SOME NOVEL ASPECTS OF THE SYNTHESIS OF OXYGEN HETEROCYCLES

A Thesis

Submitted to

Loughborough University of Technology

by

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In partial fulfilment of the Requirements

for the Degree of

Doctor of Philosophy

August 1971

To

My Wife.

SUMMARY

The reactions of benzyne and tetrachlorobenzyne with αβ-unsaturated aldehydes which form 2-H-chromen derivatives have been investigated. The mechanism was established by [^{14}C] and [^{2}H] labelling experiments and proceeds initially through a benzoxeten intermediate. Subsequent opening of these intermediates followed by thermal cyclisation of an o-quinone methide gave the products. A degradation of 5,6,7,8-tetrachloro-2-H-flaven to a tetrachlorosalicylic acid derivative was carried out, to confirm the position of the [^{14}C] radiolabel. Also described are a number of rearrangement reactions of 5,6,7,8-tetrachloro-4-H-flaven in which 2-benzoyl-dihydrobenzofuran, or 2-benzoyl-benzofuran derivatives were obtained if bromine was present in the reaction mixture.

2,4-Disubstituted-tetrachloro-1,3-benzodioxan derivatives have been obtained when a number of aromatic aldehydes were used to trap tetrachlorobenzyne. These adducts were shown to contain two molecules of aldehyde to one of tetrachlorobenzyne. In the presence of simple ketones 2,3-butandione or para-nitrobenzaldehyde were found to react with tetrachlorobenzyne to form 1,4-benzodioxan derivatives. We established the structure of these adducts by degradations and showed that the para-nitrobenzaldehyde or 2,3-butandione moiety resided at position-4. The mechanism of formation

of these adducts is suggested as involving the addition of the simple ketone to form a 1,4-dipolar intermediate followed by reaction with the 2,3-butandione or *para*-nitrobenzaldehyde. Under acidic conditions the 5,6,7,8-tetrachloro-2,2-dialkyl-4-methyl-4-acetyl-1,3-benzodioxans were found to rearrange to benzofuran derivatives and the mechanism of this reaction was studied using deuterio-sulphuric acid.

Enol ethers have also been obtained from the reaction of tetrachlorobenzyne with simple ketones and we have established their structures. Tetrachloroanthranilic acid has been mainly used as the aryne precursor. However as tetrachloroanthranilic acid will condense with carbonyl compounds to form 2-substituted-1,2-dihydro-3,1-benzoxazin-4-ones we have therefore developed alternative aryne precursors; namely - 2-carboxytetrachlorobenzenediazonium-chloride and 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyl-triazene.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr.H.Heaney for his considerable help and encouragement throughout the course of this work. I would also thank Dr.K.G.Mason for the many discussions and advice he has given me.

I am indebted to the Science Research Council for a research studentship, and to Loughborough University of Technology for the privilege of working in their laboratories. Thanks are also due to the Science Research Council through the P.C.M.U.

Finally I would like to thank my typist for typing this manuscript; and also those people who provide the background services necessary in any laboratory.

CONTENTS

INTRODUCTION

The chemistry of benzyne has become well established over the past twenty years.[1] Reactions of arynes with carbonyl compounds could provide possible syntheses of oxygen heterocycles.

Industrial processes such as the hydrolysis of non-activated aryl halides which were in use at the end of the 19th century were known to involve rearrangements,[2] but the intermediacy of an aryne was not suggested. Roberts and his co-workers[3] in 1953, showed by using radio-labelled chlorobenzene, that the amination of chlorobenzene proceeded via benzyne. This was the first confirmation of the intermediacy of benzyne. More recent evidence for the existence of aryne intermediates includes the preparation of nickel carbonyl complexes of both benzyne and tetrafluoro-benzyne.[4] Appropriate peaks have also been observed in the mass spectra of known aryne precursors;[5] and the half-life of benzyne has been measured by time of flight mass-spectro-metry[6] and by the flash photolysis of benzenediazonium-2-carboxylate[7] and phthalic anhydride.[8]

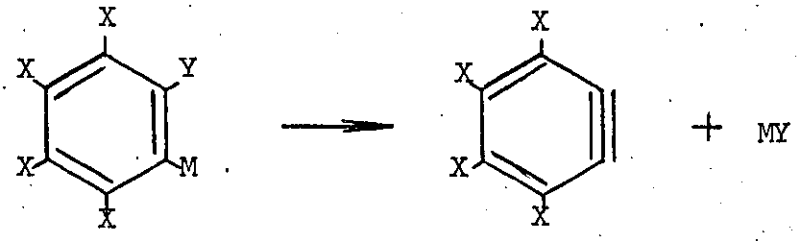
The structure of benzyne has been discussed extensively.[9] The removal of the two adjacent hydrogen atoms from benzene leaves two sp^2-orbitals orthogonal to the π cloud of the aromatic ring. These sp^2-orbitals can interact to give a singlet or a triplet species, but recent calculations predict that benzyne (o-dehydrobenzene) is a ground state singlet

species with the two electrons in the lower symmetric orbital.[10]

Thermal cycloaddition reactions of benzyne with 1,3-dienes are allowed concerted processes by the conservation of orbital symmetry.[11] Conversely the thermal $2\pi s$ cyclo-addition reactions of benzyne with isolated olefins are not thermally allowed concerted processes and should occur by stepwise mechanisms. The expected stereospecificity has been observed in the reactions of benzyne with trans-trans-hexa-2,4-diene.[12,13] However with cis and trans-1,2-dichloroethylene[13] benzyne has been found to add in a nonstereospecific fashion to give a moderate, but not complete, loss of stereochemistry. The cis-olefin gave 35% of the trans-benzocyclobutene, and the trans-olefin gave 20% of the cis-benzocyclobutene. The results obtained in the 1,4-cycloaddition reactions of the tetrahalogenobenzynes clearly indicate that the latter are substituted benzynes.[14]

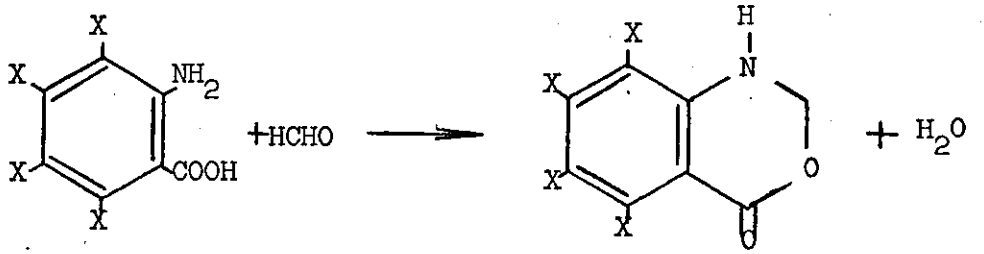
Earlier theories which postulated that benzyne generated from different precursors could have different structures have now been discounted in the light of more recent evidence.[15] As benzynes can be generated from a number of different precursors[16-22] so tetrahalogenobenzynes are also available from several sources. All methods of generation of benzynes involve the abstraction of atoms or groups from adjacent carbon atoms in the aromatic nucleus. The abstracted species are small thermodynamically stable moieties such as metal halides, nitrogen, carbon dioxide, and sulphur dioxide. The use of organometallic precursors has proved convenient for the studies

of reactions of tetrafluorobenzyne and tetrachlorobenzyne with arenes,[14] but this type of precursor does not allow reactions to be undertaken involving carbonyl compounds.



X = F or Cl Y = F, Cl, Br M = Li, Na, MgCl, MgBr

A number of precursors are available which do not react with carbonyl compounds, amongst them are: 1-aminobenzotriazole,[16] benzenediazonium-2-carboxylate,[17] 1,2,3-benzothiadiazole-1,1-dioxide,[18] benzenediazonium-2-carboxylate hydrochloride,[19] and diphenyliodonium-2-carboxylate.[20] Anthranilic acid may be diazotised *in situ* to form the thermally unstable benzenediazonium-2-carboxylate which decomposes to form benzyne;[21] however anthranilic acid[22] and tetrachloro-anthranilic acid[23] are known to condense with formaldehyde to form a dihydro-3,1-benzoxazin-4-one.



X = H or Cl

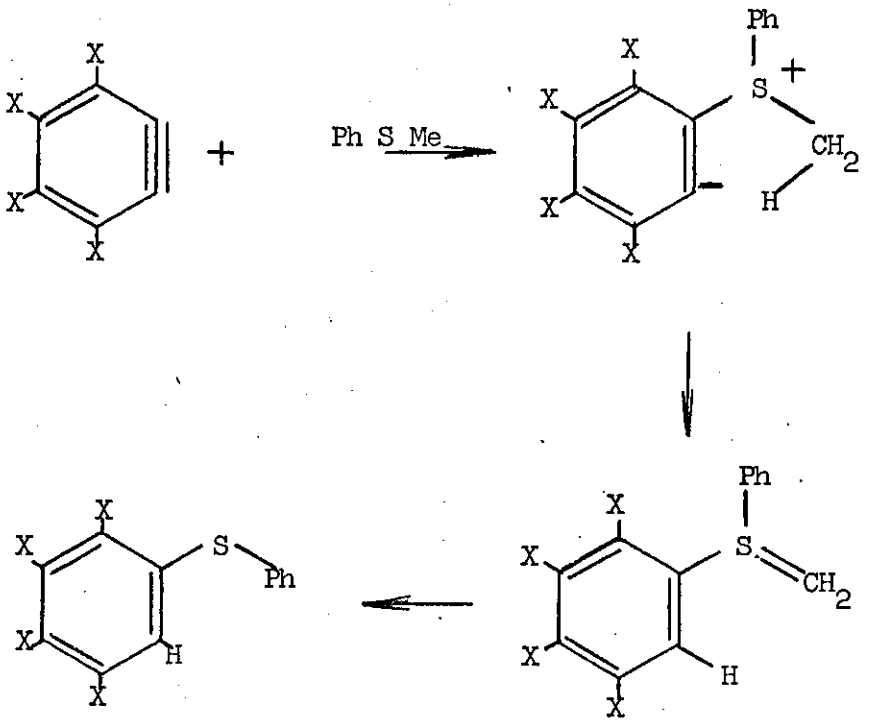
This reaction has been used to synthesise substituted dihydro-3,1-benzoxazin-4-ones.[24]

Tetrachloroanthranilic acid has however been used in the majority of cases for the generation of tetrachlorobenzyne by aprotic diazotisation *in situ*. The original preparation of tetrachloroanthranilic acid[23] has been modified to give reproducibly an almost quantitative yield, and thus provides a convenient precursor. The possibility of using 3,4,5,6-tetrachlorobenzenediazonium-2-carboxylate as a precursor was examined, but it was not used as it is extremely shock sensitive. 3,4,5,6-Tetrachlorobenzene-diazonium-2-carboxylate hydrochloride has been prepared,[25] but it has also been found to be unstable, contrary to expectations, and was only used when other methods proved unsatisfactory. The thermal decomposition of 1-(2-carboxyphenyl)-3,3-dimethyltriazene to form benzyne in good yield has been reported recently.[26] It has been found possible to form the tetrachloro analogue from 3,4,5,6-tetrachlorobenzene-diazonium-2-carboxylate hydrochloride, and to compare the efficiency of it with that of tetrachlorobenzyne generated from the aforementioned precursors.

Tetrafluoro-,[27] tetrabromo-,[28] and tetraiodo-anthranilic[29] acids are reported in the literature. Tetrabromo- and tetraiodo-anthranilic acids have been used to generate the respective tetrahalogenobenzynes, and reactions of these arynes have been studied in this laboratory.[30] No reactions involving carbonyl compounds have been undertaken however. The increased electrophilicity of the tetrahalogenobenzynes compared to that of benzyne, caused by the presence of four

electron withdrawing substituents, has resulted in significantly higher yields of products in reactions analogous to those of benzyne. Different products[31] have also been observed in some reactions and in certain instances cycloaddition reactions have occurred with systems[32] which did not react with benzyne.

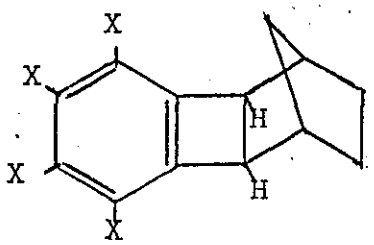
Benzynes are known to react with strong nucleophiles[1] and zwitterionic intermediates have been reported for the reaction of benzyne with thio-ethers.[33] With thioanisole tetrachlorobenzyne and tetrafluorobenzyne do not form cycloadducts;instead 1,2,3,4-tetrahalogeno-5-phenylthiobenzenes are formed.[34]

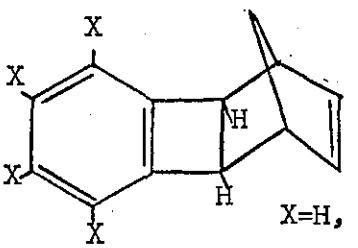


X = F or Cl

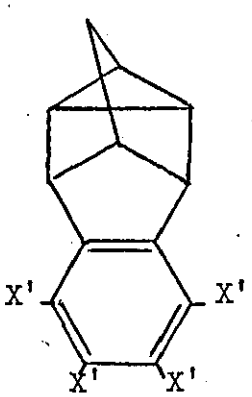
With ethers benzyne is known to cleave only 1,2-dimethoxyethane;[35] however a number of aliphatic ethers are cleaved in good yield when tetrahalogenoanthranilic acids are diazotised in situ.[31,36]

The reaction of benzyne with bicyclohept[2.2.1]ene and bicyclohepta[2.2.1]diene in which a (2 + 2) π concerted cycloaddition was suggested to explain the exclusive formation of exo-adducts,[37] has been examined using tetrafluorobenzyne and tetrachlorobenzyne.[38] The products obtained were analogous to those of the benzyne reactions except that a further product was obtained with bicyclohepta[2.2.1]diene, which was presumed to be formed by an orbital symmetry allowed 2 π s + 2 π s + 2 π s concerted cycloaddition.





X=H, F or Cl

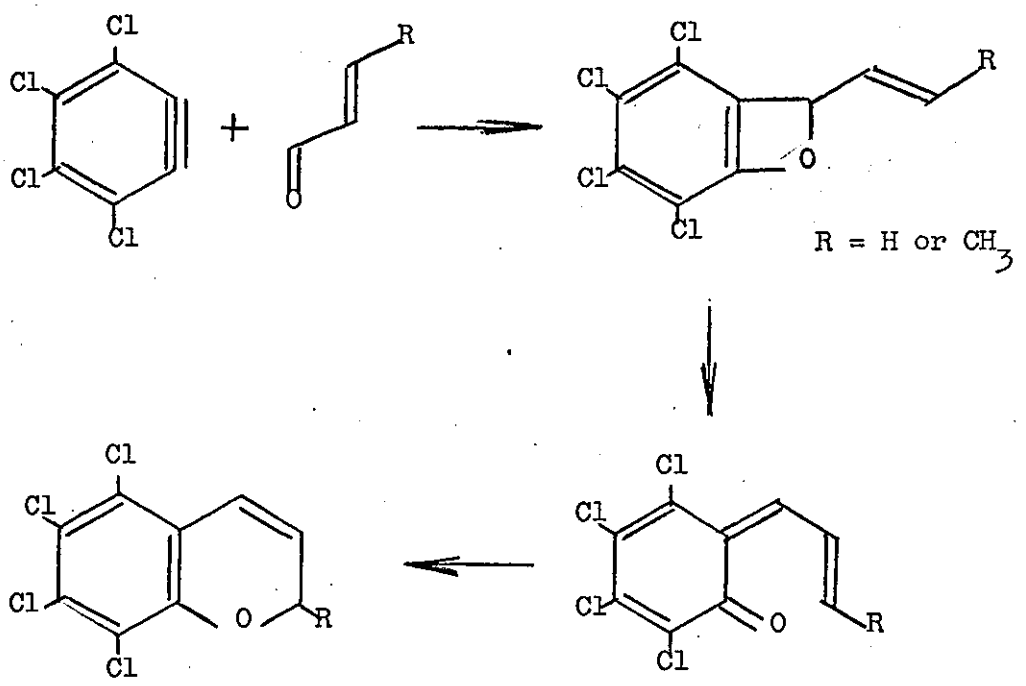


X' = F or Cl

The suggestion that a (2 + 2) π concerted cycloaddition occurred violates the Woodward and Hoffmann rules. It is known however that a number of (2 + 2) π cycloadditions involving arynes, although stereoselective, are not stereospecific.[39] The stereospecificity of the (2 + 2) π cycloadditions undoubtedly arises from the steric impossibility of forming a trans-benzocyclobutene which is itself fused to a highly strained system. The

absence of rearrangement products must arise from the very rapid collapse of the intermediate dipolar species.[40]

The publication,[41] from this laboratory, of the formation of a 2-H-chromen derivative, when either crotonaldehyde or acrolein was used to trap tetrachlorobenzyne, was unexpected and the mechanism invoked without direct precedent.



A 4-H-chromen derivative would be the expected product of a Diels-Alder type reaction. α,β-Unsaturated carbonyl compounds are known to undergo Diels-Alder type condensations with many types of dienophiles, in particular with simple olefins.[42]

It was to examine the above reaction further, and also the reaction of tetrachlorobenzyne with other carbonyl compounds, that the work described in this thesis was undertaken.

SECTION I

The Reaction of Tetrachlorobenzyne with αβ-Unsaturated Aldehydes and Investigation of the Mechanism Involved.

INTRODUCTION

Interest in the chemistry of chromen derivatives has in many cases been confined to the field of natural products.[43] Most 2-H-chromens found naturally are 2,2-dimethylchromen derivatives; the biosynthetic pathway of their formation involving the condensation of an isoprene unit with a phenolic residue. When the 2-position of the chromen is not di-substituted oxidation of the heterocyclic ring occurs easily. This is found with 2-phenyl-2-H-chromens, more commonly known as 2-H-flavens, which, as the flavylium salts, are present in a large variety of plants.

The reduction of chromens to chromans is also easily accomplished. In the laboratory catalytic hydrogenation at atmospheric pressure has usually given high yields of the chroman.[44] Naturally occurring chromans have also been studied, in particular the polyhydroxylated species which provide the fundamental structure of the tocopherols. Recently interest has been shown in the stereochemistry of substituted chromans and flavans, particularly flavan-3,4-diols.[45]

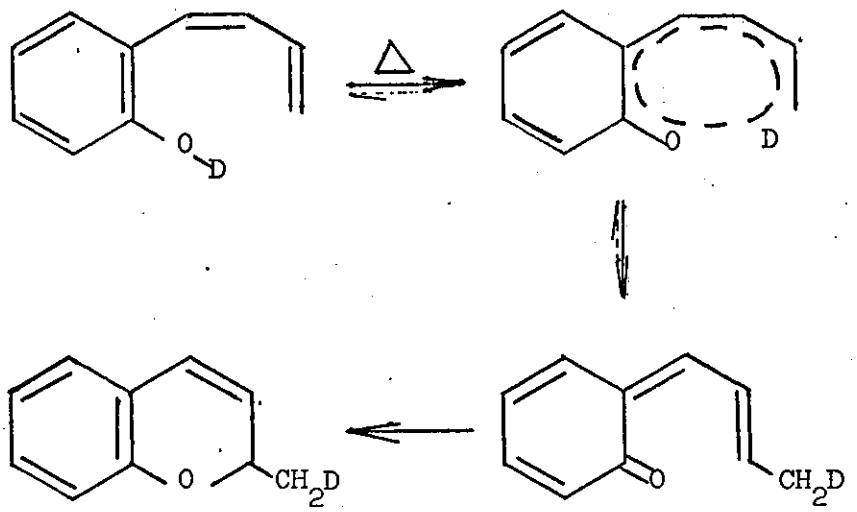
The synthesis of 2-H-chromen systems has involved in many cases a chalcone or dihydro-chalcone intermediate and concommitant ring closure to the chromen derivative. However, it has been suggested that the biosynthetic pathway to 2-H-chromens involves an o-quinone methide intermediate.[46] This type of intermediate was also postulated in the formation of 5,6,7,8-tetrachloro-2-H-chromen and 5,6,7,8-tetrachloro-2-methyl-2-H-chromen from the reaction of tetrachlorobenzyne

with acrolein and crotonaldehyde respectively.[41]

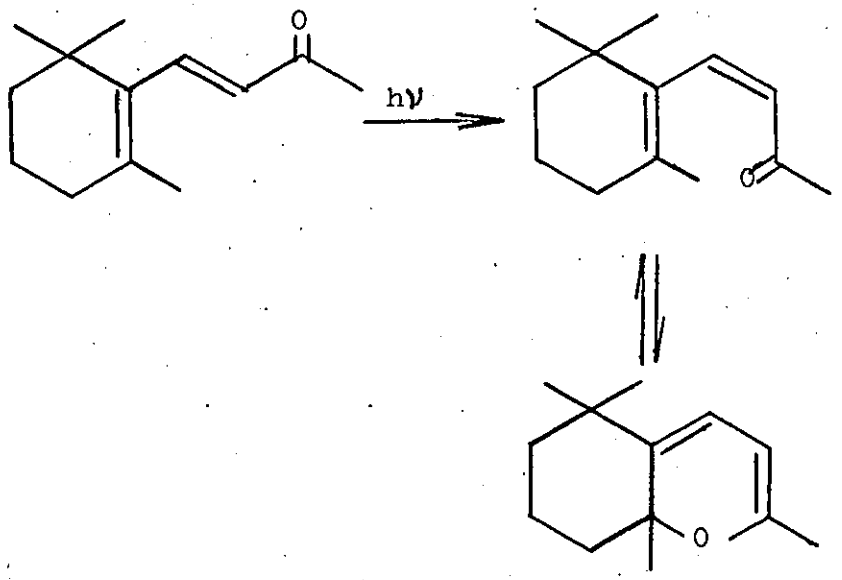
Subsequent to the publication of the above synthesis of 2-H-chromens an o-quinone methide intermediate has been postulated to explain the cyclodehydrogenation of certain o-allyl phenols.[47] Schweizer and his co-workers[48] have also shown that when cis-butadiene-phenol (scheme 1) was heated a 2-H-chromen was formed, in which the deuterium originally present on the phenol was found totally in the methyl group at the C-2 position.

