)propane.

This was isolated as a byproduct during the purification of (18); recrystallisation from benzene gave white needles, m.p. 155 -

157°C;

m.s. m/e 228 (M^+), base peak at m/e 213;

ν_{max} (KBr disc) 3350 (broad), 2965 (m), 1610 (m), 1598 (m), 1508 (s), 1444 (m), 1434 (m), 1361 (m), 1235 (s), 1218 (s), 828 (s), 564 (s), 552 (s) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 3.2 (8H, m, aromatics), 5.36 (2H, s, hydroxyl protons), 8.38 (6H, s, $C(CH_3)_2$);

(Found : C, 78.90; H, 7.08. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06%).

4-p-Hydroxyphenyl-2,2,4-trimethyl-7,8-benzothiachroman, (19).

A mixture of phenol (4.0 g) and 4-methyl-4-(1-naphthylthio)pentan-2-one (5.0 g) prepared by condensation of naphthalene-1-thiol and mesityl oxide (see Section 1, Experimental) was saturated (6 hours) at 0°C with dry gaseous HCl. The resulting dark-green, viscous liquid which had changed to a pale brown solid after 24 hours, was set aside in a flask equipped with a drying tube. After the removal of excess phenol in boiling water (6 x 30 ml) there remained a pale yellow glass which solidified on standing; three recrystallisations from benzene gave (19) as white needles, m.p. 152 - 154°C, 52%;

m.s. m/e 334 (M^+), other prominent peaks at m/e 319, 277, 263;

ν_{max} (KBr disc) 3535 (m), 3465 (sh), 3420 (m), 2970 (m), 1504 (s), 1172 (s), 836 (s), 823 (s), 809 (s), 748 (s), 739 (s), 540 (m) cm^{-1};

$\tau(CDCl_3)$ 1.6 - 1.9 and 2.2 - 3.5 (10H, m, aromatics), 5.23 (1H, s, -OH), 7.64 (2H, AB q, J = 14 Hz, $-CH_2-$),

8.14, 8.50 and 8.77 (each 3H, 3s, ring CH_3 and $C(CH_3)_2$);

(Found : C, 78.88; H, 6.70. $C_{22}H_{22}OS$ requires C, 79.01; H, 6.63%).

4-p-Hydroxyphenyl-2,2,4-trimethyl-5,6-benzothiachroman, (20).

A mixture of phenol (28.0 g) and 4-methyl-4-(2-naphthylthio)pentan-2-one (30.0 g) prepared by condensation of naphthalene-2-thiol and mesityl oxide (see Section 1, Experimental) was saturated (6 hours) at 0°C with dry, gaseous HCl. The resulting black, viscous liquid was set aside in a flask fitted with a drying tube. After 18 months the excess phenol was removed by extracting with boiling water (7x100 ml) leaving a black tar containing at least seven components (t.l.c.). Chromatography on both Mallinckrodt silicic acid (ratio 40:1, elution with 20% ethyl acetate in light petroleum) and modified Sephadex LH-20 (identical column and conditions as before) allowed their partial separation, but none of the fractions yielded a compound with spectral parameters consistent with structure (20). A different approach involved condensation of 2,2,4-trimethyl-5,6-benzo-2H-thiachromene (79 mg), prepared by PPA cyclisation of the corresponding ketosulphide (see Section 1, Experimental), with phenol (831 mg) by saturating (30 mins) the mixture at 50°C with dry gaseous HCl. The flask containing the resulting orange solution was fitted with a drying tube and placed in an oven at 45°C for 9 days; gradually the colour of the contents changed to dark green and finally to wine-red. Excess phenol was removed by extraction with boiling water (2x5 ml), the residue being dissolved in benzene and dried over anhydrous sodium sulphate. Solvent removal left a green oil (115 mg) consisting of three major and several minor components (t.l.c. in $CHCl_3$); the most polar of the major components had an R_f value similar to that of (19) and was separated from the mixture by preparative t.l.c. (solvent $CHCl_3$).