Flow pyrolysis of o-hydroxybenzyl methyl ether produces o-quinone methide which has been trapped in liquid nitrogen.[49] At these low temperatures o-quinone methide is stable and may for example by reduced with lithium aluminium hydride.[49] Allowing it to warm up in the presence of styrene has been shown to give flavan.[50] Above -20° o-quinone methide is thermally unstable, and it reacts with itself to yield a trimer.[51]

Orbital symmetry considerations[11] predict that the o-quinone methide exemplified in scheme 1 should cyclise by a thermally allowed concerted disrotatory process. This requires that the exocyclic diene must exist in a cis configuration. An analogy for this cyclisation is available. Trans-β-ionone is thermally stable, however upon irradiation (scheme 2)isomerisation occurs to yield a cis situation which can readily cyclise thermally.[52] This type of electrocyclic ring closure has also been postulated to explain the formation of iso-chromens.[53]



Scheme 1

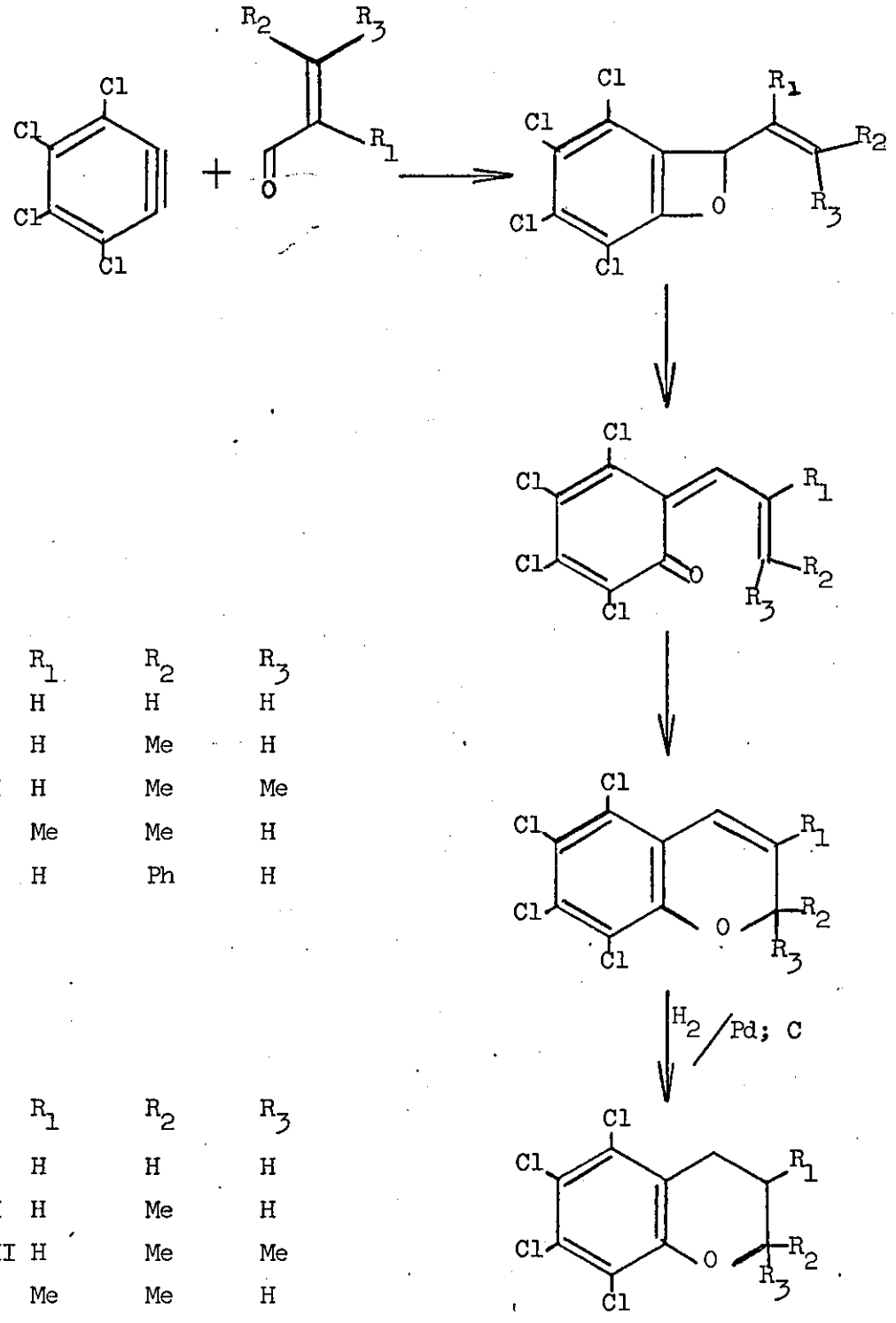


Scheme 2

DISCUSSION

We undertook to confirm the generality of the reaction of α β-unsaturated aldehydes with tetrachlorobenzyne, and to establish conclusively the mechanism involved (scheme 3).

The structures of the adducts (I and II) obtained from acrolein and crotonaldehyde respectively had been established by Jablonski by means of the following evidence. The ultra-violet spectra of the 2-H-chromens showed the presence of a styrene chromophore, which was not present in the respective chromans (VI and VII) obtained by hydrogenation of the 2-H-chromens in the presence of palladium on carbon catalyst. Elemental analysis of the chromens and chromans confirmed their composition. Further evidence was obtained from the ^{1}H n.m.r. spectrum of 5,6,7,8-tetrachloro-2-H-chromen (I). Analysis of the spectrum by first order methods (table 1) and comparison with that of 2-H-chromen[54] and 4-H-chromen[55] confirmed the 2-H-chromen structure. The position of substitution of the methyl group in 5,6,7,8-tetrachloro-2-methyl-2-H-chromen was confirmed from spin-spin decoupling experiments on the ^{1}H n.m.r. spectrum of the chroman (VII). The multiplet centred at τ 5.78 (methine proton) was shown to be spin-spin coupled to the methyl group (τ 8.52).



	R_1	R_2	R_3
I	H	H	H
II	H	Me	H
III	H	Me	Me
IV	Me	Me	H
V	H	Ph	H

	R_1	R_2	R_3
VI	H	H	H
VII	H	Me	H
VIII	H	Me	Me
IX	Me	Me	H
X	H	Ph	H

Scheme 3

Table 1

Compound	Chemical Shifts (τ) (multiplicity) 2-H	3-H	4-H	2-Me	Other	Coupling Constants (Hz.) J_{2-3}	J_{3-4}	J_{2-4}	J Other
(I)	5.05 (dxd)	4.00 (dxt)	3.15 (dxt)	-	-	3.4	10.3	1.7	-
(II)	4.91(dxdxq)	4.19 (dxd)	3.32 (dxd)	8.5(d)	-	3.4	10.3	1.7	R_2-R_3=6.4
(III)	-	4.27 (d)	3.36 (d)	8.54(s)	-	-	10.8	-	-
(IV)	5.15(dxq)	-	3.63(s)	8.63(d)	(3-Me)8.12(s)	-	-	1.7	R_2-R_3=6.4
(V)*	4.15(s^+)	4.0 (q^+)	3.15(q^+)	-	(2-Ph)2.71(b.s.)	-	-	-	-
(VI)	5.76(t)	7.9(m)	7.16(t)	-	-	5.4	6.8	-	-
(VII)	5.78(m)	8.0(m)	7.2(m)	8.52(d)	-	-	-	-	R_2-R_3=6.0
(VIII)	-	8.21(t)	7.27(t)	8.68(s)	-	-	7.2	-	-
(IX)	5.70(dxq)	7.8(m)	7.3(m)	8.74(d)	(3-Me)9.04(d)	3.0	-	-	R_2-R_3=6.5 R_1-H =6.0
(X)	4.78 (dxd)	7.7(m)	7.05(m)	-	(2-Ph)2.51(b.s.)	4.0 and 9.0	-	-	-

* Determined at 100 M Hz. by P.C.M.U.

s = singlet; d= doublet; t=triplet; q=quartet; b=broadened; + = apparent multiplicity.

The adducts (III and IV), obtained when 3,3-dimethylacrolein and 2,3-dimethylacrolein respectively were used as trapping agents for tetrachlorobenzyne, were shown to have the same molecular formulae from an examination of their mass spectra and elemental analyses. The chromans derived by catalytic hydrogenation of the 2-H-chromens were also isomeric. The ultraviolet spectra of 5,6,7,8-tetrachloro-2,2-dimethyl--2-H-chromen (III) and 5,6,7,8-tetrachloro-2,3-dimethyl-2--H-chromen (IV) showed the presence of styrene chromophores which were absent in the respective chromans (VIII and IX).

Analysis of the ^{1}H n.m.r. spectra of the adducts (III, IV, VIII and IX) by first order methods was possible (table 1). The spectrum of the 2,2-dimethylchromen (III) showed the expected AB quartet associated with a cis-β-substituted styrene. In the corresponding chroman (VIII) spectrum the methylene protons appeared as broadened triplets (τ 7.27 and τ 8.21), the half chair [56] conformation of the heterocyclic ring causing the non-equivalence of these protons. As would be expected from the suggested mechanism there was no methine proton in the ^{1}H n.m.r. spectrum of 5,6,7,8-tetrachloro-2,2--dimethylchroman. The spectrum of 5,6,7,8-tetrachloro-2,3--dimethyl-2-H-chromen indicated that the two methine protons (τ 3.63 and τ 5.15) were vinylically coupled (1.7 Hz). The ^{1}H n.m.r. spectrum of the 2,3-dimethylchroman confirmed that there was one methyl group (τ 8.74) at position-2 spin-spin coupled to the methine proton at τ 5.70.

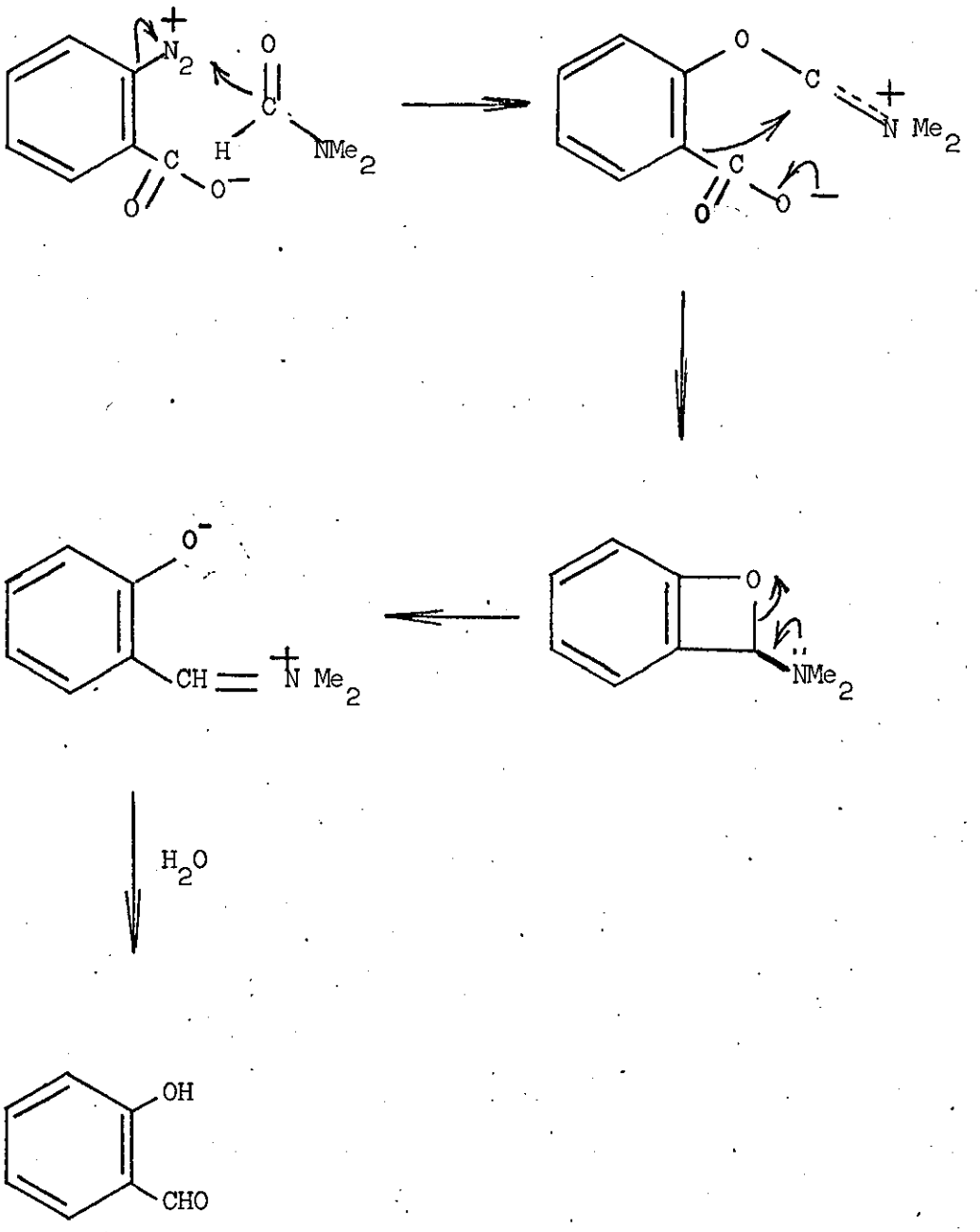
Consideration of these two pieces of information indicates that the other methyl group (τ 9.04) must be attached at position-3.

To examine the reaction of tetrachlorobenzyne with α β-unsaturated aldehydes further, cinnamaldehyde was used as co-reactant. There were now three distinct pathways by which the tetrachlorobenzyne could react. Cycloaddition across the benzene ring could occur,[57] or a phenanthrene derivative may be formed by a styrene type reaction,[31] or a 2-H-chromen derivative could be formed. The only adduct isolated when tetrachloroanthranilic acid was aprotically diazotised in the presence of cinnamaldehyde was 5,6,7,8--tetrachloro-2-H-flaven (V). The molecular formula was established by mass spectrometry and elemental analysis; as was that of the reduced adduct, 5,6,7,8-tetrachloroflavan (X). The ultraviolet spectrum of adduct (V) was similar to the 2-H-chromens discussed previously, and the styrene chromophore was absent in the flavan (X). Analysis of the ^{1}H n.m.r. spectra by first order methods was not possible, however comparison of the respective spectra of the adducts (V)and (X) with spectra of 2-H-flaven[58] and flavan,[59] confirmed their structures.

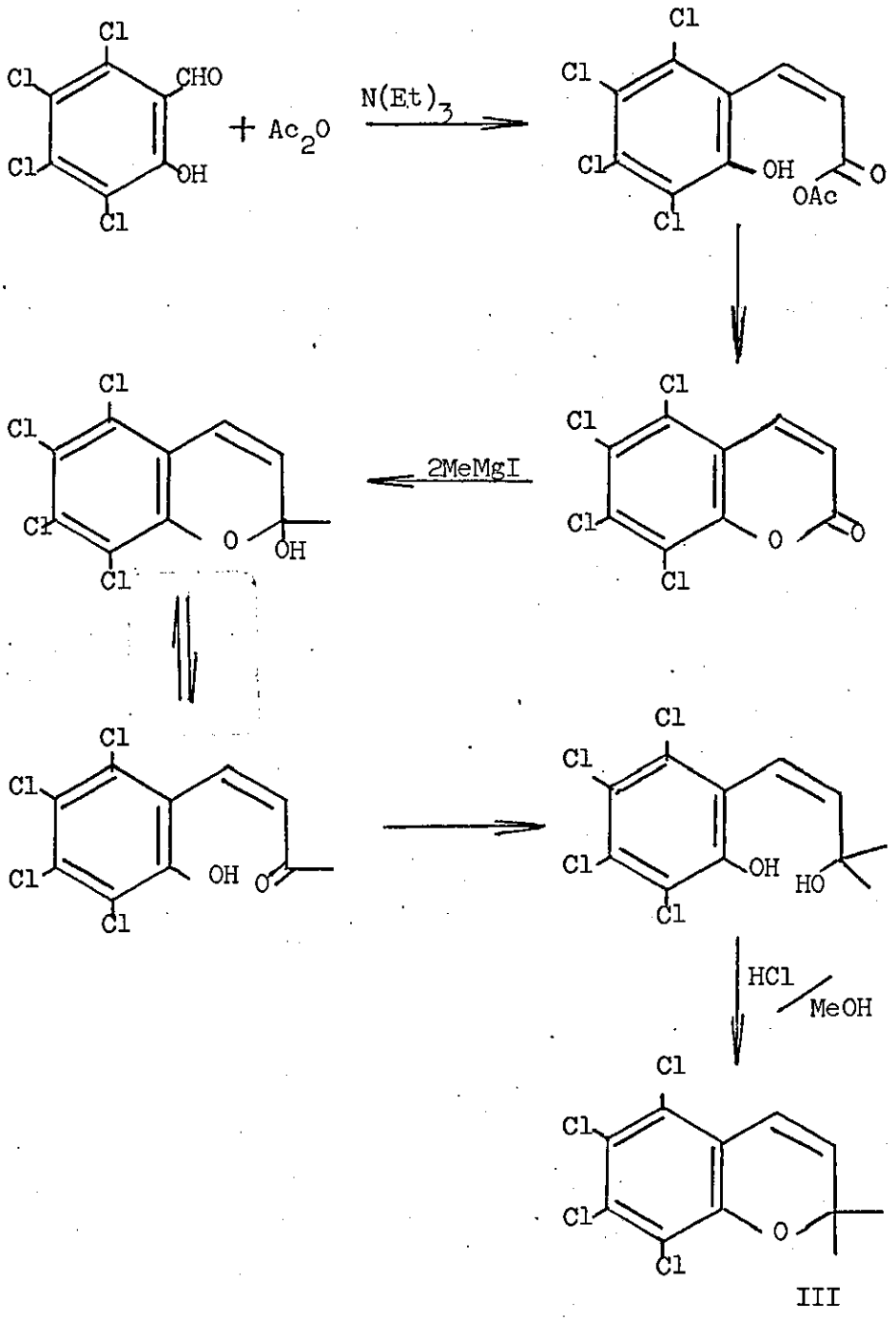
In order to confirm conclusively that the compounds we had prepared were 2-H-chromens we decided to synthesise one of the aryne products by using a classical 2-H-chromen synthesis. Tetrachlorosalicylaldehyde would be an acceptable

precursor, and a convenient synthesis of this was found to be the aprotic diazotisation of tetrachloroanthranilic acid in dry dimethylformamide. Benzenediazonium-2-carboxylate was reported[60] to react with dry dimethylformamide to give an immonium ion intermediate which could be hydrolysed to salicylaldehyde in low yield (17%) (scheme 4). In our isolation procedure we did not use a separate hydrolysis stage. The oil obtained on removal of excess of dimethylformamide was immediately eluted through a silica column with benzene, the conditions on the column causing the hydrolysis.

A Perkin condensation with triethylamine as the base[61] converted the tetrachlorosalicylaldehyde into 5,6,7,8-tetrachlorobenzo-2-pyrone (scheme 5). With excess of methylmagnesium iodide[62] a carbinol was produced which was cyclised by heating in a solution of methanol containing hydrochloric acid[63] to give 5,6,7,8-tetrachloro-2,2-dimethyl-2-H-chromen (III). A comparison of the i.r., u.v., ^{1}H n.m.r. and mass spectra of this synthetic product and that obtained from the reaction of tetrachlorobenzyne with 3,3-dimethylacrolein showed them to be identical.



Scheme 4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HCl
MeOH
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O
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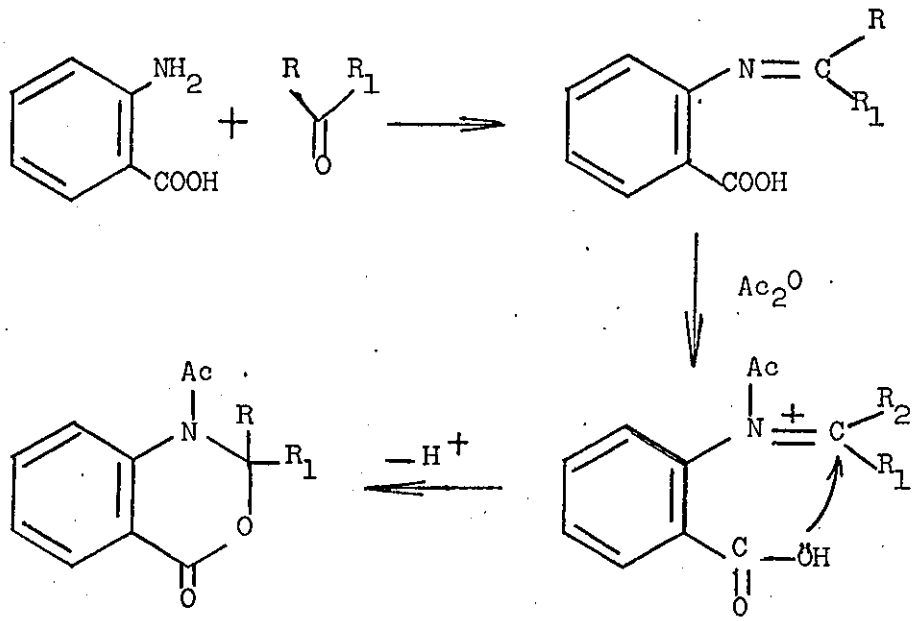
III

Scheme 5

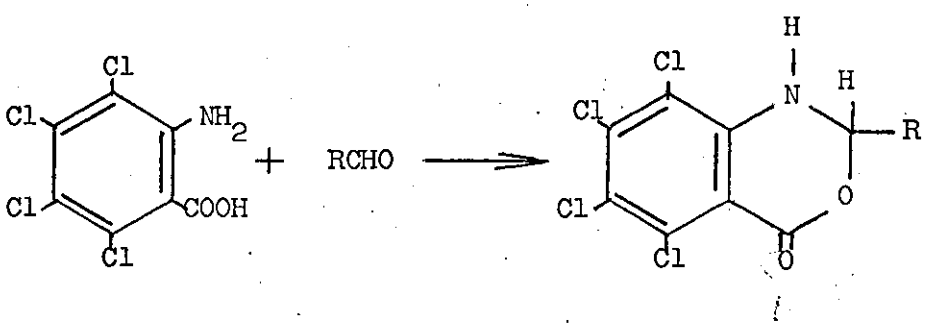
The method employed in our initial experiments used diethyl ether as solvent for the tetrachloroanthranilic acid, and excess of 3-methylbutyl nitrite to effect the diazotisation, with the result that 2,3,4,5-tetrachlorophenyl ethyl ether [64] and 2,3,4,5-tetrachlorophenyl-3'-methylbutyl ether[65] were major by-products. We modified the conditions and changed the solvent systems to a concurrent addition of tetrachloroanthranilic acid, dissolved in acetonitrile, and 3-methylbutyl nitrite in dichloromethane. This modification had produced an increase in yield of from 27% to 67% when benzene was used as co-reactant.[66] We found however that the yield of 5,6,7,8-tetrachloro-2-H-flaven was only increased from 32% to 37% by this procedure.