This compound was found to have spectral parameters identical to one of the products obtained via silicic acid and gel chromatography (again no component was consistent with structure (20)); sublimation (115°C/0.07 mm Hg) and recrystallisation from benzene gave an almost-white solid, probably (22), which was never freed of minor impurities, m.p. 129 - 135°C;

m.s. m/e 334, other prominent peaks at m/e 319, 199, 184;

ν_{max} (CCl_4) 3605 (s), 3050 (m), 2960 (s), 2920 (m), 1608 (w), 1172 (s), 1157 (m) cm^{-1};

τ ($CDCl_3$) 2.0 - 3.4 (10H, m, aromatics), 5.34 (1H, s, -OH), ca. 6.3 (2H, m, methine protons), 8.65 and 8.81 (each 3H, 2s, $C(CH_3)_2$), 8.79 (3H, d, J = 6 Hz, $CHC\underline{H}_3$).

Selectivity Experiments on Clathrate Hosts (2), (16) and (18).

An equimolar mixture of cyclopentane (3.5095 g), cyclohexane (4.2078 g) and cycloheptane (4.9098 g) was made up and checked by ^1H n.m.r. analysis. p-Hydroxyphenyl-2,2,4-trimethylthiachroman (61.3 mg) and the above solution (about 3 ml) were sealed in a tube at atmospheric pressure and heated to 120°C. The heat was removed and the tube allowed to cool to room temperature over several hours. The crystalline product was removed after one day, dried for 1 hour at 0.01 mm Hg /room temperature and its ^1H n.m.r. spectrum recorded with C_6D_6 or C_6H_6 as solvent. Similarly 54.5 mg of (16) and 130.0 mg of (18) were each crystallised from about 2 ml and about 5 ml of the equimolar mixture. Recoveries were 62.5 mg, 40.8 mg and 38.4 mg respectively. The results are included in the Discussion Section; repeating the recrystallisations gave identical incorporation of the cycloalkanes.

p-Tolylacetoacetate.

Freshly-distilled diketene (83.7 g) was added dropwise during 1 hour to an agitated mixture of p-cresol (107.7 g) and triethylamine (0.5 ml) at 72 - 75°C according to the method of Lacey[61]. After heating for a further 0.5 hours the stirring was stopped and the reaction product allowed to cool overnight; solvent removal under vacuum gave a white solid which was recrystallised from light petroleum/chloroform (1:1) yielding white needles, m.p. 67 - 68°C (lit. 65 - 66°C), 78%;

ν_{max} (nujol mull) 1770 (s), 1725 (s), 1510 (m), 1262 (s), 1202 (s), 1148 (s), 924 (s), 838 (s), 772 (m) cm^{-1};

$\tau(CDCl_3)$ 2.7 - 3.1 (4H, m, aromatics), 6.33 (2H, s, $-CH_2-$), 7.65 (6H, s, methyls);

(Found : C, 68.68; H, 6.36. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%).

4,6-Dimethylcoumarin.

p-Tolylacetoacetate (132 g) was stirred for 24 hours with 75% sulphuric acid (200 ml) at 53°C; the cooled solution was poured into iced water (800 ml) to form a yellow precipitate which on two recrystallisations from aqueous ethanol gave white needles, m.p. 152 - 153°C, 66%;

ν_{max} (KBr disc) 1712 (s), 1572 (m), 1382 (m), 1199 (m), 1178 (m), 936 (m), 858 (m), 828 (m) cm^{-1};

$\tau(CDCl_3)$ 2.5 - 2.9 (3H, m, aromatics), 3.73 (1H, q, J = 1.5 Hz, olefinic proton), 7.56 (6H, s, both methyls);

$\tau(C_6H_6)$ 8.03 (3H, s, aromatic ring CH_3),

8.41 (3H, d, J = 1.5 Hz, olefinic CH_3);

(Found : C, 76.07; H, 5.94. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%).

2-(2-Hydroxy-5-methylphenyl)4,4-dimethylbut-2-en-4-ol, (24).

A solution of methyl iodide (140.8 g) in anhydrous diethylether (200 ml) was added dropwise over 1.5 hours to magnesium turnings (24.4 g) in ether (250 ml) under a nitrogen atmosphere[62]. 4,6-Dimethylcoumarin (54.0 g) in ether (2 l) was introduced with stirring over 2 hours giving a pale yellow precipitate. After stirring overnight at room temperature the excess Grignard reagent was destroyed using 22% acidified ammonium chloride solution (500 ml) and the ether layer separated. The aqueous fraction was extracted with ether (2x100 ml) and the combined ether extracts dried over magnesium sulphate. Solvent evaporation left a pale yellow solid, 57%, which on recrystallisation from light petroleum gave (24) as white prisms, m.p. 94 - 96°C;

m.s. peaks at m/e 188, 173 (base peak), 128, 115 - molecular ion not observed;

ν_{max} (KBr disc) 3350 (s), 3110 (broad), 2976 (s), 1646 (w), 1604 (w), 1505 (m), 1428 (m), 1412 (s), 1275 (s), 1252 (s), 1206 (m), 1146 (s), 810 (s) cm^{-1};

$\tau(CDCl_3)$ 2.9 - 3.4 (3H, m, aromatics), 4.23 (1H, q, J = 1.5 Hz, olefinic proton), 7.75 (3H, s, aromatic ring CH_3), 8.06 (3H, d, J = 1.5 Hz, olefinic CH_3), 8.78 (6H, s, $C(CH_3)_2$);

(Found : C, 75.52; H, 8.85. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

2,2,4,6-Tetramethylchromene, (23).

The above diol (1.17 g) was subjected to chromatography on Mallinckrodt silicic acid (30 g) with benzene as eluant to give a yellow oil. Short path distillation (50°C/0.01 mm Hg) yielded a colourless liquid, (23), 37%;

m.s. m/e 188 (M^+), other prominent peaks at m/e 173, 128, 115;

ν_{max} (thin film) 2985 (s), 2950 (sh), 1657 (w), 1495 (s), 1385 (s), 1364 (s), 1274 (s), 1220 (s), 1178 (s), 1145 (s), 950 (s), 824 (s) cm^{-1};

τ ($CDCl_3$) 2.9 - 3.5 (3H, m, aromatics), 4.63 (1H, q, J = 1.5 Hz, olefinic proton), 7.73 (3H, s, aromatic ring CH_3), 8.01 (3H, d, J = 1.5 Hz, olefinic CH_3), 8.63 (6H, s, $C(CH_3)_2$);

λ_{max} (EtOH) 223 (log ε 4.42), 262 (3.63), 315 (3.51) nm;

(Found : C, 82.64; H, 8.50. $C_{13}H_{16}O$ requires C, 82.93; H, 8.57%).

The above chromene (60.4 mg) was added to a mixture of 2M magnesium chloride (2 ml) and 22% ammonium chloride solution (2 ml) and refluxed for 3 hours. The product was extracted with ether (3x10 ml) and dried over magnesium sulphate. Solvent evaporation left a colourless oil, the spectral parameters of which were identical to those of the starting material, thus showing that hydration of the carbon - carbon double bond does not occur, at least under these conditions.

4-p-Hydroxyphenyl-2,2,4,6-tetramethylchromene, (27).

The above diol (24) (18.0 g) was added to phenol (19.9 g) at 45°C, and dry gaseous HCl passed in for 4 hours. The resulting dark-

45°C, and dry gaseous HCl passed in for 4 hours. The resulting dark-

red, viscous liquid was set aside in an oven at 45°C for 6 days. The excess phenol was removed by extraction with boiling water (5x50 ml), ethanol (25 ml) introduced and the gum allowed to crystallise. Recrystallisation from ethanol gave large, white, single prisms, (27), m.p. 135 - 136°C, 52%;

m.s.	m/e 282 (M^+), other prominent peaks at m/e 267, 225, 211;
ν_{max} (KBr disc)	3385 (s), 2978 (s), 1612 (m), 1513 (s), 1496 (s), 1275 (s), 1198 (s), 1179 (s), 908 (m), 834 (s), 815 (s) cm^{-1};
τ (d_6 - acetone)	1.92 (1H, s, -OH), 2.8 - 3.4 (7H, m, aromatics), 7.75 (3H, s, aromatic ring CH_3), 7.81 (2H, AB q, J=14Hz, $-CH_2-$), 8.36, 8.71 and 9.12 (each 3H, 3s, other methyls);

(Found : C, 81.01; H, 7.92. $C_{19}H_{22}O_2$ requires C, 80.81; H, 7.85%).

Samples of (27) grown from a range of solvents (for example, methanol, cyclopentane, toluene, nitromethane and carbon tetrachloride) exhibited no inclusion behaviour.

4,7-Dimethylcoumarin.