It was known that tetrachloroanthranilic acid will react with formaldehyde [23] to form 5,6,7,8-tetrachloro--1,2-dihydro-3,1-benzoxazin-4-one. Also with anthranilic acid a large number of aldehydes and ketones have been reported to condense to form the benzylidene derivatives but cyclisation has not occurred.[67] N-acyl-benzoxazin-4-ones have been obtained from these benzylidene compounds by heating in the presence of acetic anhydride [67] (scheme 6), the mechanism suggested involving acetylation as an intermediate in the ring closure.

We believed that either a benzylidene derivative of tetrachloroanthranilic acid and the respective aldehyde, or the corresponding benzoxazin-4-one, might have been the



Scheme 6



XI R = Ph-CH=CH-

XII R = Ph-C≡C-

cause for the low yields of 2-H-chromen derivatives. The isolation technique used in our reactions had always involved column chromatography of the crude material, and as the benzylidene type compounds would not be expected to be easily eluted they may not have been detected. To test the postulate we heated cinnamaldehyde and tetrachloroanthranilic acid under reflux in ether for 24 hours. The crude oil obtained after removal of solvent showed only one peak in the infrared spectrum at 3400 $cm.^{-1}$; there was no doublet present, associated with the primary amine of tetrachloroanthranilic acid. When kept, the oil crystallised and was purified by recrystallisation from chloroform. It was found impossible to obtain a ^{1}H n.m.r. spectrum as the material was not sufficiently soluble in any of the usual solvents. The infrared spectrum suggested that the compound was a dihydro-benzoxazin-4-one derivative (NH 3400 $cm.^{-1}$, C=O 1730 $cm.^{-1}$) and an accurate mass measurement of the M-1 ion, together with an elemental analysis, confirmed the molecular formula. The behaviour of 5,6,7,8-tetrachloro--2-styryl-1,2-dihydro-3,1-benzoxazin-4-one (XI) on thin layer chromatography, where it remained on the base line irrespective of which solvent was used to elute the plate, explains why these dihydrobenzoxazin-4-ones were not isolated from the tetrachlorobenzyne reactions.

A number of other carbonyl compounds were found to react with tetrachloroanthranilic acid, and are described in section 3. One reaction does warrant mention here.

Tetrachloroanthranilic acid was added to a solution of phenylpropargyl aldehyde and 3-methylbutyl nitrite in acetonitrile. The only product obtained involving phenylpropargyl aldehyde was 5,6,7,8-tetrachloro-2-phenylpropargyl-1,2-dihydro-3,1-benzoxazin-4-one (XII) which separated from the reaction mixture overnight. Infrared spectroscopy showed the presence of a primary amine (3400 $cm.^{-1}$), an acetylene linkage (2240 $cm.^{-1}$), and an ester carbonyl (1735 $cm.^{-1}$);and the molecular formula was confirmed from the mass spectrum and elemental analyses. The yield of adduct (XII) was 36% which indicates that the addition of tetrachloroanthranilic acid to the aldehyde must be occurring rapidly.

As dihydro-3,1-benzoxazin-4-ones could not be isolated from reactions involving aprotic diazotisation of tetrachloroanthranilic acid in the presence of αβ-unsaturated aldehydes; we decided to compare the yields of 5,6,7,8-tetrachloro-2-H-flaven when other precursors were used to generate tetrachlorobenzyne in the presence of cinnamaldehyde. Tetrachlorobenzenediazonium-2-carboxylate was too unstable to be of value, however 2-carboxy-tetrachlorobenzenediazonium chloride (XIII)[25] was easily prepared. Tetrachloroanthranilic acid was converted to the hydrochloride with dry hydrogen chloride in tetrahydrofuran, and then diazotised below 0° with 3-methylbutyl nitrite. The diazonium chloride (XIII) was filtered off and washed well with ether. It was kept wet with ether until required as it decomposed very slowly at room temperature to form tetrachlorobenzyne, and in a dry state was found to be easily detonated.

Determination of the chloride ion content by titration of the solid, suspended in aqueous solution, with standardised silver nitrate was the only form of analysis we were able to obtain; due to the instability of the compound.

1-(2'-carboxyphenyl)-3,3-dimethyltriazene has recently been reported[26] and the tetrachloro analogue appeared an attractive precursor. We found that the diazonium chloride (XIII) could be converted to 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV) by slowly adding it to a cold aqueous solution of dimethylamine. The triazene structure was confirmed from the following data. Mass spectra and elemental analyses confirmed the molecular formula of (XIV), and also that of the methyl ester formed by treatment of (XIV) with ethereal diazomethane. The i.r. spectrum of (XIV) showed an acid carbonyl (1705 $cm.^{-1}$), and an ester carbonyl (1742 $cm.^{-1}$) was found for the methylated product. The triazene (XIV) was stable at room temperature but decomposed to tetrachlorobenzyne smoothly when heated under reflux in p-xylene for 1 hr., giving a 60% yield of 1,4-dihydro-2,10-dimethyl-5,6,7,8-tetrachloro-1,4-etheronaphthalene.[57] The diazonium chloride (XIII) when heated under reflux in p-xylene for ½ hr. gave 71% yield of adduct. Both compounds were thus found to be satisfactory tetrachlorobenzyne precursors.

When 2-carboxytetrachlorobenzenediazonium chloride (XIII) was thermally decomposed in a refluxing chloroform solution containing cinnamaldehyde a 58% yield of 5,6,7,8-tetrachloro-2-H-flaven was obtained. This increased yield, compared to 37% yield when aprotic diazotisation of tetrachloroanthranilic acid

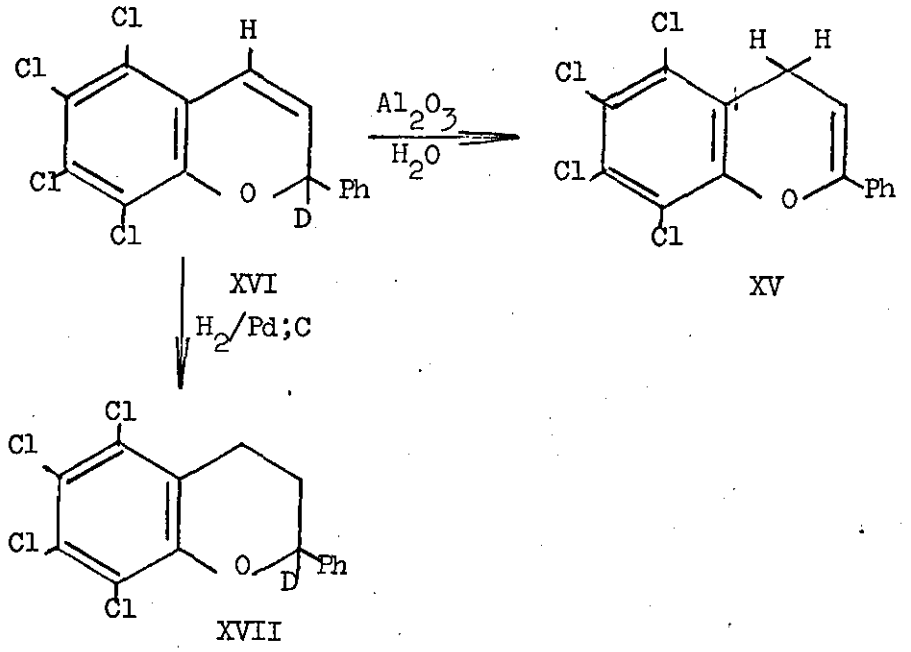
was used as precursor, confirmed our view that there was a competing reaction for the anthranilic acid.

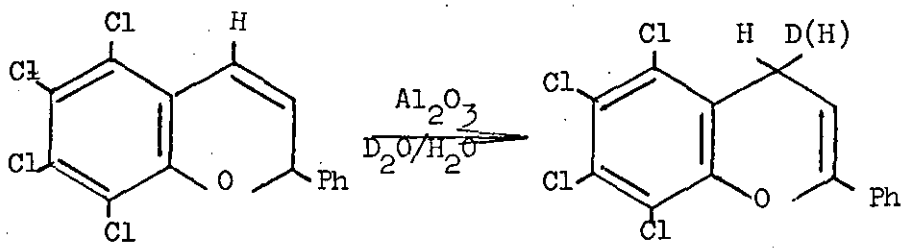
1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV) gave only a 35% yield of adduct (V) when it was decomposed by heating under reflux in tetrachloroethylene (b.p. 120°) containing cinnamaldehyde. To attempt to improve this yield we heated the triazene (XIV) under reflux in cinnamaldehyde for 15 min.. No 5,6,7,8-tetrachloro-2-H-flaven (V) was found, instead there was a 22% yield of compound (XV) which ran faster on thin layer chromatography, but because of low solubility, required heating to 80° to obtain a ^{1}H n.m.r. spectrum in deuteriochloroform. The mass spectrum and elemental analysis indicated that adducts (V) and (XV) were isomeric. Hydrogenation of adduct (XV) over palladium on carbon catalyst gave 5,6,7,8-tetrachloroflavan (X). The ^{1}H n.m.r. spectrum contained a methine proton (τ 4.47) coupled (J= 4.0 Hz.) to methylene protons (τ 6.47), and confirmed that the product was 5,6,7,8-tetrachloro-4-H-flaven (XV) (scheme 7).

Subsequently we were able to show that the 2-H-flaven (V) was isomerised to the 4-H-flaven (XV) if heated for 15 min. under reflux in cinnamaldehyde, however only a 50% recovery was obtained. A similar rearrangement of this type was reported[68] during the course of this work. A substituted phenoxymagnesium bromide when reacted with cinnamaldehyde gave a 2-H-flaven which then rearranged to the 4-H-flaven in the presence of excess of phenoxymagnesium bromide.

We found that elution of the 2-H-flaven (V) with light petroleum from activated alumina (Brockman activity I) gave an almost quantitative conversion to 5,6,7,8-tetrachloro-4-H-flaven (XV). To investigate this further 2-deuterio-5,6,7,8-tetrachloro-2-H-flaven was prepared (scheme 8).

Phenylmorpholine acetonitrile was prepared from benzaldehyde, morpholine perchlorate, and sodium cyanide. The formyl proton was exchanged for a deuterium atom by treatment with sodium hydride and quenching the reaction mixture with deuterium oxide.[69] The morpholinonitrile was hydrolysed to return benzaldehyde deuterated at the formyl-position. A mixed aldol condensation with acetaldehyde and fractional distillation of the product gave β-[^{2}H]cinnamaldehyde containing 96% deuterium (by mass spectrometry). Treatment of this with excess tetrachlorobenzyne gave an oil which was eluted from a short column of activated alumina. Two products were obtained and were separated by preparative layer chromatography on silica to give 5,6,7,8-tetrachloro-4-H-flaven (XV) containing no deuterium, and 5,6,7,8-tetrachloro-2-[^{2}H] flaven (XVI) containing 94% deuterium. This indicated that the rearrangement was an intermolecular process. Further confirmation of this was obtained when 5,6,7,8-tetrachloro-2-H-flaven was eluted through an alumina column which had been deactivated with deuterium oxide. A 19% incorporation of deuterium was found in the 4-H-flaven obtained from the column, and the 2-H-flaven (V) which had not rearranged was found to contain no deuterium (by mass spectrometry).

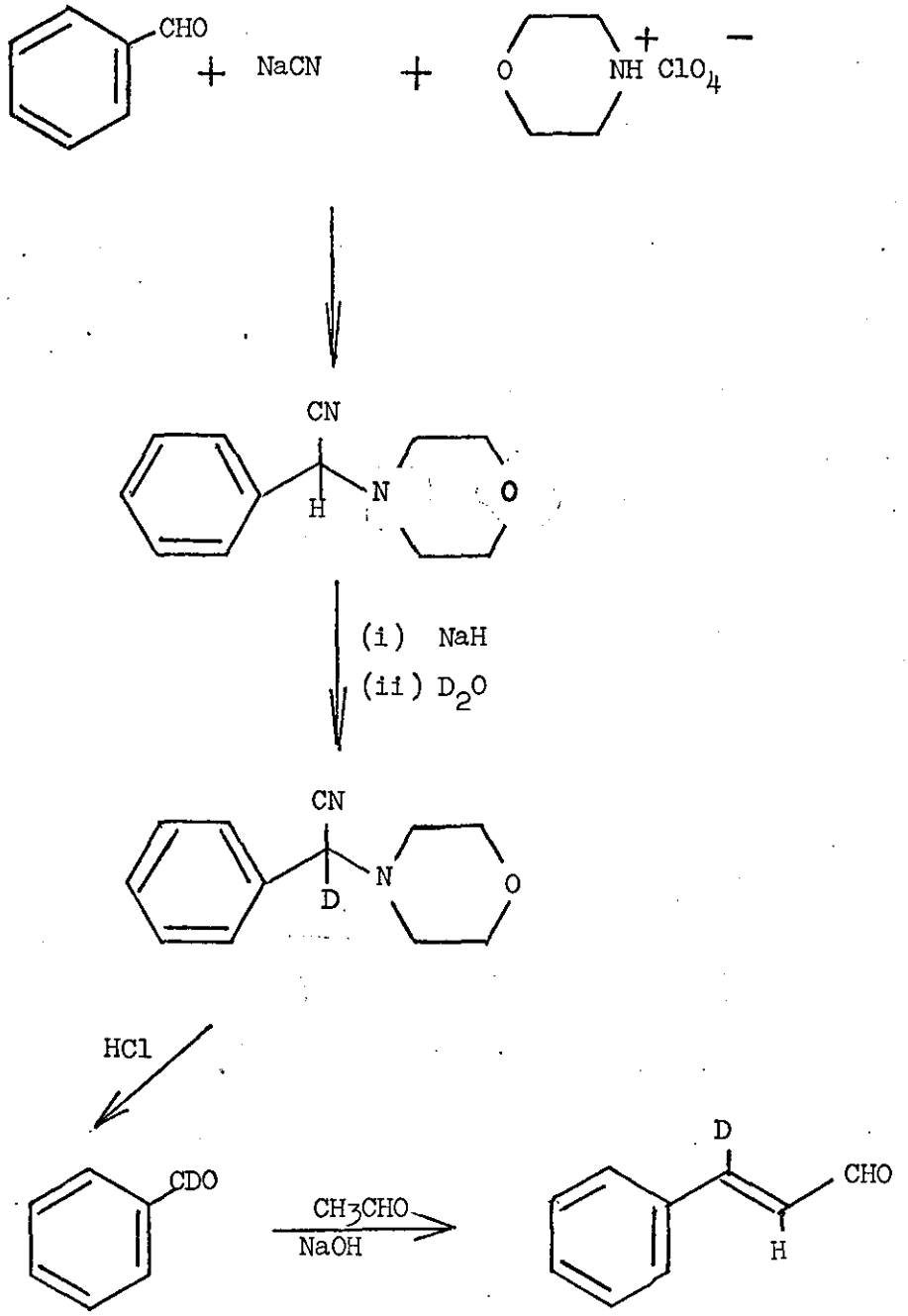




^{1}H n.m.r.

	Chemical Shift (τ) (multiplicity)			Coupling Constants (Hz)
	H_3	H_4	Ph	J_{3-4}
XVI	4.01 (d)	3.25 (d)	2.72 (s)	10.5
XVII	7.7 (m)	7.1 (m)	2.68 (s)	-
XV	4.46 (t)	6.46 (d)	2.5 (m)	4.2

Scheme 7


CHO
NaCN
O
NH ClO4
CN
H
N
O
(i) NaH
(ii) D2O
CN
D
N
O
HCl
CDO
CH3CHO
NaOH
D
CHO
H

Scheme 8

The ^{1}H n.m.r. of 5,6,7,8-tetrachloro-2-[^{2}H]flaven (XVI) was much simpler than that for the adduct (V). The AB quartet for the cis-β-substituted styrene system, which was no longer part of an ABX system, could now be analysed by first order methods (scheme 7).

The suggested mechanism[41] for the reaction which occurred when tetrachloroanthranilic acid was aprotically diazotised in the presence of certain aldehydes is shown in scheme 3. An alternative formation of the benzoxetene intermediate may be a stepwise mechanism, as suggested for the reaction of benzenediazonium-2-carboxylate with dimethylformamide (scheme 4).[60] Of the precursors we had used to generate tetrachlorobenzyne both tetrachloroanthranilic acid and 1-carboxy-2,3,4,5-tetrachlorobenzenediazonium chloride (XIII), by analogy with the unchlorinated precursors[70] may be expected to decompose in a stepwise manner. The mode of decomposition of 1-(2'-carboxybenzenediazonium)-3,3-dimethyltriazene (XIV) was suggested[26] (scheme 9) as involving protonation of the tertiary nitrogen to form a dipolar intermediate. This may then decompose to form the benzenediazonium-2-carboxylate and hence benzyne.

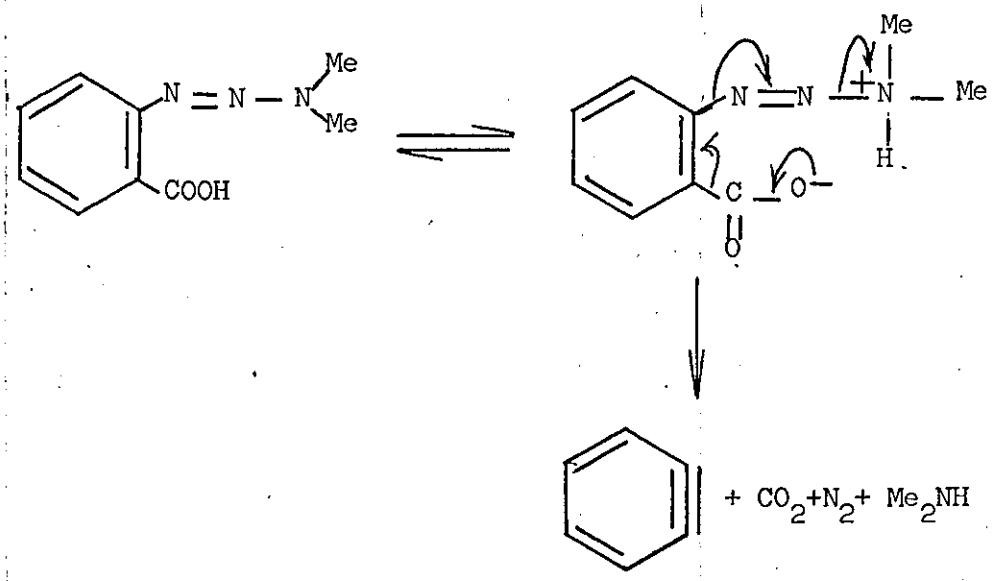
The decomposition of (XIV) at 120° in the presence of dimethylaniline was negligible,[71] the dimethylaniline being a stronger base than the triazene would, we presume, preferentially abstract the carboxylic proton and so prevent zwitterion formation.

We also examined the reaction of (XIII) with dimethylaniline. At low temperature (30°) the only product obtained

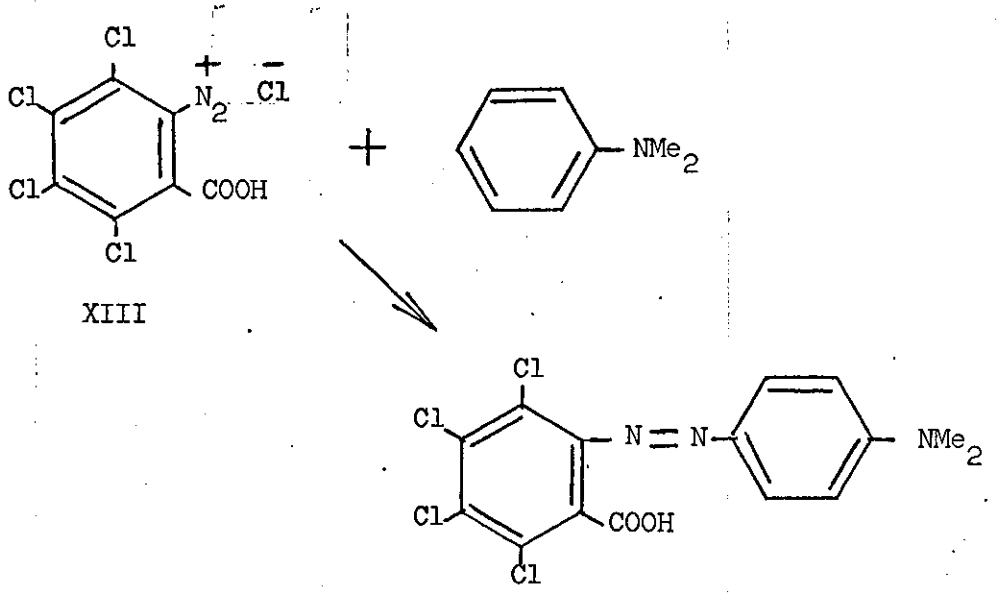
by Ward[25] was (4'-N,N-dimethylaminobenzene)-2-carboxy-3,4,5,6-tetrachloroazobenzene. We added the diazonium chloride (XIII) to dimethylaniline at 100° in minute quantities, as (XIII) exploded on contact with the hot reaction solution. The only product we obtained was the same as that found by Ward, no tetrachlorobenzyne products could be detected (scheme 10).