Freshly-distilled diketene (64.0 g) was added dropwise during 1.5 hours to a stirred mixture of m-cresol (82.0 g) and triethylamine (0.5 ml) at 65 - 70°C. Heating was continued for a further 0.5 hour then the reaction product was allowed to cool to room temperature. No attempt was made to isolate the intermediate m-tolylacetoacetate, and 75% sulphuric acid (400 ml) was introduced. The solution was stirred for 16 hours at 58°C, allowed to cool and poured into iced water (1200 ml) giving a pale yellow solid, 90 g. Recrystallisation from ethanol yield white needles, m.p. 132 - 133°C;

ν_{max} (KBr disc) 3060 (w), 1720 (sh), 1705 (s), 1621 (m), 1393 (m), 1382 (m), 1148 (m), 1066 (m), 876 (m), 807 (m) cm^{-1};

$\tau(CDCl_3)$ 2.4 - 3.0 (3H, m, aromatics), 3.83 (1H, q, J = 1.5 Hz, olefinic proton), 7.57 (3H, s, aromatic ring CH_3), 7.61 (3H, d, J = 1.5 Hz, olefinic CH_3);

(Found : C, 76.08; H, 5.80. $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%).

2-(2-Hydroxy-4-methylphenyl)4,4-dimethylbut-2-en-4-ol, (28).

A solution of methyl iodide (85.3 g) in anhydrous diethylether (100 ml) was added dropwise over 1 hour to magnesium turnings (14.7 g) in ether (200 ml) under a nitrogen atmosphere. 4,7-Dimethylcoumarin (30.0 g) in sodium-dried benzene (1 l) was introduced with stirring over 2.5 hours, then stirred for a further 17 hours at room temperature. Excess Grignard reagent was destroyed with 22% ammonium chloride solution (300 ml) to which concentrated HCl (5 ml) had been added. Standard work-up gave a yellow solid which was twice recrystallised from ethanol to give (28) as white prisms, m.p. 114 - 115°C, 45%;

m.s. peaks at m/e 188, 173 (base peak), 158, 128 - molecular ion not observed;

ν_{max} (KBr disc) 3330 (s), 3055 (broad), 2975 (s), 1648 (m), 1612 (m), 1440 (sh), 1420 (s), 1236 (m), 1155 (s), 1142 (s), 902 (m), 809 (s) cm^{-1};

$\tau(CDCl_3)$ 2.9 - 3.5 (3H, m, aromatics), 4.24 (1H, q, J = 1.5 Hz, olefinic proton), 7.74 (3H, s, aromatic ring CH_3), 8.06 (3H, d, J = 1.5 Hz, olefinic CH_3), 8.79 (6H, s, $C(CH_3)_2$);

(Found : C, 75.79; H, 8.66. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

4-p-Hydroxyphenyl-2,2,4,7-tetramethylchromene, (29).

The above diol (3.54 g) was added to phenol (4.0 g) at 48°C, and dry gaseous HCl passed in for 6 hours. The resulting dark-red, viscous liquid was set aside in an oven at 55°C for 6 days. The excess phenol was removed by extraction with boiling water (4x50 ml), methanol (10 ml) was added and the solution boiled. No crystals formed on cooling but solvent removal left a solid (81%) with a persistent grey colour which was not eliminated by successive recystallisations from toluene and cyclohexane. Sublimation (98°C/ 0.01 mm Hg) of the material gave colourless prisms, m.p. 129 - 130°C;

m.s. m/e 282 (M^+), other prominent peaks at m/e 267, 225, 159;

ν_{max} (KBr disc) 3382 (s), 2970 (s), 1612 (m), 1512 (s), 1504 (s), 1262 (s), 1208 (s), 1167 (s), 1136 (s), 835 (s), 812 (s) cm^{-1};

τ ($CDCl_3$) 2.7 - 3.4 (7H, m, aromatics), 4.91 (1H, s, -OH), 7.68 (3H, s, aromatic ring CH_3), 7.85 (2H, AB q, J=14 Hz, $-CH_2-$), 8.35, 8.66 and 9.10 (each 3H, 3s, other methyls);

(Found : C, 80.93; H, 7.98. $C_{19}H_{22}O_2$ requires C, 80.81; H, 7.85%).

Recrystallisation of (29) from a range of solvents (for example cyclopentane, carbon tetrachloride, ethanol and nitromethane) showed no evidence of inclusion behaviour.

o-Tolylacetoacetate, (30).

Freshly-distilled diketene (76.5 g) was added dropwise during 0.75 hour to an agitated mixture of o-cresol (98.4 g) and triethyl-

amine (0.5 ml) at 65°C. After a further period of stirring at this temperature the reaction product was allowed to cool to room temperature and 75% sulphuric acid (500 ml) was added giving a violent reaction. Overnight stirring at 50°C and standard work-up left a dark-red, polymeric resin, insoluble in organic solvents. Repeating the experiment using different amounts of acid resulted in the formation of a similar intractable product. An attempt was then made to distil out the intermediate o-tolylacetoacetate but this proved difficult owing to its apparent decomposition to o-cresol and fine, white needles later identified as dehydracetic acid; a ^1H n.m.r. spectrum of the least impure fraction (b.p. 96 -98°C/0.02 mm Hg) showed aromatic absorption at 2.7 - 3.3 τ ($CDCl_3$) and singlets at 6.35, 7.71 and 7.80 as would be expected but there were also other unexplained signals in the region 7 - 8 τ. Sulphuric acid catalysed cyclisation of this material produced identical resins to those previously encountered.

Dehydracetic acid, (31).

During the reaction of o-cresol with diketene, and in the distillation of o-tolylacetoacetate, there was formed (31) as white needles, m.p. 110 - 111°C;

m.s.	m/e 168 (M^+), other prominent peaks at m/e 153, 111, 98;
ν_{max} (KBr disc)	3420 (broad), 3085 (w), 1720 (s), 1640 (s), 1615 (sh), 1550 (s), 1372 (m), 1350 (m), 995 (s) cm^{-1};
τ ($CDCl_3$)	ca. -6.6 (1H, s, -OH), 4.08 (1H, m, olefinic proton), 7.33 (3H, s, CH_3CO-), 7.73 (3H, s, olefinic methyl);

(Found : C, 57.38; H, 4.98. $C_9H_8O_4$ requires C, 57.14; H, 4.80%).

4-p-Hydroxyphenyl-2,4-dimethylchroman, (32).

A mixture of phenol (67.1 g) and 3-penten-2-one (15.0 g) was saturated (6 hours) at 0°C with anhydrous HCl[17]. The resulting black viscous liquid was set aside in an oven at 45°C for 4 days. Standard work-up left a gum which did not crystallise on the addition of ethanol; chromatography on Mallinckrodt silicic acid (ratio 25:1, elution with 50% ethyl acetate in benzene) yielded a black oil which solidified with the introduction of ethanol. The brown prisms obtained from a recrystallisation from benzene required a sublimation (110°C/ 0.01 mm Hg) for their decolourisation. A ^{1}H n.m.r. spectrum of the sublimed material showed it to be a mixture of (32) and Dianin's compound, the separation of which was accomplished by gel chromatography (previous column and conditions, S.E.V. about 100). Samples of (32) grown from cyclohexane (41% recovery) and carbon tetrachloride (83% recovery, m.p. 156 - 160°C) exhibit inclusion behaviour as revealed by ^{1}H n.m.r. and microanalysis respectively;

m.s. m/e 254 (M^+), other prominent peaks at m/e 239, 211, 145;

ν_{max} (KBr disc) 3275 (broad), 2960 (w), 1602 (m), 1574 (m), 1501 (s), 1480 (s), 1443 (s), 1298 (s), 1230 (s), 1218 (sh), 834 (s), 815 (m), 785 (m), 760 (s) cm^{-1};

τ ($CDCl_3$) 2.7 - 3.4 (8H, m, aromatics), 5.20 (1H, s, -OH), ca. 6.1 (1H, m, -CH-), ca. 8.0 (2H, m, $-CH_2-$), 8.29 (3H, s, tertiary CH_3), 8.72 (3H, d, J = 6.5 Hz, secondary CH_3);

(Found : C, 73.83; H, 6.50; Cl, 8.28. $C_{17}H_{18}O_2 \cdot 1/6(CCl_4)$ requires C, 73.64; H, 6.48; Cl, 8.44%).

A similar reaction with phenol (78.3 g) and methyl vinyl ketone (14.6 g) was worked up after 15 months giving a black glass which was still acidic even after prolonged extraction with boiling water. Further purification of the mixture was not attempted.