Therefore, to test the mechanism of benzoxetene formation we generated benzyne from three different precursors in the presence of cinnamaldehyde. Anthranilic acid[21] gave 2-H-flaven in 15% yield, which was confirmed by elemental analysis, and by comparison of the ^{1}H n.m.r. spectrum with published spectral data,[58] and also reduction to the crystalline flavan.[59,72] A 15% yield of 2-H-flaven was also obtained when 1,2,3-benzothiadiazole-1,1-dioxide was used as the benzyne precursor. The mechanism of fragmentation of benzothiadiazole-1,1-dioxide[18] almost certainly involves the concerted loss of nitrogen and sulphur dioxide. Diphenyliodonium-2-carboxylate was also used, as the mode of decomposition may involve an anionic intermediate, formed by the initial loss of carbon dioxide.[20] The yield however in the latter's case was only of the order of 6%. This was most probably due to the high temperature required (200°) to decompose the diphenyliodonium-2-carboxylate. The compatible yields obtained in the above three reactions confirmed in our minds that the reactions do involve benzyne[15] and, by analogy, tetrachlorobenzyne.

The mechanism suggested earlier (scheme 3) is supported by our results using various αβ-unsaturated aldehydes.



Scheme 9



Scheme 10

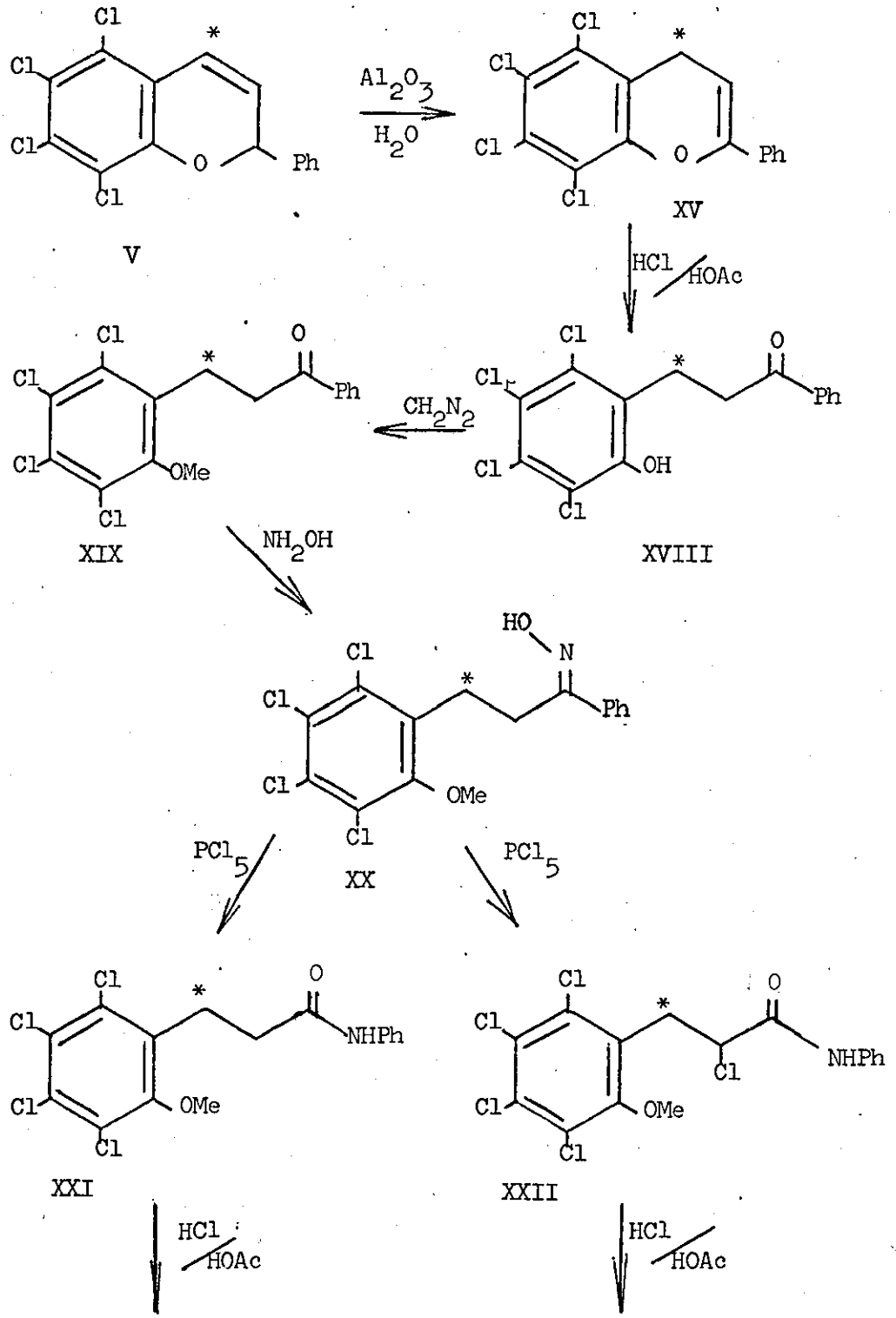
Alternative mechanisms, for example an initial 1,4-cycloaddition of tetrachlorobenzyne to the αβ-unsaturated aldehyde followed by migration to form the relevant 2-H-chromen seem most unlikely. To obtain final confirmation of the mechanism we decided to use cinnamaldehyde labelled with ^{14}C in the formyl group. This would prove that an initial 1,2-addition to form the benzoxetene and subsequent opening to an o-quinone methide occurred, as the labelled carbon atom would be found at position-4 in the 2-H-flaven.

Before we could attempt a labelled synthesis of 5,6,7,8-tetrachloro-2-H-flaven (V),it was necessary to obtain a satisfactory degradation (scheme 11) (the asterisk indicates the ^{14}C atom). A large number of degradations of 2-H-flavens[73] and 2-H-chromens are reported in the literature, but a number of trial experiments showed that none of these enabled us to degrade the tetrachlorochromens to a derivative of tetrachlorosalicylic acid in good yield. For example, the oxidation of tetrachloro-2-H-chromen by excess potassium permanganate in acetone[73d] gave only a 1% yield of the chromandiol. Most of the degradations described in the literature involved oxidation. This is known to cause extensive decomposition of chromens which are not disubstituted at position -2; the intermediate suggested[43a] is the chromylium salt.

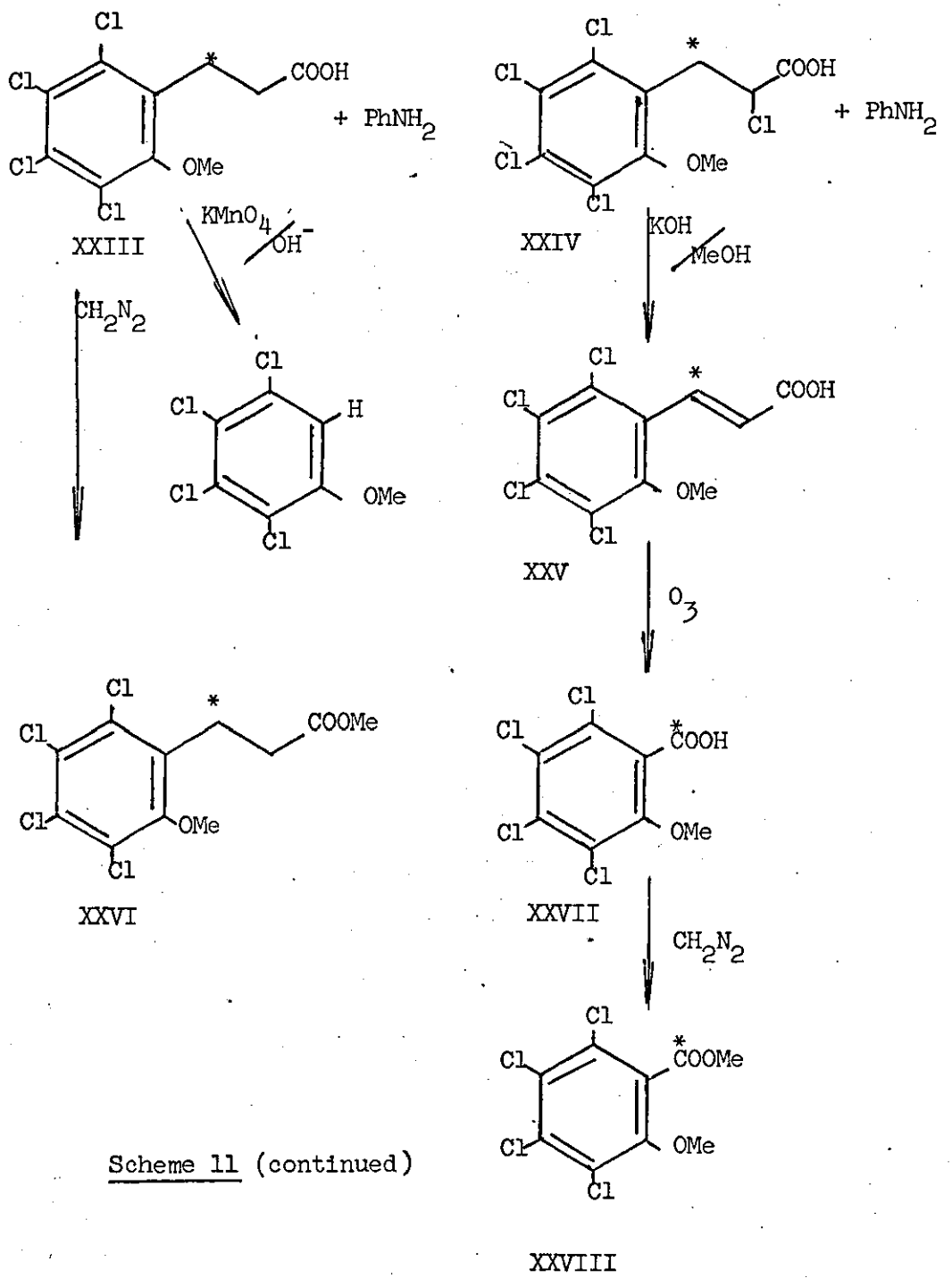
However, a modification of the previously reported[74] hydrolytic ring opening of a 4-H-flaven to the corresponding o-hydroxydihydrochalcone was found to be successful with the compound (XV). A suspension of (XV) in acetic acid and

hydrochloric acid was heated under reflux until the initial yellow colouration disappeared. A quantitative yield of phenyl-2'-(2-hydroxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XVIII) was obtained which was methylated to give (XIX). The structures of these two compounds were confirmed from the following data. Mass spectra and elemental analyses confirmed their respective molecular formulae. The hydrogen bonding between the phenolic hydrogen and the carbonyl group of (XVIII) gave rise in the i.r. spectrum to a low carbonyl stretching frequency (1666 $cm.^{-1}$), which in (XIX) appeared at 1678 $cm.^{-1}$, as would be expected for a phenyl alkyl ketone. The ^{1}H n.m.r. spectrum of (XVIII) showed an exchangeable proton (τ 1.1), five aromatic protons, and a multiplet (τ 6.35 - 6.95) of four protons. The hydrogen bonding between the phenolic hydrogen and the carbonyl group may cause the extra multiplicity of the methylene protons in the alkyl side chain as free rotation would be restricted. With (XIX) as there was no hydrogen bonding, the four protons may have been expected to appear as two triplets; however only a singlet (τ 6.77) of four protons was seen. Coincidentally the fields experienced by the two methylene groups must have been identical.

The ^{1}H n.m.r. of the oxime (XX), obtained from the ketone (XIX) by treatment with hydroxylamine hydrochloride and pyridine, also showed a four proton singlet (τ 7.01). The exchangeable oxime proton was seen at τ -1.22. U.v., i.r., and mass spectra, together with an elemental analysis


Cl
Cl
Cl
Cl
*
O
Ph
V
Al_2O_3
H_2O
XV
HCl
HOAc
XVIII
CH_2N_2
OMe
OH
XIX
NH_2OH
HO
N
XX
PCl_5
NHPh
XXI
XXII
HCl
HOAc

Scheme 11



Scheme 11 (continued)

confirmed the structure of (XX). The oxime was found to exist as only one of the isomers, namely anti-phenyl-2'-(2-methoxy-3,4,5,6-tetrachlorophenyl) ethyl ketoxime, by an examination of the products obtained from a Beckmann rearrangement and subsequent hydrolysis.

Treatment of (XX) with a 4-molar excess of phosphorus pentachloride in dry diethyl ether gave a mixture of two products separable by preparative layer chromatography. The less mobile product was N-phenyl-2-(2-methoxy-3,4,5,6-tetrachlorophenyl) ethylamide (XXI), the expected amide for an anti-oxime. The more mobile product (XXII), was the 2-chloro-derivative of (XXI). Mass spectra indicated their respective molecular structures, and elemental analysis confirmed that of adduct (XXII). The amide stretching frequencies in the i.r. spectra were noticeably different (XXI) (C=O, 1646 $cm.^{-1}$), (XXII) (C=O, 1675 $cm.^{-1}$) the 2-chlorine atom causing the shift to higher frequency. The ^{1}H n.m.r. spectrum of the amide (XXI) showed two multiplets each of 2 protons, which were not possible to analyse by first order methods. In the ^{1}H n.m.r. spectrum of the α-chloro-amide (XXII) the methine proton was seen as a doublet of doublets (τ 5.07) (J=9.0 and 6.0 Hz.), whilst the methylene protons were a multiplet.

When the Beckmann rearrangement was carried out using a fifteen-fold excess of phosphorus pentachloride only the 2-chloro-amide (XXII) was obtained, and crystallised in better than 90% yield from the hydrolysed reaction mixture. The

mechanism of the chlorination is not known. The expected chlorination by phosphorus pentachloride of the amide (XXI) does not occur, and carefully controlled Beckmann rearrangements of (XX) gave only (XXI), (XXII), or unreacted starting material. Attempted chlorination of the oxime (XX) with, for example, N-chlorosuccinimide was not successful, no reaction occurred. A choice of mechanisms appears possible, either an initial chlorination occurs, the oxime of which rearranged spontaneously; or an intermediate in the rearrangement is chlorinated. We have no evidence to prove or disprove either mechanism.

Hydrolysis of the amides yielded respectively the acid (XXIII) and α-chloro-acid (XXIV), and aniline was obtained in both cases. This was confirmed by the conversion to acetanilide. The structure of 3'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-propanoic acid (XXIII) was confirmed from the following information. The mass spectrum and elemental analysis indicated the molecular formula, and the i.r. spectrum showed the presence of an acid carbonyl (1710 $cm.^{-1}$) which was shifted to 1735 $cm.^{-1}$ upon methylation with ethereal diazomethane. The two methylene signals of the aromatic side chain in the ^{1}H n.m.r. spectrum appeared as multiplets, as had been found with the amide (XXI). Oxidation of (XXIII) with alkaline potassium permanganate did not give the salicylic acid derivative (XXVII), instead 1-methoxy-2,3,4,5-tetrachlorobenzene was obtained in 50% yield. This method of degradation was thus of no use with respect to confirming the position of the ^{14}C label.

The α-chloro-acid (XXIV) was not analysed, but the mass spectrum indicated the correct molecular weight and the i.r. spectrum showed the presence of an α-chloro-acid (C=O, 1740 cm.$^{-1}$). The ^{1}H n.m.r. gave, in this case, the expected sharp doublet (τ 6.44, 2H) and triplet (τ 5.24, 1H) (J=7.0 Hz.). Treatment of (XXIV) with methanolic potassium hydroxide gave the cinnamic acid (XXV), in 98% yield from the amide (XXII). Elemental analysis and mass spectrometry confirmed the molecular formula and the i.r. spectrum indicated an αβ-unsaturated acid(C=O, 1700 cm.$^{-1}$). The ^{1}H n.m.r. showed the presence of a trans-AB quartet (J 17.0 Hz., δ 0.98), a 3-proton singlet (τ6.21), and an exchangeable proton (τ2.4-2.7) as would be expected for (XXV).

To obtain 2-methoxy-3,4,5,6-tetrachlorobenzoic acid (XXVII) from (XXV) ozonolysis and oxidation of the molozonide intermediate by performic acid was found to be satisfactory. The acid was not analysed, but the i.r., ^{1}H n.m.r., and mass spectra were in agreement with the purposed structure. Esterification with ethereal diazomethane gave methyl-2-methoxy-3,4,5,6-tetrachlorobenzoate (XXVIII); the structure of which was confirmed from the i.r., ^{1}H n.m.r., and mass spectra together with an elemental analysis. Further as (XXVIII) was a key compound; it would be required to have the same specific activity as that of the ^{14}C formyl labelled cinnamaldehyde starting material to prove our mechanism; we synthesised it by an alternative route to confirm conclusively the structure.

Tetrachlorosalicylaldehyde, previously described, was used and after methylation with ethereal diazomethane was oxidised by chromium III oxide in acetic acid. Further methylation gave methyl-2-methoxy-3,4,5,6-tetrachlorobenzoate identical to (XXVIII) by i.r. spectroscopy.

We had now established a satisfactory degradative route of the 2-H-flaven (V), and by optimisation and non-isolation of many of the intermediates we were able to obtain a 67% yield of the cinnamic acid (XXV), and an overall yield to the o-methoxy-benzoate (XXVIII) of 35%.

^{14}C Formyl labelled cinnamaldehyde was then prepared (scheme 12). The stages which are now described briefly were again optimised before the radiolabelling experiment was undertaken. Acetic acid containing [1-^{14}C] sodium acetate was converted to acetamide[61] and then to acetonitrile.[61] Addition of 2-methyl-2,4-pentane diol to an acidic solution of the acetonitrile gave a dihydro-oxazine.[75] Treatment of the dihydro-oxazine with n-butyl lithium, followed by benzaldehyde has been shown[76] to add the benzaldehyde to the methyl group at position-2. Reduction of this adduct with sodium borohydride at pH 7 gave a tetrahydro-oxazine, and this was hydrolysed to form [1-^{14}C]cinnamaldehyde. Steam distillation from the reaction mixture gave a 6% overall yield of the aldehyde.

To confirm that the ^{14}Clabel was in the formyl position a portion of the active cinnamaldehyde was oxidised to cinnamic acid. After dilution the cinnamic acid was converted to dibromo-dihydrocinnamic acid, and thence to cis-β-bromostyrene[77] which was shown to contain no activity (scheme 12).

The reaction of tetrachlorobenzyne generated by aprotic diazotisation *in situ* with the [1-^{14}C]cinnamaldehyde gave (V), and this was degraded as described (scheme 11). The specific activities of a number of intermediates were obtained and are recorded (table 2). As cinnamaldehyde would be difficult to obtain sufficiently pure for counting purposes the semicarbazone was formed; this was the only derivative found to be sufficiently soluble in the scintillation solution.

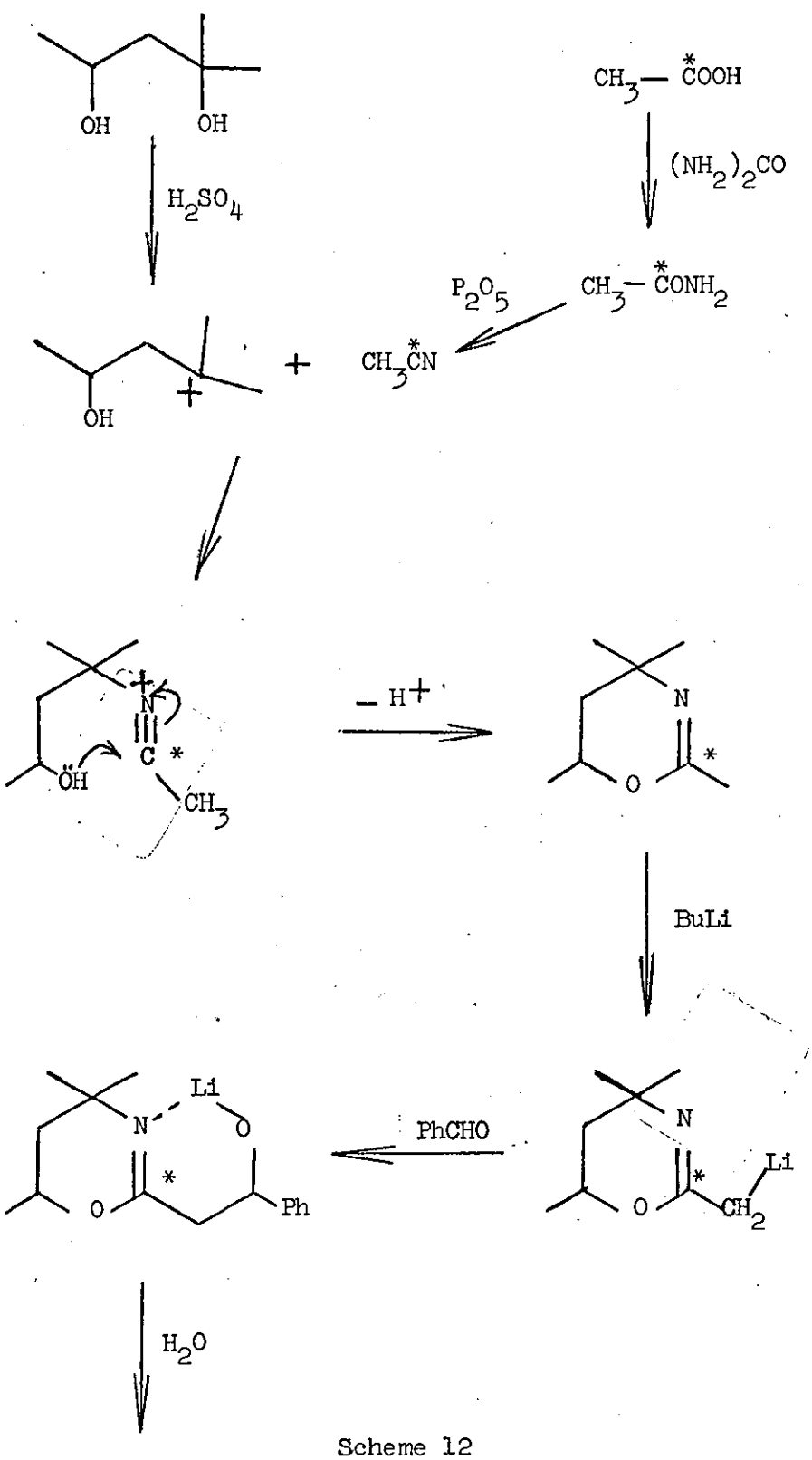
Table of Specific Activities of Intermediates

Acetic acid[(a)]	2.64	x 10^9dis.min.$^{-1}$mol.$^{-1}$
Cinnamaldehyde Semicarbazone	2.53 ± 0.13	"
5,6,7,8-tetrachloro-2-H-flaven (V)	2.76 ± 0.13	"
5,6,7,8-tetrachloro-4-H-flaven (XV)	2.73 ± 0.13	"
Phenyl-2'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XX)	2.78 ± 0.13	"
3'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-propenoic acid (XXV)	2.78 ± 0.13	"
Methyl-2-methoxy-3,4,5,6-tetrachlorobenzoate (XXVIII)	2.54 ± 0.13	"

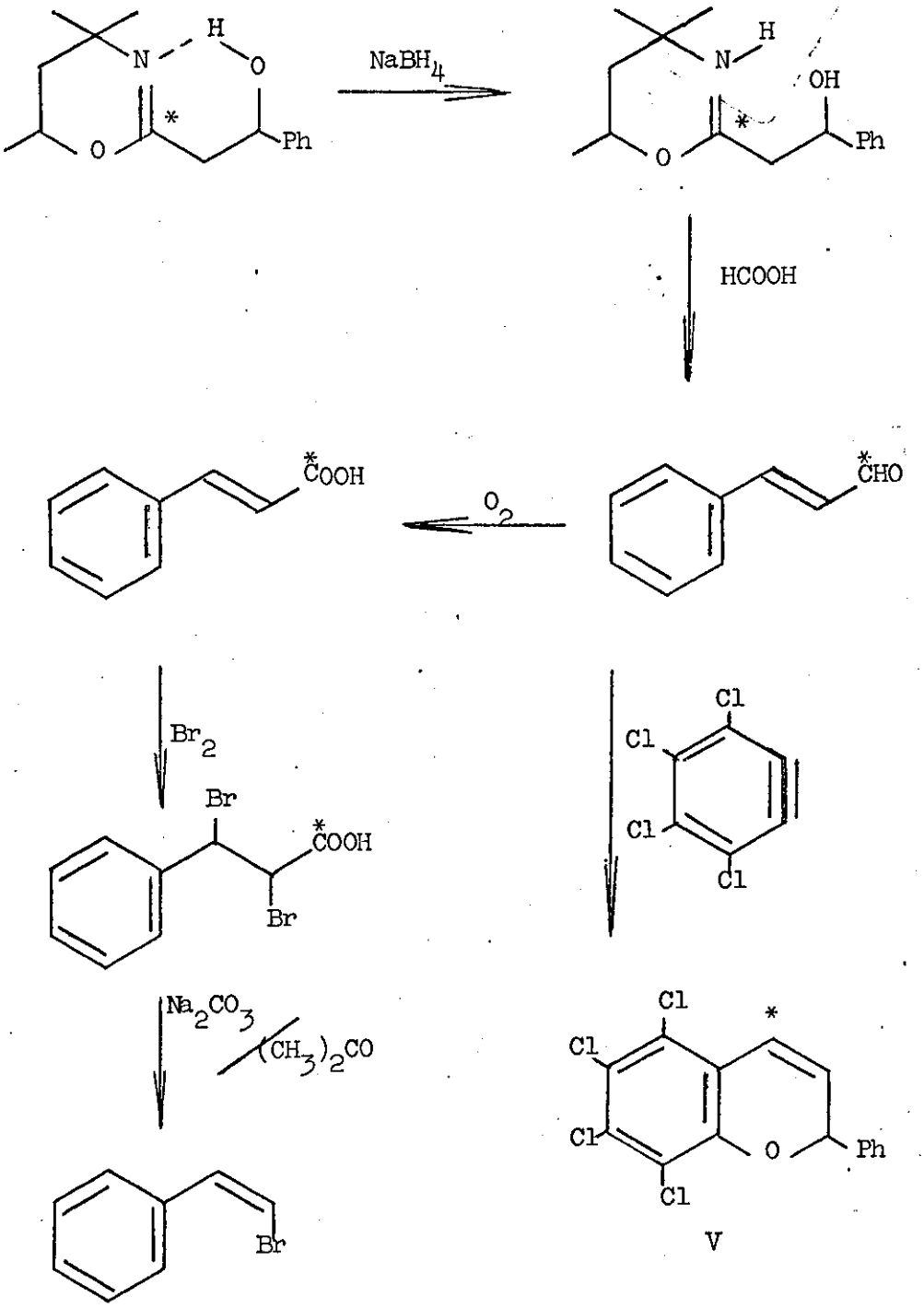
(a) The specific activity of acetic acid is that calculated from the dilution of the purchased [1-^{14}C] sodium acetate in acetic acid.

Table 2

It can be seen from the table that the specific activities of the various intermediates are constant within experimental error, and hence we feel confident that the mechanism proposed initially[41] is correct.


OH
OH
H_2SO_4
$CH_3-\overset{*}{C}OOH$
$(NH_2)_2CO$
$CH_3-\overset{*}{C}ONH_2$
P_2O_5
$CH_3\overset{*}{C}N$
OH
+
$\ddot{O}H$
N
C *
CH_3
$-H^+$
N
O
*
BuLi
Li
N
O
*
O
Ph
PhCHO
N
Li
*
O
CH_2
H_2O

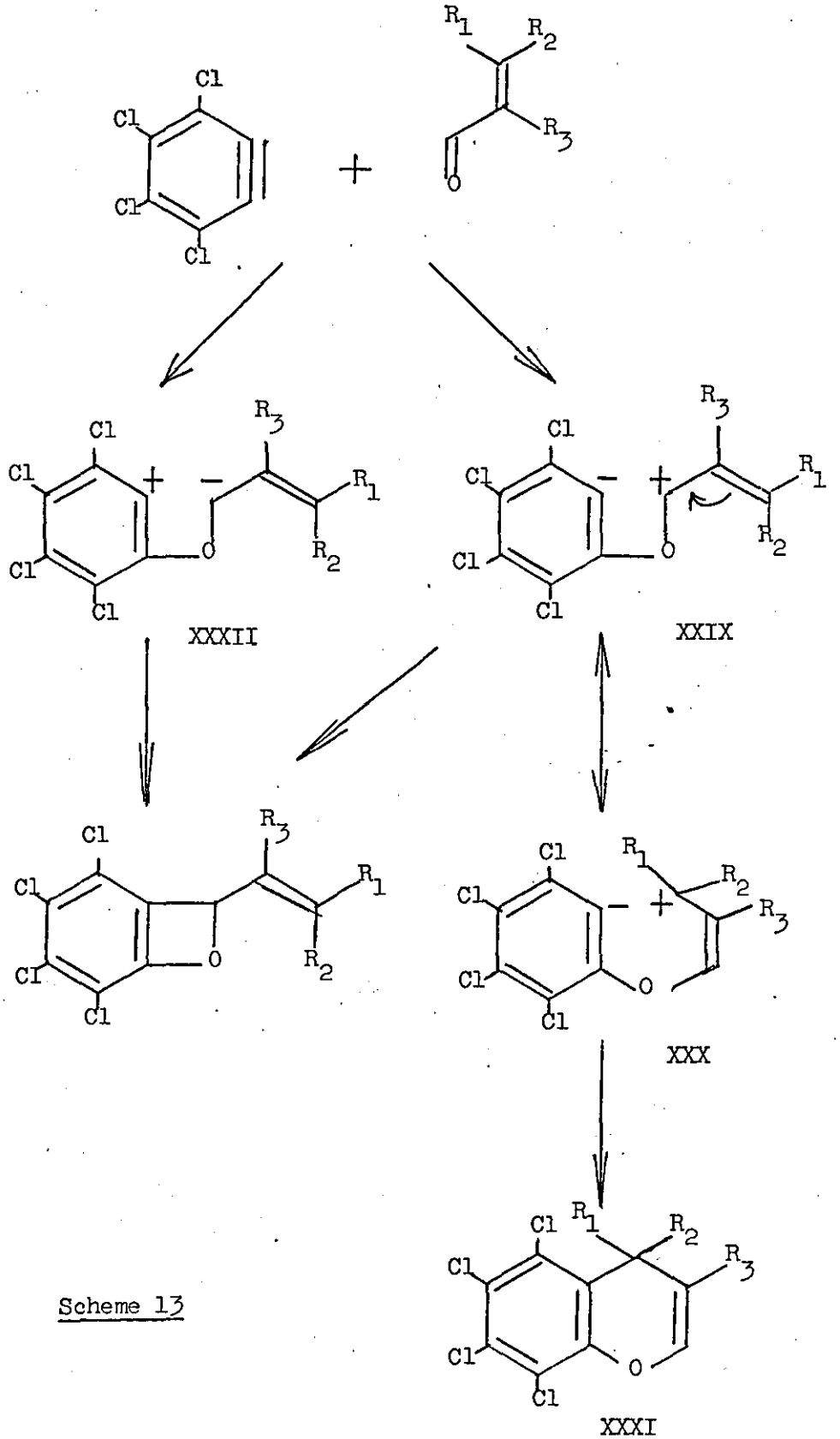
Scheme 12



Scheme 12 (continued)

One final question now remained to be answered. The 1,2-cycloaddition of an aryne to the carbonyl function of an αβ-unsaturated aldehyde cannot be considered as an allowed thermal concerted process,[11] unless some type of $2\pi s + 2\pi a$ cyclisation is envisaged. To explain the formation of a benzoxetene intermediate stepwise mechanisms may be considered (scheme 13). Nucleophilic attack by the carbonyl group would lead to the dipolar species (XXIX), the carbonium ion of which is allylically stabilised (XXX). Cyclisation could then occur in two fashions, either (XXIX) could ring close to give the required benzoxetene, or there is the attractive possibility of (XXX) cyclising to form (XXXI). We have conclusively established that there are no 4-substituted adducts of the type (XXXI) and hence we believe that this stepwise mechanism is unlikely. Alternatively the aryne may act as the nucleophile, and the intermediate dipolar species (XXXII) could then only cyclise to the benzoxetene. There are a small number of reports[1] of nucleophilic benzyne, but in our situation where we have four chlorine atoms attached to the aromatic nucleus, nucleophilic behaviour seems most unlikely.

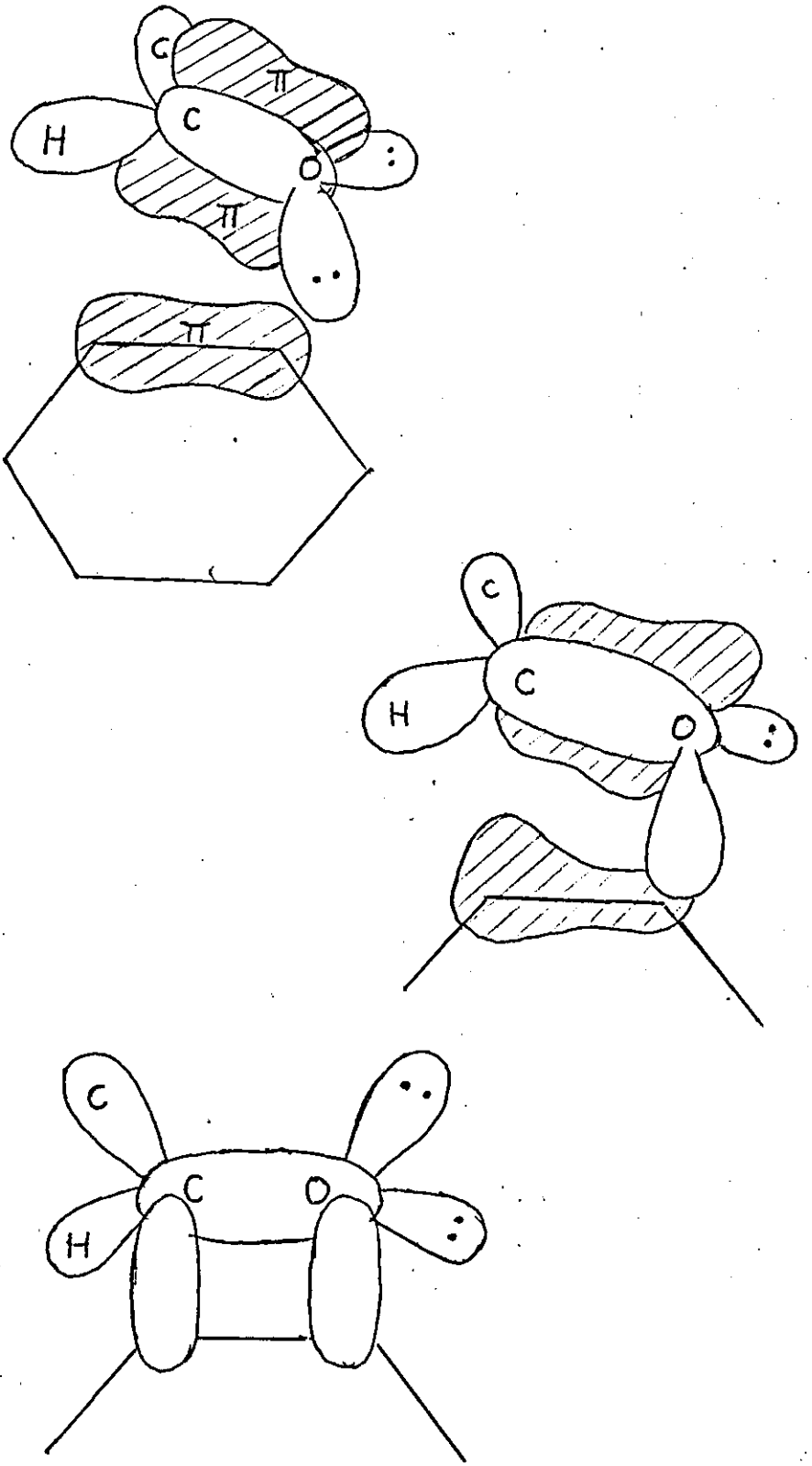
A further mechanism may be considered where a lone pair of electrons on the carbonyl oxygen becomes involved in the cyclisation (scheme 14).



Scheme 13

When a number of αβ-unsaturated ketones, for example styryl-methyl ketone and styryl-t-butyl ketone, were used as coreactants for the trapping of tetrachlorobenzyne, no 2-H-chromen type adducts were obtained. An examination of scale molecular models indicates that the aldehyde function is able to approach the aryne more closely than a ketone. The only expected type of addition for a ketone would be a stepwise nucleophilic attack by the oxygen and this has been found with certain simple ketones, and is described in section 3. With the aldehyde, by using the oxygen lone pair to attack the aryne (scheme 14) a situation is set up such that the position ortho to attack is electron rich and the carbonyl oxygen is electron deficient. As the π cloud of the carbonyl bond migrates towards the oxygen the incipient carbonium ion, which would be expected to be allylically stabilised, could then be attacked by the electron rich aromatic site; the hydrogen atom on the carbonyl carbon allowing the atom to be close enough to the aromatic ring to allow this cyclisation. Thus an extremely rapid stepwise ring closure could occur to give the required benzoxetene.

The benzoxetene could then open thermally in a concerted[11] fashion to form the quinone methide and a six electron electrocyclic ring closure would yield the 2-H-chromen product.



Scheme 14

EXPERIMENTAL

General Methods

Infrared spectra were determined using potassium bromide discs for solids; or solutions in chloroform for liquids, on Perkin-Elmer 237 or 257 grating spectrophotometers. Ultraviolet spectra for hexane solutions, except where stated, were determined in a Unicam SP800 spectrophotometer.

^{1}H n.m.r. spectra were determined at 60 M Hz., except where stated, for solutions in deuteriochloroform, using tetramethylsilane as internal standard, with a Perkin-Elmer R10 spectrometer. Mass spectra were determined with A.E.I. MS9 and MS12 spectrometers. The observed molecular weights of adducts from tetrachlorobenzyne, as determined by mass spectrometry, refer to the major molecular ion in the isotopic cluster.

Light petroleum (b.p. 60-80°), diethyl ether and benzene were dried over sodium wire. Tetrahydrofuran was dried initially over sodium wire, then distilled from lithium aluminium hydride. Dimethylformamide was dried by heating under reflux for five hours with calcium hydride. Acetone was stored over anhydrous magnesium sulphate, and as such was used as dry acetone. Organic extracts from aqueous phases were dried over anhydrous magnesium sulphate unless otherwise stated.

All compounds described are colourless solids, unless otherwise specified. Melting points are uncorrected and were determined on a Kofler hot stage.

Preparative layer chromatography used silica (Merck PF_{254}) as support spread as 0.5 mm. layers on 1m. x 20 cm. plates.

Radioactive assays were determined by scintillation counting using a Beckman CPM 100 instrument. The efficiency of counting was determined using [1-^{14}C]hexadecane of specific activity (1.73×10^3 dis. min.$^{-1}$ mg.$^{-1}$) The compound (ca. 0.5 mg.) was dissolved in dry dimethylformamide (0.1 ml.) and scintillator solution (5 ml.) added and ^{14}C activity determined. Scintillator solution was prepared by dissolving 2,5-diphenyloxazole (1.9 g.) and dimethyl-1,4-di-2-(5-phenyloxazolyl)-benzene in toluene (500 ml.).

Preparation of Tetrachloroanthranilic acid

Ammonia (20 ml., 0.88) was added to tetrachlorophthalic anhydride (28.5 g., 0.1 mol.) and the mixture stirred vigorously for 30 sec., by which time most of the solid had reacted. The reaction was then stopped by addition to a solution of sulphuric acid (20 ml.) in ice/water (200 g.). The white precipitate which formed was filtered off and washed well with water before adding to an alkaline solution of sodium hypobromite. This was prepared by adding bromine (8 ml., 0.15 mol.) to a cold solution of sodium hydroxide (30 g., 0.75 mol.) in water (300 ml.). After standing for 10 min. the solution was digested at 80° for 2 hr. When cool the red solution was filtered and the filtrate acidified with hydrochloric acid. Tetrachloroanthranilic acid came out of solution and was extracted

into diethyl ether. The diethyl ether layer was filtered to remove tetrachloro-o-phenylenediamine, washed with water, and concentrated to leave a light brown solid. Crystallisation from methanol:water (4:1) gave tetrachloroanthranilic acid (25 g., 90%), as a pale amber solid m.p. 178-180°, (lit.[23] m.p. 182°).

Preparation of 2-Carboxy-3,4,5,6-tetrachlorobenzenediazonium chloride (XIII)

Dry hydrogen chloride was passed through a stirred solution of tetrachloroanthranilic acid (4.0 g.) in dry tetrahydrofuran (60 ml.) until a precipitate formed (about 1-1½ hr.). The suspension was then cooled to -10° and 3-methylbutyl nitrite (4 ml.) added dropwise. After stirring for a further 15 min. at -10° the pale yellow precipitate was filtered off and washed well with ether, ensuring that the solid never became dry.* The product was removed from the sinter whilst still wet with diethyl ether, and air dried. This gave 2-carboxy-3,4,5,6-tetrachlorobenzenediazonium chloride (XIII) (2.2 g., 41%), an initially cream amorphous solid, which rapidly darkened.

Determination of the chloride ion content by titration of an aqueous suspension of the compound (XIII) with standardised silver nitrate solution gave Cl, 10.5%. $C_7H\,Cl_5N_2O_2$ requires Cl 11.0%.

* The dry compound was found to DETONATE if heated or scratched.

Preparation of 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV)

Dry hydrogen chloride was passed through a solution of tetrachloroanthranilic acid (27.5 g., 0.1 mol.) in dry tetrahydrofuran (300 ml.) for 2 hr. The suspension formed was then cooled to -10° and 3-methylbutyl nitrite (20 ml.) was added. After stirring at -10° for 15 min. the precipitate was filtered off and whilst still wet added in small portions to a stirred solution of sodium carbonate (20 g.) in ice/water (500 g.) containing dimethylamine (35 ml.). The mixture was stirred for 1 hr. to dissolve all of the solid and then allowed to warm to room temperature. The solution was acidified with hydrochloric acid (5N) and extracted with diethyl ether (3 x 100 ml.). The combined extracts were dried and concentrated to give: 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV) (14.8 g., 43.5%), m.p. 155-160° with decomposition (from benzene:petrol, 5:1).

(Found: C, 32.75; H, 2.3; N, 12.6%; M [mass spectrometry] 331. $C_9H_7Cl_4N_3O_2$ requires C, 32.65; H, 2.15; N, 12.7%; M 331). τ -2.70 (s, 1H), 6.45 (b.s., 3H), 6.74 (b.s., 3H). $\nu_{max.}$ 3300-2700, 1705, 1450, 1485, 1435, 1394, 1350, 1335, 1275, 1100, 812, 665 cm.$^{-1}$

An excess of a solution of diazomethane in diethyl ether was added to the compound (XIV) (465 mg.) in diethyl ether, and gave on removal of the solvent 1-(2'-carboxymethyl-tetrachlorophenyl)-3,3-dimethyltriazene (450 mg., 91%),

m.p. 88-89° (from light petroleum).

(Found: C, 34.75; H,2.7; N, 12.3%; M [mass spectrometry] 345. $C_{10}H_9Cl_4N_3O_2$ requires C, 34.8; H, 2.6; N, 12.2; M 345).