4-p-Hydroxyphenyl-2,2,4-trimethylchroman, (1).

The ethanol clathrate of (1) was prepared from phenol (300 g) and mesityl oxide (208 g) according to Baker et al.[17] giving white hexagonal crystals, m.p. 164 - 165°C, 36%;

m.s.	m/e 268 (M^+), other prominent peaks at m/e 253, 211, 159;
ν_{max} (KBr disc)	3300 (broad), 2985 (m), 1610 (m), 1603 (m), 1595 (m), 1575 (m), 1505 (s), 1484 (s), 1445 (s), 1304 (s), 1240 (s), 1205 (s), 1178 (s), 838 (s), 822 (s), 764 (s), 575 (s) cm^{-1};
τ (d_6 - acetone)	2.7 - 3.4 (8H, m, aromatics), 7.75 (2H, AB q, J = 14 Hz, $-CH_2-$), 8.34, 8.67 and 9.03 (each 3H, 3s, methyls).

Dimethylmercury clathrate of 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman, (2).

The ethanol clathrate of (2) (3 g), prepared by a standard method[41], was dissolved in hot 2N sodium hydroxide (30 ml) and the solution boiled, a white precipitate forming after about 10 mins. With the solution still boiling, carbon dioxide was bubbled in until pH ~ 7 (after about 1 hour); the solid material was filtered off and vacuum dried over P_2O_5 giving a fine white powder, m.p. 104 - 106°C

87% (desolvation can also be achieved by a flash distillation). This desolvated material (100 mg) was placed in a flask with dimethylmercury (about 3 ml) and heated on a water bath to 75°C until dissolution was complete. On cooling, the excess dimethylmercury was decanted and the crystalline product (67 mg) dried under vacuum; the mass spectrum of the included species can be recorded (see Discussion) while that of the host is always present as a background;

m.s. m/e 284 (M^+), other prominent peaks at m/e 269, 227, 213, 121, ;

ν_{max} (KBr disc) 3335 (broad), 2960 (s), 1608 (m), 1588 (m), 1506 (s), 1470 (m), 1432 (m), 1228 (sh), 1209 (s), 1179 (s), 838 (s), 788 (s), 760 (s), 740 (m), 570 (m) cm^{-1};

$\tau(CDCl_3)$ 2.7 - 3.4 (8H, m, aromatics), 4.64 (1H, s, -OH), 7.74 (2H, AB q, J = 14 Hz, $-CH_2-$), 8.26, 8.60 and 8.91 (each 3H, 3s, methyls);

(Found : C, 69.33; H, 6.81; Hg, 10.42. $C_{18}H_{20}OS.1/6((CH_3)_2Hg)$ requires C, 68.20; H, 6.55; Hg, 10.35%).

trans-anti-trans-anti-trans-Perhydrotriphenylene, (34).

Dodecahydrotriphenylene was catalytically hydrogenated (10% Pd on C; 10 days, 250 atmospheres, 300°C) using the method of Farina[74] to give a high yield of (34) as white prisms, m.p. 124 - 125°C;

m.s. m/e 246 (M^+), other prominent peaks at m/e 204, 189, 121;

ν_{max} (KBr disc) 2950 (s), 2910 (s), 2848 (s), 1445 (m), 1210 (w), 898 (w), 835 (w) cm^{-1};

$\tau(CDCl_3)$ 7.7 - 8.5 and 8.5 - 9.4 (multiplet);

(Found : C, 87.83; H, 12.30. $C_{18}H_{30}$ requires C, 87.73; H, 12.27%).

Recrystallisation from tetramethylsilane and hexamethyldisilane gave some incorporation but vacuum drying of the crystals caused the guest to escape.