$\nu_{max.}$ 2940-2900, 1742, 1465, 1420, 1364, 1320, 1235, 1225, 1104, 1083, 955, 860, 680 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with Cinnamaldehyde

Method I. A solution of tetrachloroanthranilic acid (10.0 g., 0.036 mol.) in diethyl ether (40 ml.) and dichloromethane (120 ml.) was added dropwise during 1 hr. to a stirred solution of cinnamaldehyde (50 ml., 0.5 mol.) and 3-methylbutyl nitrite (10 ml.) in dichloromethane maintained at 40°. After stirring the reaction mixture for a further ½ hr. at 40°, removal of the solvents and distillation of the residue under reduced pressure, to remove excess cinnamaldehyde, a red oil was obtained. An examination of the oil by analytical thin layer chromatography indicated that three products were present. A comparison with authentic samples showed that the two fast moving products were 2,3,4,5-tetrachlorophenyl-ethyl ether[64] and 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether.[65] Elution from a column of silica with light petroleum gave, in order of decreasing R_f value: 2,3,4,5-tetrachlorophenyl-ethyl ether (2.1 g., 23%), 2.3.4.5-tetrachlorophenyl-(3'-methylbutyl) ether (1.0 g., 9%), and a pale yellow oil which crystallised on standing. Recrystallisation from light petroleum gave: 5,6,7,8-tetrachloro-2-H-flaven (V) (4.0 g., 32%), m.p. 98-99° (from light petroleum).

(Found: C, 52.3; H, 2.35%; M[mass spectrometry] 346. $C_{15}H_8Cl_4O$ requires C, 52.05; H, 2.35%; M 346).

$\lambda_{max.}$ (MeOH) 234 ($\log_{10}\varepsilon$ 4.56), 238 (4.59), 247 (4.47), 282 (3.89), 289 (3.83), 327 (3.53), 335 (3.50) nm.

$\nu_{max.}$ 2860, 1637, 1564, 1413, 1403, 1210, 1045, 884, 758, 705 $cm.^{-1}$

Method II. A solution of tetrachloroanthranilic acid (2.13 g., 0.008 mol.) in dichloromethane (10 ml.) and acetonitrile (30 ml.), and a solution of 3-methylbutyl nitrite (1 ml., 0.009 mol.) in dichloromethane (10 ml.), were added concurrently, during 15 min., to a stirred solution of cinnamaldehyde (6.1 g., 0.004 mol.) in dichloromethane (10 ml.), which was maintained at 40°. After a further 15 min., the solvents were removed to leave a red oil. Examination of the oil by analytical thin layer chromatography indicated the presence of one major product and a trace of a faster moving compound, which was shown to be 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether by comparison with an authentic sample. Elution from a column of silica gave the adduct (V) (0.997 g., 37.5%).

Method III. A solution of 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (2.4 g., 0.007 mol.) and cinnamaldehyde (2.0 g., 0.015 mol.) in tetrachloroethylene (30 ml.) was heated under reflux for 1 hr. The solvent was removed by distillation under reduced pressure to leave a red oil. Elution from a column of silica gave adduct (V) (0.77 g., 35%).

Method IV. 2-Carboxy-3,4,5,6-tetrachlorobenzenediazonium chloride (0.4 g., 0.0012 mol.) was added to a solution of cinnamaldehyde (1.0 g., 0.008 mol.) in chloroform (30 ml.). The mixture was heated under reflux for 15 min., during which time the solid went into solution. Removal of the solvent left a red oil which was eluted from a column of silica and gave the adduct (V) (0.247 g., 58%).

The adduct (V) (165 mg.) was hydrogenated in ethanol (20 ml.) in the presence of a palladium on carbon catalyst (10 mg., 10%) to give, after the removal of the catalyst and solvent, 5,6,7,8-tetrachloroflavan (X) (164 mg., 97%), m.p. 121-122° (from methanol).

(Found: C, 51.8; H, 3.05%; M[mass spectrometry] 348. $C_{15}H_{10}Cl_4O$ required C, 51.7; H, 2.9; M 348).

$\nu_{max.}$ 3050, 2980, 2940, 1540, 1499, 1404, 1315, 1187, 1015, 903, 883, 778, 758, 697 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with Acrolein

The procedure described for Method I was followed using tetrachloroanthranilic acid (5.5 g., 0.02 mol.) and acrolein (50 ml.) to give: 5,6,7,8-tetrachloro-2-H-chromen (I) (17%), m.p. 150° (from ethanol), (lit.[65] m.p. 150°).

Adduct (I) was hydrogenated in ethanol in the presence of palladium on charcoal catalyst, to give after the removal of the catalyst and solvent: 5,6,7,8-tetrachlorochroman (VI), m.p. 102° (from ethanol) (lit.[65] m.p. 102°).

Reaction of Tetrachlorobenzyne with Crotonaldehyde

The procedure described for Method I was followed using tetrachloroanthranilic acid (5.5 g., 0.02 mol.) and crotonaldehyde (50 ml.) to give: 5,6,7,8-tetrachloro-2-methyl-2-H-chromen (II) (34%), m.p. 56° (from ethanol), (lit.[65] m.p. 56°).

Adduct (II) was hydrogenated in ethanol in the presence of palladium on charcoal catalyst, to give after the removal of the catalyst and solvent: 5,6,7,8-tetrachloro-2-methyl-chroman (VII), m.p. 82° (from ethanol), (lit.[65] m.p. 82°).

Preparation of 3,3-Dimethylacrolein.[78]

Sodium (23 g., 1.0 mol.) was added in small portions to liquid ammonia (1,000 ml.) whilst a stream of dry acetylene was passed through. The addition rate was such that the solution never became entirely blue. Dry acetone (64 g., 1.1 mol.) was then added slowly to the stirred ammonia solution. Acetylene was still passed through during the addition of acetone and for a further 1 hr. The ammonia was allowed to evaporate overnight and the residue hydrolysed with water and then acidified with sulphuric acid (50%). The aqueous phase was extracted with diethyl ether and the combined ether extracts were dried over anhydrous potassium carbonate. Concentration left an oil which was distilled under reduced pressure to give dimethyl ethynyl carbinol (49 g., 58%), b.p. 58-63° 140 mm.Hg. (lit.[79] b.p. 120 mm. Hg.).

A mixture of acetic anhydride (12.2 g.) and ortho-phosphoric acid (0.18 g.) was added to dimethyl ethynyl carbinol stirred under nitrogen, which was warmed gently to initiate the reaction and then maintained at 50° for 1 hr.

The mixture was then added to a suspension of silver acetate (0.1 g.) and sodium carbonate (0.5 g.) in acetic acid (29.5 g., 80%) and heated under reflux in a nitrogen atmosphere for 1 hr. After cooling, the mixture was poured into water (200 ml.) and extracted with light petroleum. The combined extracts were washed with water, dried, and concentrated to leave 3,3-dimethylacrolein (2.6 g., 31%).

Reaction of Tetrachlorobenzyne with 3,3-dimethylacrolein

The procedure described for Method I was followed using tetrachloroanthranilic acid (5.5 g., 0.02 mol.) and 3,3-dimethylacrolein (2.5 g.) and gave 5,6,7,8-tetrachloro-2,2-dimethyl-2-H-chromen (III) (0.65 g., 11%), m.p. 58-59°(from light petroleum).

(Found: C, 44.2; H, 2.75%; M[mass spectrometry] 298.
$C_{11}H_8Cl_4O$ requires C, 44.3; H, 2.7%; M 298).

$\lambda_{max.}$ 210 ($\log_{10} \varepsilon$ 4.17), 231 (4.53), 237 (4.56) 245 (4.36), 278 (3.92), 290 (3.86), 328 (3.50), 340 (3.47) nm.

$\nu_{max.}$ 2985, 2940, 1640, 1400, 1365, 1355, 1203, 1111, 883, 867, 795 $cm.^{-1}$

Adduct (III) (37 mg.) was hydrogenated in ethanol (15 ml.) in the presence of palladium on carbon catalyst (5 mg., 10%) to give after the removal of the catalyst and solvent, 5,6,7,8-tetrachloro-2,2-dimethylchroman (VIII) (37 mg., 95%), m.p. 104-105° (from ethanol).

(Found: C, 43.89; H, 3.27%; M [mass spectrometry] 300.
$C_{11}H_{10}Cl_4O$ requires C, 44.03; H, 3.36%; M 300).

$\nu_{max.}$ 2985, 2950, 1564, 1543, 1408, 1386, 1345, 1195, 1098, 789 $cm.^{-1}$

Preparation of 2,3-Dimethylacrolein.[80]

A mixture of acetaldehyde (22 g., 0.5 mol.) and propanal (29 g., 0.5 mol.) was added dropwise to a stirred solution of sodium hydroxide (50 ml., 4%) maintained at 10°. The solution was cooled to 0° and extracted with ether. The combined extracts were washed with water, dried, and concentrated to leave an oil which was distilled to give 2,3-dimethylacrolein (8 g., 19%), b.p. 117-122° (lit.[80] b.p. 117-118°).

Reaction of Tetrachlorobenzyne with 2,3-Dimethylacrolein

The procedure described for Method I was followed using tetrachloroanthranilic acid (5.5 g., 0.02 mol.) and 2,3-dimethylacrolein (8.0 g.) and gave 5,6,7,8-tetrachloro-2,3-dimethyl-2-H-chromen (IV) (0.24 g., 4%), m.p. 80-81° (from methanol: benzene, 1:1).

(Found: C, 44.3; H, 2.8%; M [mass spectrometry] 298.
$C_{11}H_8Cl_4O$ requires C, 44.3; H, 2.7%; M 298).

$\lambda_{max.}$ 208 ($\log_{10}\varepsilon$ 4.20), 232 (4.51), 238 (4.53), 246 (4.35), 281 (3.99), 292 (3.93), 326 (3.52), 336 (3.51) nm.

$\nu_{max.}$ 2980, 1660, 1537, 1416, 1392, 1203, 1045, 845, 820, 735, 660 $cm.^{-1}$

Adduct (IV) (101 mg.) was hydrogenated in ethanol (20 ml.) in the presence of palladium on carbon catalyst to give after the removal of the catalyst and solvent, 5.6.7.8-tetrachloro-2,3-dimethylchroman (IX) (85 mg., 83%), m.p. 64-66° (from methanol:benzene, 3:1).

(Found: C, 44.15; H, 3.45%; M [mass spectrometry] 300.
$C_{11}H_{10}Cl_4O$ requires C, 44.05; H, 3.35%; M 300).

$\nu_{max.}$ 2980, 2940, 1565, 1539, 1409, 1385, 1194, 1096, 1001, 886, 814, 788, 674 $cm.^{-1}$

Preparation of tetrachlorosalicylaldehyde

A solution of tetrachloroanthranilic acid (5.5 g., 0.02 mol.) in dry dimethylformamide (25 ml.), and a solution of 3-methylbutyl nitrite (3.5 ml.) in dry dimethylformamide (11.5 ml.), were added concurrently to dry dimethylformamide stirred at 40°. When the additions were complete the solution was stirred for a further 30 mins. Removal of excess dimethylformamide by distillation under reduced pressure left a red oil which upon elution from a column of silica with benzene gave tetrachlorosalicylaldehyde (1.4 g., 25%), pale yellow crystals, m.p. 178-180° (from diethyl ether).
(Found: C, 32.15; H, 0.8%. M [mass spectrometry] 260. $C_7H_2Cl_4O_2$ requires C, 32.4; H, 0.8%; M 260).
$\lambda_{max.}$ (MeOH) 241 ($\log_{10}\varepsilon$ 3.81), 278 (3.70), 303 (3.28), 326 (3.28), 352 (3.14) nm.
$\nu_{max.}$ ($CHCl_3$) 3200-2500 , 1653, 1600, 1587, 1413, 1390, 1374, 1280, 1270, 1187, 1000, 938 $cm.^{-1}$

Preparation of 5,6,7,8-tetrachlorobenzo-2-pyrone

A solution of acetic anhydride (10 ml.) and trimethylamine (4 ml.) containing tetrachlorosalicylaldehyde (1.1 g.) was heated under reflux for 3 hr. The cold solution was added to sodium bicarbonate solution (100 ml. 20%) and extracted with diethyl ether (3 x 50 ml.). The combined extracts were shaken with hydrochloric acid (2 x 25 ml.), washed with water and dried. Removal of the solvent left an oil which was purified by preparative layer chromatography to give: 5,6,7,8-tetrachlorobenzo-2-pyrone (376 mg., 31%), m.p. 189-190° (from

benzene:light petroleum 1:1).

(Found: C, 38.15; H, 0.8%; M [mass spectrometry] 284.

$C_9H_2Cl_4O_2$ requires C, 38.05; H, 0.7%; M 284).

τ 2.64 (AB q. [δ = 1.40 p.p.m., J = 10.5 Hz.], 2H).

$\lambda_{max.}$ (MeOH) 232 ($\log_{10}\varepsilon$ 4.19), 291 (4.14), 333 (3.58) nm.

$\nu_{max.}$ 1790, 1762, 1750, 1715, 1613, 1565, 1393, 1377, 1226, 1180, 1102, 1012, 970, 890, 835, 755, 680 $cm.^{-1}$

Preparation of 5,6,7,8-tetrachloro-2,2-dimethylchromen (III)

To a solution of methylmagnesium iodide, prepared by the addition of a solution of methyl iodide (0.7 g.) in dry diethyl ether (10 ml.) to magnesium (0.1 g.) stirred in dry diethyl ether (10 ml.) under nitrogen, was added a solution of 5,6,7,8-tetrachlorobenzo-2-pyrone (350 mg.) in dry benzene (30 ml.). After stirring for 1 hr. at room temperature the solution was heated under reflux for 30 min. When cool, water (20 ml.) was added and the organic phase separated. Removal of the solvent gave an oil which was dissolved in methanol (20 ml.) containing hydrochloric acid (10 ml., 2N), and heated under reflux for 3 hr. The solution was concentrated and extracted with chloroform (2 x 25 ml.). The combined extracts were washed with water and dried to leave, on removal of solvent, an oil which was purified by preparative layer chromatography to give: 5,6,7,8-tetrachloro-2,2-dimethyl-2-H-chromen (III) (60 mg., 14%),m.p. 58-59 (from light petroleum). This was identical by i.r., u.v., ^1H n.m.r. and mass spectrometry to the product obtained from the reaction of tetrachlorobenzyne with 3,3-dimethylacrolein.

Reaction of Tetrachloroanthranilic acid with Cinnamaldehyde

A solution of tetrachloroanthranilic acid (2.75 g., 0.01 mol.) and cinnamaldehyde (1.32 g., 0.01 mol.) in diethyl ether was heated under reflux for 24 hr. Removal of the solvent left a red oil which crystallised. Recrystallisation from benzene gave: 5,6,7,8-tetrachloro-2-styryl-1,2-dihydro-3,1-benzoxazin-4-one (XI) (1.75 g., 45%), pale cream solid m.p. 175-177°.

(Found: C, 49.3; H, 2.4; N, 3.55%; M [mass spectrometry] 389. $C_{16}H_9NO_2Cl_4$ requires C, 49.4; H, 2.35; N, 3.6%; M 389). ($^{M-1}$/e 385.9314, $C_{16}H_8NO_2{}^{35}Cl_4$ requires $^{M-1}$/e 385.9311). $\nu_{max.}$ 3400, 1735, 1580, 1455, 1400, 1330, 1250, 1215, 1200, 1145, 975, 860, 785, 680 cm.$^{-1}$

Attempted Diazotisation of Tetrachloroanthranilic acid in the presence of Phenylpropargylaldehyde.[81]

A solution of tetrachloroanthranilic acid (5.5 g., 0.02 mol.) in acetonitrile (60 ml.) was added dropwise to a stirred solution of acetonitrile (20 ml.) containing phenylpropargyl-aldehyde (7.0 g.) and 3-methylbutyl nitrite maintained at 40°. After the addition was complete stirring was continued for a further 30 min. The solution, when cool, was filtered to remove octachloroacridone (200 mg.) and concentrated to leave an oil, which crystallised, and was recrystallised from chloroform. Examination of the mother liquors by thin layer chromatography indicated one product, which was found to be: 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether by comparison with an authentic sample. Recrystallisation from chloroform

gave: 5,6,7,8-tetrachloro-2-phenylpropargyl-1,2-dihydro-3,1-benzoxazin-4-one (XII) 2.8 g., 36%), pale cream crystals m.p. 180-182°.

(Found: C, 49.65; H, 1.7%; M[mass spectrometry] 387. $C_{16}H_7Cl_4N\,O_2$ requires C, 49.65; H, 1.8%; M 387).

$\nu_{max.}$ 3400, 2240, 2190, 1735, 1550, 1490, 1465, 1400, 1364, 1275, 1215, 1140, 940, 815, 780, 750, 680 $cm.^{-1}$

Decomposition of 2-Carboxy-3,4,5,6-tetrachlorobenzenediazonium chloride (XIII) in p-xylene

Compound (XIII) (1.2 g.) was suspended in p-xylene (20 ml.) and then heated to 140° over ½ hr. and kept at this temperature for a further ½ hr, during which time the solid (XIII) dissolved. Removal of the p-xylene under reduced pressure left a pale amber solid which was taken up in light petroleum. Elution from a short column of alumina gave: 1,4-dihydro-2,10-dimethyl-5,6,7,8-tetrachloro-1,4-ethenonaphthalene (0.86 g., 71%), m.p. 128-129° (lit. [57] 128-130°). Identical by i.r. and ^1H n.m.r. spectra to authentic spectra.

Decomposition of 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV) in Cinnamaldehyde

Compound (XIV) (1.0 g.) was heated under reflux for 15 min. in a solution of cinnamaldehyde (5.0 g.). The excess cinnamaldehyde was removed under reduced pressure and the residue was placed on a column of silica. Elution with light petroleum gave 5,6,7,8-tetrachloro-4-H-flaven (XV) (0.4 g., 22%), m.p. 184-186° (from chloroform).

(Found: C, 51.7; H, 2.55%; M [mass spectrometry] 346.
$C_{15}H_8O\,Cl_4$ requires C, 52.1; H, 2.3%; M 346).
$\lambda_{max.}$ (MeOH) 222 ($\log_{10}\varepsilon$ 3.58), 240 (3.48), 247 (3.36), 306 (2.22) nm.
$\nu_{max.}$ 2880, 1688, 1554, 1408, 1190, 1059, 784, 754, 748, 707, 684 $cm.^{-1}$

Adduct (XV) (67 mg.) was hydrogenated in chloroform (25 ml.) in the presence of palladium on carbon catalyst (5 mg., 10%) and gave after the removal of catalyst and solvent, 5,6,7,8-tetrachloroflavan (X) (60 mg., 86%), m.p. 121-122° (from methanol). Identical by i.r. and ^1H n.m.r. spectroscopy with the reduced adduct of 5,6,7,8-tetrachloro-2-H-flaven (V).

Decomposition of 1-(2'-carboxytetrachlorophenyl)-3,3-dimethyltriazene (XIV) in p-xylene

Compound (XIV) (500 mg.) was heated under reflux for 1 hr. in p-xylene (20 ml.). Removal of the p-xylene by distillation under reduced pressure left a light brown solid, which was dissolved in light petroleum. Elution from a short column of alumina gave: 1,4-dihydro-2,10-dimethyl-5,6,7,8-tetrachloro-1,4-ethenonaphthalene (280 mg., 60%), m.p. 128-129° (lit.[57] 128-130°), identical by i.r. and ^1H n.m.r. spectra to authentic spectra.

Rearrangement of 5,6,7,8-tetrachloro-2-H-flaven(V)

Method A. A solution of the adduct (V) (235 mg.) in cinnamaldehyde (5 ml.) was heated under reflux for 5 min. The solvent was removed under reduced pressure and the residue

was placed on a column of silica. Elution with light petroleum gave the compound (XV) (115 mg., 50%).

Method B. Adduct (V) (200 mg.) was taken up in diethyl ether (5 ml.) and placed on a column of alumina (100 g., Brockman activity 1). Elution with light petroleum gave a mixture of two products which were separated by preparative layer chromatography to give:

(a) R_f 0.25 compound (XV) (160 mg., 80%), and

(b) R_f 0.17 unrearranged adduct(V)(34 mg., 17%).

Preparation of [3-^{2}H]Cinnamaldehyde

(a) Phenylmorpholino [1-^{2}H]acetonitrile.[69] Sodium cyanide (5.3 g., 0.11 mol.) in water (10 ml.) was added to a solution of benzaldehyde (10.6 g., 0.1 mol.) and morpholine perchlorate (20.6 g., 0.11 mol.) in morpholine (100 ml.). The solution was heated at 80° for 1½ hr. When cool the solution was poured into ice/water (500 ml.) and the precipitate separated by filtration. Crystallisation from ether/light petroleum gave phenylmorpholino-acetonitrile (16.1 g., 83%). The product (9.7 g., 0.05 mol.) in dry dimethylformamide (150 ml.) was stirred with sodium hydride (4.8 g., 0.1 mol.) under nitrogen at 50° for 2 hr. Deuterium oxide was then added and the solution stirred at room temperature for 20 min., and acidified with thionyl chloride. Hydrochloric acid (200 ml., 2N) was then added and the aqueous phase was extracted with 1,2-dichloroethane (3 x 100 ml.). The combined extracts were dried over anhydrous sodium sulphate and concentrated to leave a solid which when crystallised from ether/light petroleum gave: phenylmorpholino[1-^{2}H]acetonitrile

(7.7 g., 79%) (containing 97% ^2H by mass spectrometry).

(b) [1-^2H]Benzaldehyde.[69] Phenylmorpholino[1-^2H] acetonitrile (11.2 g., 0.25 mol.) was heated under reflux in hydrochloric acid (300 ml., 2N) for 1 hr. After cooling to 10° the acidic phase was extracted with chloroform (3 x 100 ml.). The combined extracts were dried and concentrated to leave [1-^2H]benzaldehyde (5.5 g., 93%).

(c) [3-^2H]Cinnamaldehyde.[82] Acetaldehyde (22 g., 0.5 mol.) was added to a stirred aqueous solution of sodium hydroxide (100 ml., 1%) containing [1-^2H]benzaldehyde (5.5 g., 0.052 mol.) maintained at 50°. The mixture was stirred for 5 min., poured into ice/water (200 ml.), and acidified with hydrochloric acid (15 ml., 2N). The aqueous phase was extracted with chloroform (3 x 50 ml.) and the combined extracts washed with water (2 x 50 ml.) and dried. Removal of the solvent left a red oil which was distilled under reduced pressure and gave [3-^2H]cinnamaldehyde (1.5 g., 23%), b.p. 81-96° 2.5 mm. (containing 96% ^2H by mass spectrometry).