REFERENCES

1. Clathrates and inclusion compounds have been the subject of several reviews; for example L. Mandelcorn, Chem. Rev., 1959, 59, 827; H.M. Powell, 'Clathrates', in 'Non-stoichiometric Compounds', editor L. Mandelcorn, Academic Press, New York, 1964; S.M. Hagan, 'Clathrate Inclusion Compounds', Reinhold, New York, 1962; V.M. Bhatnagar, 'Clathrate Compounds', Chemical Publishing, New York, 1970.
2. F Wöhler, Annalen, 1849, 69, 297.
3. A. Clemm, Annalen, 1859, 110, 357.
4. F. Mylius, Ber., 1886, 19, 999.
5. D.E. Palin and H.M. Powell, J. Chem. Soc., 1947, 208.
6. H.M. Powell, J. Chem. Soc., 1948, 61.
7. D.E. Palin and H.M. Powell, Nature, 1945, 156, 334.
8. S. Tanatar, J. Soc. Phys. Chim. Russe, 1906, L40, 376.
9. M.F. Bengen, Angew. Chem., 1951, 63, 207.
10. F. Cramer, Revs. Pure Appl. Chem., 1955, 5, 143; 'Einschlussverbindungen', Springer-Verlag, Berlin, 1954.
11. H. Wieland and H. Sorge, Z. physiol. Chem., 1916, 97, 1.
12. D. Lawton and H.M. Powell, J. Chem. Soc., 1958, 2339.
13. H.M. Powell Symposium, University of Oxford, April 1974.
14. A.P Dianin, J. Soc. Phys. Chim. Russe, 1914, 46, 1310.
15. W. Baker and J.F.W. McOmie, Chem. and Ind., 1955, 256.
16. H.M. Powell and B.D.P. Wetters, Chem. and Ind., 1955, 257.
17. W. Baker, A.J. Floyd, J.F.W. McOmie, G. Pope, A.S. Weaving and J.H. Wild, J. Chem. Soc., 1956, 2010.
18. W. Baker, J.F.W. McOmie and A.S. Weaving, J. Chem. Soc., 1956, 2018.

19. L. Mandelcorn, N.N. Goldberg and R.E. Hoff, J. Amer. Chem. Soc., 1960, 82, 3297.

20. L. Mandelcorn, R.W. Auxier and C.W. Lewis, Chem. Abs., 1961, 55, 11364.

21. W.R. Lawton, Chem. Abs., 1964, 61, 3851.

22. V.M. Bhatnagar, Chem. Age India, 1963, 14, 688.

23. H.L. Hoffman, G.R. Breeden and R.W. Liggett, J. Org. Chem., 1964, 29, 3440.

24. J.L. Flippen, J. Karle and I.L. Karle, J. Amer. Chem. Soc., 1970, 92, 3749.

25. J.L. Flippen and J. Karle, J. Phys. Chem., 1971, 75, 3566.

26. F.B. Wilson, Ph. D. thesis, University of Glasgow, 1971.

27. D.C. McKean, 'Infrared and Raman Spectra of Clathrates', in in 'Vibrational Spectroscopy of Trapped Species', editor H.E. Hallam, Wiley & Sons Ltd., London, 1973.