Reaction of Tetrachlorobenzyne with [3-^2H]Cinnamaldehyde

The procedure as described for Method I was followed,and the reaction was carried out using tetrachloroanthranilic acid (5.5 g., 0.02 mol.) and [3-^2H]cinnamaldehyde (1.5 g., 0.011 mol.) to give upon elution from an activated alumina column (Brockman grade I)

(a) 5,6,7,8-tetrachloro-4-H-flaven (XV) (50 mg., 1.3%) (containing no ^2H by mass spectrometry)

and (b) 5,6,7,8-tetrachloro-[2-^{2}H]flaven (XVI) (200 mg., 5.2%)
(containing 94% ^{2}H by mass spectrometry)

Adduct (XVI) was hydrogenated in ethanol in the presence of palladium on carbon catalyst, to give on removal of solvent and catalyst, 5,6,7,8-tetrachloro-[^{2}H]flavan (XVII) (containing 94% ^{2}H by mass spectrometry).

Rearrangement of 5,6,7,8-tetrachloro-2-H-flaven (V) in the presence of deuterium oxide

Alumina (100 g.) was dried at 200° for 3 days, cooled to room temperature and shaken with deuterium oxide (0.5 ml.). It was then heated to 450° for 3 hr. and again allowed to cool to room temperature before adding deuterium oxide (1 ml.). The alumina was shaken for 2 hr. to ensure complete mixing. A solution of adduct (IV) (250 mg.) in light petroleum was placed on a column of this alumina (100 g.). Elution with light petroleum and recrystallisation gave,

(a) adduct (XV) (158 mg., 63%), (containing 19% [4-^{2}H] by mass spectrometry and ^{1}H n.m.r.), and

(b) adduct (V) (85 mg., 34%), (containing no ^{2}H by mass spectrometry).

High temperature decomposition of 2-carboxy-3,4,5,6-tetrachlorobenzenediazonium chloride (XIII) in dimethylaniline.

Compound (XIII) (1.0 g.) was added in very small portions to stirred dimethylaniline (15 g.) maintained at 100°. Each addition was accompanied by a small explosion. When the addition was complete the excess of dimethylaniline was removed by distillation under reduced pressure to leave a red oil.

The oil was taken up in sodium carbonate solution (100 ml., 5%) and extracted with diethyl ether, (2 x 50 ml.). Examination of the concentrated, combined, organic extracts by thin layer chromatography indicated that there were none of the expected tetrachlorobenzyne adducts. The aqueous phase was acidified with hydrochloric acid (2N.) and extracted with benzene (3 x 25 ml.). The combined extracts were dried and concentrated to leave a red oil which crystallised on trituration with ether to give (4'-N,N-dimethylamino)-2-carboxy-3,4,5,6-tetrachloroazobenzene (196 mg., 16%). The i.r. and ^{1}H n.m.r. spectra were identical to those obtained at a lower temperature using 2,3,4,5-tetrachlorobenzenediazonium-2-carboxylate hydrochloride.[25]

Reaction of Benzyne with Cinnamaldehyde

Method I. A solution of anthranilic acid (6.65 g., 0.05 mol.) in diethyl ether (40 ml.) and dichloromethane (80 ml.) was added dropwise to a stirred solution of cinnamaldehyde (26.4 g.) in dichloromethane (50 ml.) containing 3-methylbutyl nitrite (8.5 ml.) which was maintained at 40° during 30 min. The solution was stirred for a further 30 min. Removal of the solvents left a red oil which was filtered through a deactivated alumina column before elution from an activated alumina column (Brockman activity I) to give a pale yellow oil. Purification of the oil by preparative layer chromatography gave :

2-H-flaven (1.2 g., 15%), oil

(Found: C, 88.2; H, 6.3%. $C_{15}H_{12}O$ requires C, 86.5; H,5.8%).

τ 2.6 - 2.9 (m, 5H), 2.95 - 3.45 (m, 4H), 3.65 (d x d [J_{AB} = 9.0 Hz.], [J_{AX} = 1.0 Hz.], 2H), 4.2 - 4.5 (m, 2H), identical with the published spectrum.[58]

Method II. Diphenyliodonium-2-carboxylate (1.5 g.) was heated under reflux in cinnamaldehyde (15 ml.) for 10 min. When cool the solution was filtered through a column of deactivated alumina. The oil obtained was examined by thin layer chromatography and showed the presence of two products. Separation by preparative layer chromatography gave:

(a) iodobenzene (0.47 g., 53%), and

(b) 2-H-flaven (52 mg., 5.7 %).

Method III. To a prereduced suspension of freshly prepared palladium II oxide (0.5 g.) in water (10 ml.) was added a solution of o-nitrobenzenesulphinic acid (1.87 g.) in water (50 ml.), adjusted to pH 9 with sodium hydroxide (2N.), and hydrogenated at atmospheric pressure. The catalyst was removed by filtration and sulphuric acid (16.5 ml., 2N.) and glycerol (23 ml.) were added to the filtrate. This solution was then cooled to -15° before a saturated aqueous solution of sodium nitrite (0.57 g.) was added dropwise while keeping the temperature of the solution at $-15^{\circ} \pm 3^{\circ}$. The time for addition was 5 min. and the reaction mixture was stirred for a further 2 hr. at -15°. 1,2,3-Benzothiadiazole-1,1-dioxide was extracted with diethyl ether (6 x 20 ml.) keeping the temperature below -6°. After drying the combined extracts over calcium chloride at -20° for 4 hr. cinnamaldehyde (5 g.) was added and the solution allowed to warm to room temperature. Removal of solvent left a red oil which was eluted from an alumina column to give :

2-H-flaven (0.28 g., 15%).

2-H-flaven (1.03 g.) was hydrogenated in ethanol in the presence of palladium on carbon catalyst (50 mg., 10%), to give after the removal of the solvent and catalyst, flavan (0.64 mg., 60%) m.p. 43-45° (lit.[59] m.p. 44-45°) (Found: C, 85.8; H, 6.85%. $C_{15}H_{14}O$ requires C, 85.7; H, 6.7%).

Oxidation of 5,6,7,8-Tetrachloro-2-H-chromen (I) with Potassium Permanganate

Potassium permanganate (0.81 g.) was added to a solution of the adduct (I) (1.39 g.) in acetone (20 ml.) and water (2 ml.) and stirred for 12 hr. at ambient temperature. Excess sodium bisulphite solution was added and the aqueous phase extracted with chloroform (3 x 20 ml.). The combined extracts were dried and concentrated to leave a pale yellow oil which crystallised and gave 5,6,7,8-tetrachlorochroman-3,4-diol (100 mg. 1%), m.p. 174-175° (from acetone). (Found: C, 35.65; H, 2.1%; M [mass spectrometry] 304. $C_9H_6Cl_4O_3$ requires C, 35.55; H, 2.0%; M 304).

τ (D.M.S.O.) 4.4 (b.s., 1H), 4.7 (b.s., 1H), 5.2-5.3 (m, 1H), 5.75-6.2 (m, 3H).

$\nu_{max.}$ 3350-3050, 1570, 1550, 1415, 1185, 1055, 760 cm.$^{-1}$

Hydrolytic cleavage of 5,6,7,8-tetrachloro-2-H-flaven (XV)

5,6,7,8-Tetrachloro-2-H-flaven (XV) (623 mg.) was added to a solution of acetic acid (20 ml.) containing hydrochloric acid (5 ml.) and heated under reflux for 45 min. After this time a homogeneous solution was obtained. Water (50 ml.) was added to the cold solution and the aqueous phase was extracted with chloroform (3 x 20 ml.). The combined

extracts were concentrated, and the acetic acid removed by azeotropic distillation with benzene to leave a white solid. Recrystallisation from benzene gave : phenyl-2'-(2-hydroxy--3,4,5,6-tetrachlorophenyl)-ethyl ketone (XVIII).
(650 mg., 99%), m.p. 184-185°.
(Found: C, 49.55; H, 3.1%; M [mass spectrometry] 364.
$C_{15}H_{10}Cl_4O_2$ requires C, 49.5; H, 2.9%; M 364).
τ 1.10 (s, 1H), 1.9-2.6 (m, 5H), 6.35-6.95 (m, 4H).
$\lambda_{max.}$ (MeOH) 213 ($\log_{10} \varepsilon$ 4.66), 241 (4.33), 290 (2.44), 299 (2.45), 318 (2.17) nm.
$\nu_{max.}$ 3500, 3360-3060, 1666, 1597, 1448, 1390, 1175, 956 $cm.^{-1}$

The compound (XVIII) (200 mg.) in diethyl ether (20 ml.) and methanol (0.5 ml.) was methylated by the addition of an excess of an ethereal solution of diazomethane, to give after the removal of solvent, phenyl-2'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XIX) (196 mg., 94%), m.p. 84-85° (from methanol).
(Found: C, 50.8; H, 3.35%; M [mass spectrometry] 378.
$C_{16}H_{12}Cl_4O_2$ requires C, 50.85; H, 3.2%; M378).
τ 1.9-2.6 (m, 5H), 6.14 (s, 3H), 6.77 (s, 4H).
$\lambda_{max.}$ (MeOH) 214 ($\log_{10} \varepsilon$ 3.62), 240 (3.30), 283 (2.15) nm.
$\nu_{max.}$ 2960, 2920, 2865, 1678, 1601, 1454, 1388, 1378, 1367, 1215, 1027, 746, 689 $cm.^{-1}$

Reaction of the ketone (XIX) with hydroxylamine

The compound (XIX) (924 mg., 2.44 m mol.) was heated in benzene (5 ml.) and ethanol (30 ml.) until it dissolved,

and hydroxylaminehydrochloride (930 mg., 12 m mol.) and pyridine (1.5 ml., 17 m mol.) was added. The solution was heated under reflux for 10 min. The solution was concentrated to one third of its volume and set aside to crystallise. Recrystallisation from chloroform gave: anti-phenyl-2'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-ethyl ketoxime (XX) (900 mg., 95%), m.p. 175-176°.

(Found: C, 49.0; H, 3.45; N, 3.5%, M [mass spectrometry] 393. $C_{16}H_{13}Cl_4N O_2$ requires C, 48.9; H, 3.35; N, 3.55%; M 393).

τ - 1.22 (s, 1H), 2.1-2.6 (m, 5H), 6.11 (s, 3H), 7.01 (s, 4H).

$\lambda_{max.}$ (MeOH) 230 ($\log_{10} \varepsilon$ 3.16), 239 (3.15), 293 (1.87) nm.

$\nu_{max.}$ 3350-3000, 2940, 1453, 1445, 1380, 1345, 1023, 1011, 939, 761, 687 $cm.^{-1}$

Beckman rearrangement of the oxime (XX)

Method I. Phosphorus pentachloride (1.0 g., 4.8 m.mol.) was added to a solution of the oxime (XX) (490 mg., 1.25 m mol.) in dry diethyl ether and the mixture was heated under reflux for 1 hr. Water was then added and the diethyl ether layer separated, washed with water (10 ml.) and dried. Examination of the oil remaining after removal of the solvent by analytical thin layer chromatography indicated the presence of two products, which were separated by preparative layer chromatography and gave :

(a) R_f 0.3 N-phenyl-1'-chloro-2'(2-methoxy-3,4,5,6-tetrachlorophenyl)-ethylamide (XXII) (229 mg., 43%), m.p. 156-161° (from benzene:light petroleum)

(Found: C, 45.3; H, 2.75; N, 3.2%; M [mass spectrometry] 426. $C_{16}H_{11}Cl_5NO_2$ requires C, 45.05; H, 2.6; N, 3.3%; M 426).

τ - 0.08 (s, 1H), 2.2-3.0 (m, 5H), 5.07 (d x d [J_{AB} = 9.0 Hz.], [$J_{AB'}$ = 6.0 Hz.], 1H), 6.08 (s, 3H), 6.2-6.6 (m, 2H).

$\nu_{max.}$ 3290, 2940, 2860, 1675, 1604, 1545, 1447, 1376, 1022, 902, 811, 758, 750, 708, 690 cm.$^{-1}$

and

(b) R_f 0.05 N-phenyl-2'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-ethylamide (XXI) (275 mg., 56%), m.p. 211-212°. (M [mass spectrometry] 393. $C_{16}H_{12}Cl_4NO_2$ requires M 393).

τ 0.2-0.4 (b.s., 1H), 2.2-3.0 (m, 5H), 6.08 (s, 3H), 6.6-7.0 (m, 2H), 7.2-7.6 (m, 2H).

$\nu_{max.}$ 3290, 2940, 2860, 1646, 1605, 1598, 1537, 1445, 1385, 1375, 1030, 1010, 808, 786, 753, 707, 688 cm.$^{-1}$

Method II. The procedure described for Method I was used with phosphorus pentachloride (3.0 g., 14.4 m mol.) and the oxime (XX) (373 mg., 0.98 m mol.), and gave only the amide (XXII) (370 mg., 92%).

Attempted Reaction of the Amide (XXI) with Phosphorus Pentachloride

Phosphorus pentachloride (20 mg.) and the amide (XXI) were heated under reflux for 30 min. in dry diethyl ether. Water (5 ml.) was added and the diethyl ether solution separated, washed with water, and dried. Removal of the solvent left a white crystalline solid (20 mg.) identical by i.r. spectroscopy with starting material.

Hydrolysis of the Amide (XXI)

The amide (XXI) (300 mg., 0.76 m mol.) was heated under reflux for 2 hr. in a solution of acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.). When cool the solution was made alkaline by the addition of sodium carbonate solution and extracted with chloroform (3 x 15 ml.). The combined extracts were washed with water, dried and concentrated to leave an oil (50 mg.). The oil was warmed gently for 10 min. in a solution of diethyl ether (1 ml.) containing acetic anhydride (1 ml.). Purification of the product by preparative layer chromatography gave acetanilide (30 mg., 34%), m.p. and mixed m.p. 114°. The i.r. spectrum was also identical to that of an authentic sample.

The aqueous phase was then acidified with hydrochloric acid (2N) and extracted with chloroform (3 x 25 ml.). The combined extracts were washed with water, dried and concentrated to give: 3(2-methoxy-3,4,5,6-tetrachlorophenyl)-propanoic acid (XXIII) (120 mg., 50%) m.p. 160-163° (from benzene).
(Found: C, 37.9; H, 2.3%; M [mass spectrometry] 318.
$C_{10}H_8Cl_4O_3$ requires C, 37.75; H, 2.55%; M 318).
τ (D.M.S.O.) 0.8-1.2 (b.s., 1H), 6.12 (s, 3H), 6.6-7.0 (m, 2H), 7.2-7.7 (m, 2H).
$\nu_{max.}$ 3300-2500, 2945, 2860, 1710, 1445, 1385, 1375, 1310, 1225, 1028, 1008, 800, 790, 717 cm.$^{-1}$

The acid (XXIII) was methylated in diethyl ether with an excess of an ethereal solution of diazomethane and gave after the removal of solvent, methyl-3'-(2-methoxy-3,4,5,6-tetrachlorophenyl)propanoate (XXVI) (58 mg., 99%), oil.

τ 6.13 (s, 3H), 6.30 (s, 3H), 6.6-7.0 (m, 2H) 7.0-7.7 (m, 2H).

$\nu_{max.}$ 2945, 2855, 1735, 1448, 1438, 1375, 1172, 1030 cm.$^{-1}$

Oxidation of the Ester (XXVI)

The ester (XXVI) (62 mg.) was added to a solution of potassium hydroxide (10 ml., 50%) containing potassium permanganate (250 mg.) and heated under reflux for 2 hr. The cold solution was acidified with hydrochloric acid (2N) and extracted with chloroform (3 x 20 ml.). The combined extracts were dried and concentrated to leave an oil: 1-methoxy-2,3,4,5-tetrachlorobenzene (23 mg., 50%).[65]

τ 3.04 (s, 1H), 6.11 (s, 3H)

$\nu_{max.}$ 2950, 2855, 1575, 1427, 1355, 1046, 840, 830 cm.$^{-1}$

Hydrolysis of the Amide (XXII)

The amide (XXII) (300 mg.) was heated under reflux in a solution of acetic acid (20 ml.) and concentrated hydrochloric acid (10 ml.) for 1½ hr. The cold solution was neutralised with a solution of sodium hydrogen carbonate and extracted with chloroform (3 x 10 ml.). The combined extracts were washed with water, dried, and concentrated to leave aniline (45 mg. 70%), (i.r. spectrum identical with that of an authentic sample), and conversion to acetanilide (i.r. spectrum identical with that of an authentic sample). The aqueous phase was acidified with hydrochloric acid (2N) and extracted with chloroform (3 x 25 ml.). The combined extracts were washed with water, dried, and concentrated to leave an oil: 1'-chloro-3'-(2-methoxy-3,4,5,6-tetrachlorophenyl)propanoic acid (XXIV) (144mg.,62%).

τ 0.1-0.2 (b.s., 1H), 5.24 (t [J = 7.0 Hz.], 1H), 6.08 (s, 3H), 6.44 (d [J = 7.0 Hz.], 2H).

$\nu_{max.}$ 3300-2500, 2945, 2860, 1740, 1555, 1538, 1445, 1432, 1376, 1300, 1208, 1195, 1023, 1011, 901, 806, 735, 708 cm.$^{-1}$

The acid (XXIV) (90 mg.) was heated under reflux for 1½ hr. in methanol (30 ml.) containing potassium hydroxide (200 mg.). The cold solution was acidified with hydrochloric acid (2N) and the concentrated solution was extracted with chloroform (3 x 20 ml.). The combined extracts were washed, dried, concentrated, and gave trans-3'-(2-methoxy-3,4,5,6-tetrachlorophenyl)-propenoic acid (XXV) (78 mg., 98%), m.p. 205-206° (from benzene).

(Found: C, 38.1; H, 2.0%; M [mass spectrometry] 316. $C_{10}H_6Cl_4O_3$ requires C, 38.0; H, 1.9%; M 316).

τ 2.4-2.7 (b.s. 1H), 2.77 (AB q [δ = 0.98 p.p.m., J = 17.0 Hz.], 2H), 6.21 (s, 3H).

$\nu_{max.}$ 3300-2800, 2940, 2860, 1700, 1664, 1630, 1600, 1540, 1447, 1382, 1370, 1296, 1210, 1023, 982, 972, 905, 772, 750, 690 cm.$^{-1}$

Ozonolysis of olefinic acid (XXV)

Ozone enriched oxygen was passed for 5 min through a solution of the compound (XXV) (312 mg.) in methanol (25 ml.) and chloroform (10 ml.), at 0°. Removal of the solvents left an oil which was taken up in formic acid (10 ml., 98%) and hydrogen peroxide (5 ml., 100 vol.) was added. The solution was heated gently to initiate the reaction, then heated under

reflux for 10 min. Water (10 ml.) was added to the cold solution and the precipitate which formed was extracted into chloroform (3 x 20 ml.) The combined extracts were then extracted with potassium hydroxide solution (2 x 30 ml., 5%). The extracts were combined and acidified with hydrochloric acid (2N), and the precipitate again extracted into chloroform (3 x 20 ml.). The combined extracts were washed, dried and concentrated to leave an off-white solid: 2-methoxy-3,4,5,6-tetrachlorobenzoic acid (XXVII) (150 mg., 52%).

τ 3.1-3.7 (b.s., 1H), 6.05 (s, 3H).

$\nu_{max.}$ 3500-3200, 2955, 2860, 1730, 1680, 1555, 1455, 1422, 1398, 1311, 1220, 1022, 974, 908, 801, 755, 668 cm.$^{-1}$

The acid (XXVII) (140 mg.) was methylated in diethyl ether (5 ml.) by the addition of an excess of an ethereal solution of diazomethane, and gave, after the removal of solvent, methyl 2-methoxy-3,4,5,6-tetrachlorobenzoate (XXVIII) (141 mg., 95%), m.p. 88-90° (from light petroleum).

(Found: C, 35.45; H, 2.1%; M[mass spectrometry] 304.

$C_9H_6Cl_4O_3$ requires C, 35.55; H, 2.0%; M 304).

τ 6.05 (s, 6H).

$\nu_{max.}$ 2960, 2865, 1750, 1455, 1440, 1392, 1380, 1210, 1170, 1024, 945, 774, 720 cm.$^{-1}$

Preparation of the ester (XXVIII)

Tetrachlorosalicylaldehyde (400 mg.) was methylated by the addition of ethereal diazomethane to give on removal of solvent, 2-methoxy-3,4,5,6-tetrachlorobenzaldehyde (84 mg.,20%).

τ 0.21 (s, 1H), 6.21 (s, 3H);

$\nu_{max.}$ 2950, 2860, 1718, 1448, 1381, 1031, 1010, 980, 912, 880, 775cm.$^{-1}$; chromium (III) oxide (200 mg.) in acetic acid (20 ml.) was added to a solution of the aldehyde in benzene (20 ml.). After 30 min. water (50 ml.) was added and the aqueous phase was extracted with benzene (3 x 20 ml.). The combined extracts were concentrated and excess acetic acid was removed by azeotropic distillation with benzene. The oil remaining was taken up in diethyl ether (10 ml.) and methanol (0.5 ml.) and treated with an excess of an ethereal solution of diazomethane. Removal of the solvents gave an oil which was purified by preparative layer chromatography and gave methyl-2-methoxy-3,4,5,6-tetrachlorobenzoate (10 mg., 11%), identical by i.r. spectroscopy with the ester (XXVIII) obtained from the degradation of 5,6,7,8-tetrachloro-2-H-flaven (V).

Attempted Reaction of Tetrachlorobenzyne with Styryl-t-butyl ketone.

A solution of tetrachloroanthranilic acid (10 g.) in diethyl ether (35 ml.) and dichloromethane (115 ml.) was added dropwise to a stirred solution of styryl-t-butyl ketone (20.8 g.) in dichloromethane (100 ml.) containing 3-methylbutyl nitrite (11 ml.) which was maintained at 40°. The solution was stirred for a further 30 min. after the addition was complete. The solution was concentrated to leave a red oil which was filtered through a column of deactivated alumina and then eluted from a column of silica with light petroleum to give an oil. This was crystallised from methanol and was shown to be 2,3,4,5-tetrachlorophenylethyl ether (1.6 g.) m.p. and mixed m.p.55-56°.