28. M. Davies and W.C. Child, Spectrochim. Acta, 1965, 21, 1195.

29. M. Davies and K. Williams, Trans. Faraday Soc., 1968, 64, 529.

30. P. Gregoire and J. Meinnel, Compt. rend. C, 1971, 272, 347.

31. A.A. McConnell, D.D. MacNicol and A.L. Porte, J. Chem. Soc. (A), 1971, 3516.

32. G. B. Birrell, S.P. Van and O.H. Griffith, J. Amer. Chem. Soc., 1973, 95, 2451.

33. L.D. Kispert and J. Pearson, J. Phys. Chem., 1972, 76, 133.

34. D.H. Desty, A. Goldup and D.G. Barnard-Smith, Chem. Abs., 1965, 62, 2655.

35. A. Goldup and G.W. Smith, Separation Sci., 1971, 6, 791.

36. J.E. Kropp, M.G. Allen and G.W.B. Warren, Chem. Abs., 1971, 74, 43074.

37. C.K. Johnson, Chem. Abs., 1969, 71, 13717.

38. G.G. Kondrat'eva, Chems. Abs., 1972, 76, 113017.

39. E.N. Aslaksen, Physics Letters A, 1972, 40, 47.

40. P. Gregoire, Y. Marqueton, J. Gallier and J. Meinnel, Bull. Soc. Sci. Bretagne, 1973, 48, 91.

41. D.D. MacNicol, Chem. Comm., 1969, 836.

42. B.D. Tilak, H.S. Desai, C.V. Deshpande, S.K. Jain and V.M. Vaiya, Tetrahedron, 1966, 22, 7.

43. D.D. MacNicol, H.H. Mills and F.B. Wilson, Chem. Comm., 1969, 1332.

44. D.D. MacNicol and F.B. Wilson, Chem. Comm., 1971, 786.

45. D.D. MacNicol, Chem. Comm., 1973, 621.

46. V.M. Bhatnagar, Chem. and Ind., 1965, 717.

47. D.J. Chleck and C.A. Ziegler, Internat. J. Appl. Radiation Isotopes, 1959, 7, 141; Nucleonics, 1959, 17(9), 130.

48. R. Breslow and P. Campbell, Bioorganic Chem., 1971, 1, 140.

49. M.J.S. Dewar and B.D. Nahlovsky, J. Amer. Chem. Soc., 1974, 96, 460.

50. W.S. Rapson, D.H. Saunder and E.T. Stewart, J. Chem. Soc., 1946, 1110.

51. R.L. Van Etten, J.F. Sebastian, G.A. Clowes and M.L. Bender, J. Amer. Chem. Soc., 1967, 89, 3242.

52. D.J. Cram and J.M. Cram, Science, 1974, 183, 803.

53. H.M. Powell, Rec.Trav. chim., 1956, 75, 885.

54. D.D. MacNicol, Private Communication.

55. M.S. Newman and H.A. Karnes, J. Org. Chem., 1966, 31, 3980.

56. A.E. Lemire and J.C. Thompson, Canad. J. Chem., 1970, 48, 824.

57. V.K. Pogorelyi and I.P. Gragerov, Russ. Chem. Rev., 1970, 39, 875.

58. A.C.D. Newman and H.M. Powell, J. Chem. Soc., 1952, 3747.

59. A. Novak, Structure and Bonding, 1974, 18, 177.

60. K.B. Wiberg and B.J. Nist, J. Amer. Chem. Soc., 1961, 83, 1226.

61. R.N. Lacey, J. Chem. Soc., 1954, 854.

62. R.L. Shriner amd A.G. Sharp, J. Org. Chem., 1939, 4, 575.

63. L.I. Smith and P.M. Ruoff, J. Amer. Chem. Soc., 1940, 62, 145.

64. J.D. Hepworth and R. Livingstone, J. Chem. Soc. (C), 1966, 2013.

65. E.H. Woodruff, Org. Synth., 1944, 24, 69.

66. G. Bähr and G. Meier, Z. anorg. Chem., 1958, 294, 22.

67. R.E. Dessy, T.J. Flautt, H.H. Jaffe and G.F. Reynolds, J. Chem. Phys., 1959, 30, 1422.

68. Y. Wada and R.W. Kiser, J. Phys. Chem., 1964, 68, 2290.

69. R. Smakman and T.J. de Boer, Org. Mass Spectrometry, 1968, 1, 403.

70. D.A. Duddell, J.G. Evans, P.L. Goggin, R.J. Goodfellow, A.J. Rest and J.G. Smith, J. Chem. Soc. (A), 1969, 2134.

71. J.G. Evans, P.L. Goggin, R.J. Goodfellow and J.G. Smith, J. Chem. Soc. (A), 1968, 464.

72. M. Farina, G. Allegra and G. Natta, J. Amer. Chem. Soc., 1964, 86, 516.

73. G. Allegra, M. Farina, A. Immirzi, A. Colombo, U. Rossi, R. Broggi and G. Natta, J. Chem. Soc. (B), 1967, 1020.

74. M. Farina, Tetrahedron Letters, 1963, 2097.

RELEVANT PUBLICATIONS

Novel Ring Contraction leading to the Benzo(b)thiophene Nucleus, D.D. MacNicol and J.J. McKendrick, Tetrahedron Letters 1973, 2593.

Clathration as a Practical Method for Handling Dimethylmercury, R.J. Cross, J.J. McKendrick and D.D. MacNicol, Nature, 1973, 245, 146.

Formation of Benzo(b)thiophenes and Related Compounds by a Rearrangement involving Ring Contraction, D.D. MacNicol and J.J. McKendrick, J.C.S. Perkin I, in press.

Variation of Inclusion Properties by Structural Modification of a Clathrate Host, A.D.U. Hardy, J.J. McKendrick and D.D. MacNicol, Chem. Comm., in press.

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