Formation of [1-^{14}C]Cinnamaldehyde.

Sodium acetate (0.5 m.Ci.) was taken up in acetic acid (A.R.) (25 g.), and allowed to stand for two days. This solution had theoretically a specific activity of 2.64 x 10^9 dis.min.$^{-1}$ mol.$^{-1}$ Urea (30 g.) was added to the acetic acid and the mixture was heated in an air bath at a rate such that the temperature rose steadily to 210° during 30 min. The reaction mixture was maintained at this temperature for a further 2 hr., and allowed to cool to room temperature. The reflux condenser was replaced by a short path air condenser and the product distilled, and dried *in vacuo* and gave acetamide, 22.2 g., (90%) [specific activity of this crude material 2.29 x 10^9 dis.min.$^{-1}$ mol.$^{-1}$].

The acetamide was mixed with phosphorus pentoxide (56 g.) in a 100 ml. long necked flask. Cautious heating applied with a flame initiated the dehydration of the acetamide. The acetonitrile distilled over as it formed and was collected in a cooled receiver. When no more liquid came over water (5 ml.) was added to the distillate, followed by potassium carbonate (10 g.) in small portions. The upper acetonitrile layer was then separated and added immediately to concentrated sulphuric acid (115 g.), maintained below 0°. 2-Methyl-2,4-pentanediol (40 g.) was then added at such a rate as to ensure the temperature remained below 0°. The solution was stirred at this temperature for 30 min., then half neutralised by the addition of sodium hydroxide solution (100 ml., 40%). Unreacted organic material was extracted with chloroform (3 x 50 ml.) and the aqueous phase was made alkaline while keeping the temperature below 0°. The solution was then

extracted with diethyl ether (3 x 100 ml.) and the combined extracts washed with water (100 ml.) and dried over anhydrous potassium carbonate. Removal of the solvent and distillation of the residue gave 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine. 10.7 g., (20% from acetamide) b.p. 55-60°, 3-4 mm. Hg.

The dihydro-1,3-oxazine (10.7 g.) was dissolved in dry tetrahydrofuran (80 ml.) and cooled to -78°. n-Butyl lithium (47 ml., 1.8 molar) was added slowly to the stirred solution under nitrogen. About 10 min. after the addition was completed a yellow precipitate was obtained. Benzaldehyde (20 g.) was then added in dry tetrahydrofuran (25 ml.), to give a clear red solution. This was allowed to warm to room temperature overnight when it was poured onto ice (100 g.) and brought to pH 2 with hydrochloric acid (9N). The organic phase was separated and the acidic phase further extracted with petrol (2 x 100 ml.). The aqueous phase was made alkaline, keeping the temperature below 10°, and extracted with diethyl ether (3 x 100 ml.). The combined extracts were washed with water (100 ml.) and dried over anhydrous potassium carbonate. Removal of the solvent left an oil which was taken up in a mixture of tetrahydrofuran (80 ml.) and ethanol (80 ml.), and brought to pH7 with hydrochloric acid (9N). The solution was cooled to -40° and stirred with an efficient mechanical stirrer, while a solution containing sodium borohydride (3 g.) and sodium hydroxide solution (0.1 ml., 40%) in water (10 ml.) was added slowly. During this stage pH was continually monitored

so that the solution was kept neutral by the addition of hydrochloric acid (9N). After the addition of sodium borohydride solution was completed the mixture was stirred for a further 30 min. before it was allowed to warm to room temperature. The mixture was then made alkaline and extracted with diethyl ether (3 x 100 ml.), the combined extracts were shaken with a saturated sodium chloride solution (2 x 50 ml.) and then dried over anhydrous potassium carbonate. Removal of the solvent left a red oil (20.5 g.) which was added under nitrogen to a boiling solution of oxalic acid (50 g.) in water (100 ml.). The cinnamaldehyde which formed steam distilled and the distillate was extracted with diethyl ether (3 x 100 ml.). The combined extracts were dried over anhydrous magnesium sulphate and concentrated under vacuum at room temperature to leave [1-^{14}C]cinnamaldehyde (3.3 g. 33% from dihydro-1,3-oxazine; 6% from acetic acid).

Treatment of [1-^{14}C]cinnamaldehyde (103 mg.) in ethanol (5 ml.) with a solution containing semicarbazide hydrochloride (0.2 g.) and sodium acetate (0.25 g.) in water (5 ml.) gave cinnamaldehyde semicarbazone (103 mg. 70%) m.p. 208° crystallised from the reaction solution. Three successive recrystallisations from ethanol gave a material with a specific activity 2.65 dis.min.$^{-1}$ mol.$^{-1}$

A further sample of [1-^{14}C]cinnamaldehyde (145.5 mg.) was dissolved in diethyl ether (10 ml.) and oxygen bubbled through for 5 hr. The resultant mixture was allowed to stand for 10 days and then cinnamic acid (355 mg.) was added and the mixture

crystallised from ether/petrol. The specific activity of the cinnamic acid was 2.58×10^8 dis.min.$^{-1}$ mol.$^{-1}$. Recrystallisation gave a sample with specific activity 2.52×10^8 dis.min.$^{-1}$ mol.$^{-1}$.

The cinnamic acid (500 mg.) was dispersed in gently refluxing dry carbon tetrachloride (30 ml.) and bromine (0.5 g.) in dry carbon tetrachloride (10 ml.) added. After 1 hr. the solution was allowed to cool and the crystals which formed collected to give dibromo-dihydrocinnamic acid (710 mg., 68%). This compound was dissolved in dry acetone (20 ml.) and heated under reflux for 18 hr. with sodium hydrogen carbonate (0.6 g.). Removal of the acetone followed by the addition of water (5 ml.) and extraction with ether gave cis-β-bromostyrene. Purification of the product by preparative layer chromatography gave cis-β-bromostyrene with a specific activity of 6.8×10^4 dis.min.$^{-1}$ mol.$^{-1}$; which may be compared with the specific activity of cis-β-bromostyrene (ex. Koch Light) 3.9×10^4 dis.min.$^{-1}$ mol.$^{-1}$.

Reaction of [1-^{14}C]Cinnamaldehyde with Tetrachlorobenzyne and Degradation of the Product (V).

[1-^{14}C]Cinnamaldehyde (3 g.) was dissolved in acetonitrile (25 ml.) and stirred at 40-50°, while tetrachloroanthranilic acid (10.0 g.) in acetonitrile (100 ml.) and 3-methylbutyl nitrite (5.5 ml.) in acetonitrile (10 ml.) were added concurrently. The resultant solution was stirred overnight. Removal of the solvent left a red oil (12.8 g.) which was eluted from a column of silica with light petroleum to give 5,6,7,8-tetrachloro-2-H-flaven (V) (1 g., 17%). Three successive crystallisations from petrol gave a material with specific activity 2.73×10^9

dis.min.$^{-1}$ mol.$^{-1}$.

The 2-H-flaven (V) was eluted in light petroleum through a column containing alumina which had been dried at 450° for 12 hr. prior to use. The 5,6,7,8-tetrachloro-4-H-flaven obtained from the column was crystallised from acetone/petrol and had a specific activity of 2.71 x 10^9 dis.min.$^{-1}$ mol.$^{-1}$ Recrystallisation gave a material with specific activity of 2.66 x 10^9 dis.min.$^{-1}$ mol.$^{-1}$ and 2.79 x 10^9 dis.min.$^{-1}$mol.$^{-1}$ for two samples of the same material.

A portion of 5,6,7,8-tetrachloro-4-H-flaven (XV) (352.2 mg.) in acetic acid (20 ml.) and hydrochloric acid (5 ml.) was heated under reflux for 5 min. After allowing the solution to cool to room temperature, water (20 ml.) was added, and the white solid which formed was extracted into chloroform (3 x 25 ml.). Removal of the solvent and azeotropic distillation with benzene left a white solid (XVIII) which was dissolved in ether (30 ml.) and treated with an excess of an ethereal solution of diazomethane. After 30 min. the solvent was removed to leave an oil (XIX), which was dissolved in a mixture of ethanol (15 ml.) and benzene (10 ml.). Hydroxylamine hydrochloride (360 mg.) in ethanol (10 ml.) and pyridine (0.5 ml.) were added and the solution was heated under reflux for 10 min. The oxime (XX) crystallised from the solution and had a specific activity of 2.78 dis.min.$^{-1}$ mol.$^{-1}$

The oxime (XX) (179 mg.) was warmed in a mixture of dry diethyl ether (10 ml.) and dry benzene (10 ml.) until dissolved

and phosphorus pentachloride (0.5 g.) was added and the mixture was heated under reflux for 1.5 hr. Water (20 ml.) was then added dropwise and the organic phase separated. The aqueous layer was further extracted with ether (20 ml.) and the combined organic phases dried and concentrated to leave an oil (XXII) which crystallised on standing. This oil was dissolved in acetic acid (20 ml.) and hydrochloric acid (5 ml.) was added. The solution was heated to reflux for 30 min. and kept at 80° overnight to ensure complete hydrolysis of the amide (XXII). Water (50 ml.) was added to the cold solution and the mixture was extracted with chloroform (3 x 25 ml.). Removal of the solvent and azeotropic distillation with benzene left a pale yellow oil (XXIV) which was dissolved in methanol (50 ml.) and potassium hydroxide (1 g.). The solution was heated under reflux for 1 hr., then concentrated to about 10 ml. Dilute hydrochloric acid (20 ml., 2N.) was added to the cold solution and the mixture was extracted with chloroform (3 x 25 ml.). The combined extracts were washed with water (25 ml.), dried and concentrated to leave a white solid which was crystallised from diethyl ether/light petroleum, and gave the cinnamic acid derivative (XXV) with a specific activity of 2.78 dis.min.$^{-1}$mol.$^{-1}$

A solution of this acid (120 mg.) in chloroform (20 ml.) was treated with ozone for 10 min. at 0° and gave, on removal of the solvent, a pale yellow oil. This was dissolved in formic acid (10 ml.); hydrogen peroxide (5 ml., 98%) was then added and the solution was warmed to initiate the ensuing exothermic reaction. Water (50 ml.) was added to the cold solution and

the mixture was extracted with chloroform (3 x 20 ml.) The combined chloroform extracts were then shaken with a solution of sodium hydroxide (20 ml., 5% x2) and the aqueous phases were separated. The combined alkaline solutions were then acidified with dilute hydrochloric acid and extracted with chloroform (3 x 25 ml.). The combined chloroform extracts were washed with water (20 ml.), dried and concentrated to leave an oil (93 mg.) (XXVII). The oil was dissolved in diethyl ether (20 ml.) and treated with an excess of an ethereal solution of diazomethane. After 30 min. the solvent was removed and the product was purified by preparative layer chromatography using benzene as eluant to give methyl-2-methoxy-tetrachlorobenzoate (XXVIII) (46 mg.), specific activity 2.54×10^{9} dis.min.$^{-1}$ mol.$^{-1}$.

SECTION 2

Some Rearrangement Reactions of 5,6,7,8-Tetrachloro-4-H-flaven

INTRODUCTION

In the previous section a successful degradation of 5,6,7,8-tetrachloro-4-H-flaven was described. As with most problems in chemistry the answer was not achieved immediately. In this section some of the other attempted degradation reactions are described.

As has been previously mentioned[43] oxidation of 2-H-chromen systems was known to be a poor method of cleaving the heterocyclic ring system. We therefore confined our attention to a hydrolytic ring opening. In order that, at a later stage, we could generate an unsaturated centre a number of brominations were attempted and it was these and hydrolysis of the compounds that provided a number of interesting reactions.

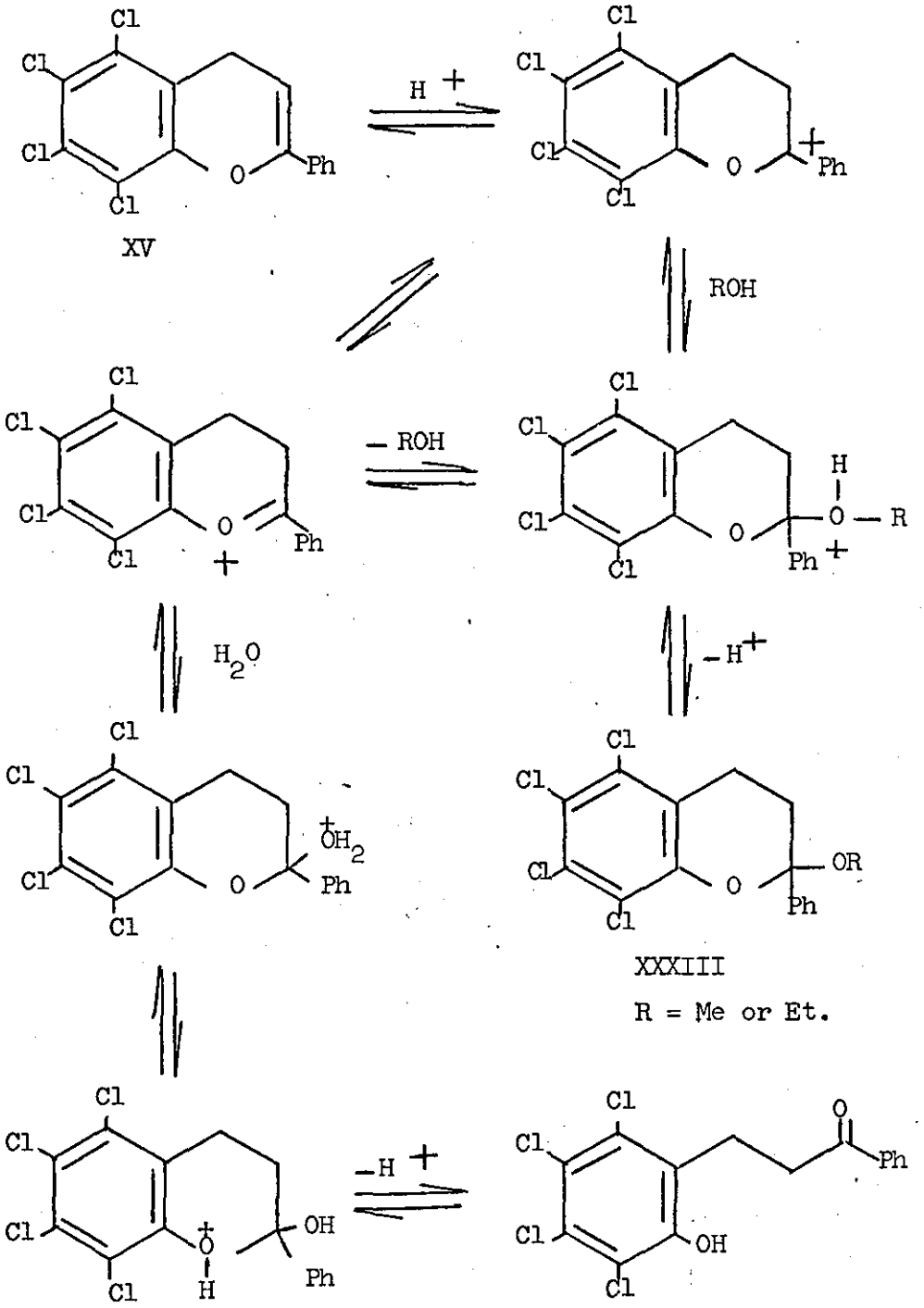
DISCUSSION

The equilibrium which exists between a ketal,hemiketal and ketone is well established.[83] With 5,6,7,8-tetrachloro-4-H-flaven (XV) the addition of an alcohol across the vinyl double bond should generate a ketal (XXXIII);[84] alternatively water would generate the hemiketal (XXXIV). In strong acid either of these should form the ketone (XVIII). Our initial reaction involved heating adduct (XV) in methanolic hydrochloric acid from which was obtained an 80% yield of the ketal (XXXIII, R=Me) (scheme 1). We were also able to show that treating the ketone (XVIII) under similar conditions gave a 78% yield of the ketal (XXXIII, R=Me). When ethanol was used in place of methanol a mixture of the ketal (XXXIII, R=Et) and the ketone (XVIII) was obtained.

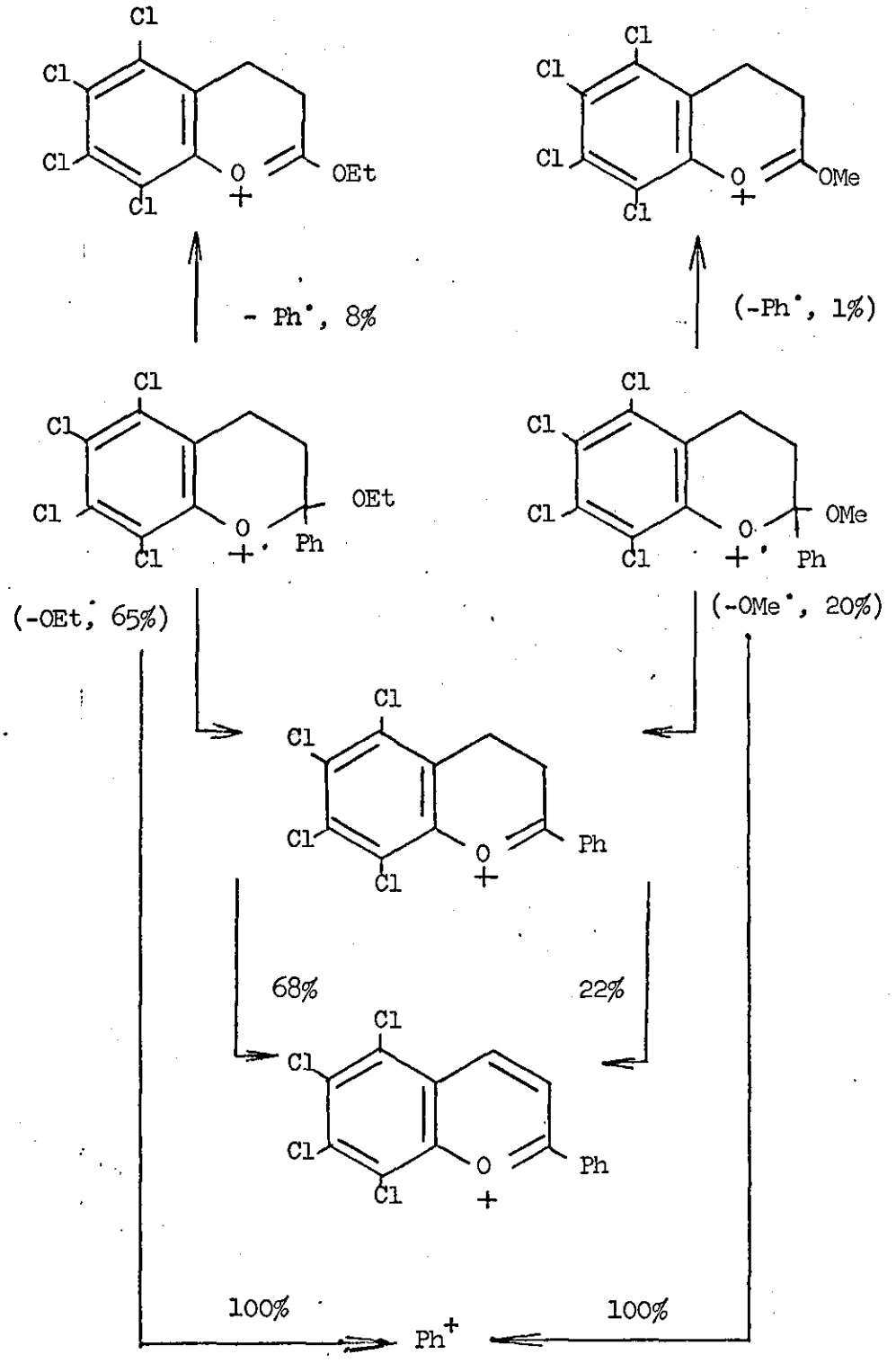
Acid catalysed ring closures of 2-(o-hydroxyphenyl)-ethyl aryl ketones to form the hemiketals and subsequent dehydrations to 4-H-flavens have been reported in the literature.[85] However, we had hoped to force the equilibrium between the open chain form and cyclic hemiketal towards the open chain form. As described in the previous section hydrochloric acid in acetic acid was in fact found to give an almost quantitative yield of the dihydrochalcone (XVIII). Another method of opening a 4-H-flaven to a phenolic dihydrochalcone derivative was described[73b] using hydrogen peroxide in acetic acid. This was found to form the ketone (XVIII) but only in mediocre yield.

The structures of the ketals (XXXIII R=Me and R=Et) were established by elemental analysis and an examination of their i.r., ^{1}H n.m.r., u.v. and mass spectra. The absence of a carbonyl stretching frequency and also of a hydroxy function indicated that the products were not in an open chain form and their respective mass spectra show a similar decomposition pattern (scheme 2) which is in agreement with the proposed structures.

We had, at this stage, an efficient method of opening the 4-H-flaven ring, and our thoughts turned to finding a method of degrading the tetrachlorophenyl side chain. A bromine atom either in the α or β position to the carbonyl group of the compound (XVIII) would provide a precursor to a chalcone derivative, which could then be oxidised to a salicylic acid derivative. The brominating agent which we chose to react with compound (XV) was N-bromosuccinimide. It is known to undergo either a homolytic dissociation to free radicals[86] or a heterolytic dissociation to give bromonium ions.[87] The reaction most often observed with this reagent and simple olefins[86] is an allylic substitution of bromine by a free radical mechanism. The presence of an electron releasing group adjacent to the double bond should, however, increase the tendency towards a polar mechanism with an electrophilic reagent such as positive bromine. Dihydropyran, which may be considered as a model compound for our system, has been shown[88] to react by a polar mechanism to give a 7.6% yield

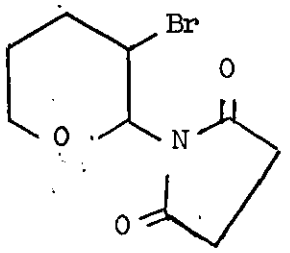

Cl
Cl
Cl
Cl
O
Ph
H +
XV
ROH
− ROH
H
O
R
Ph +
H_2O
OH_2
− H^+
OR
XXXIII
R = Me or Et.
OH
H
−H +
XVIII.

Scheme 1



Scheme 2

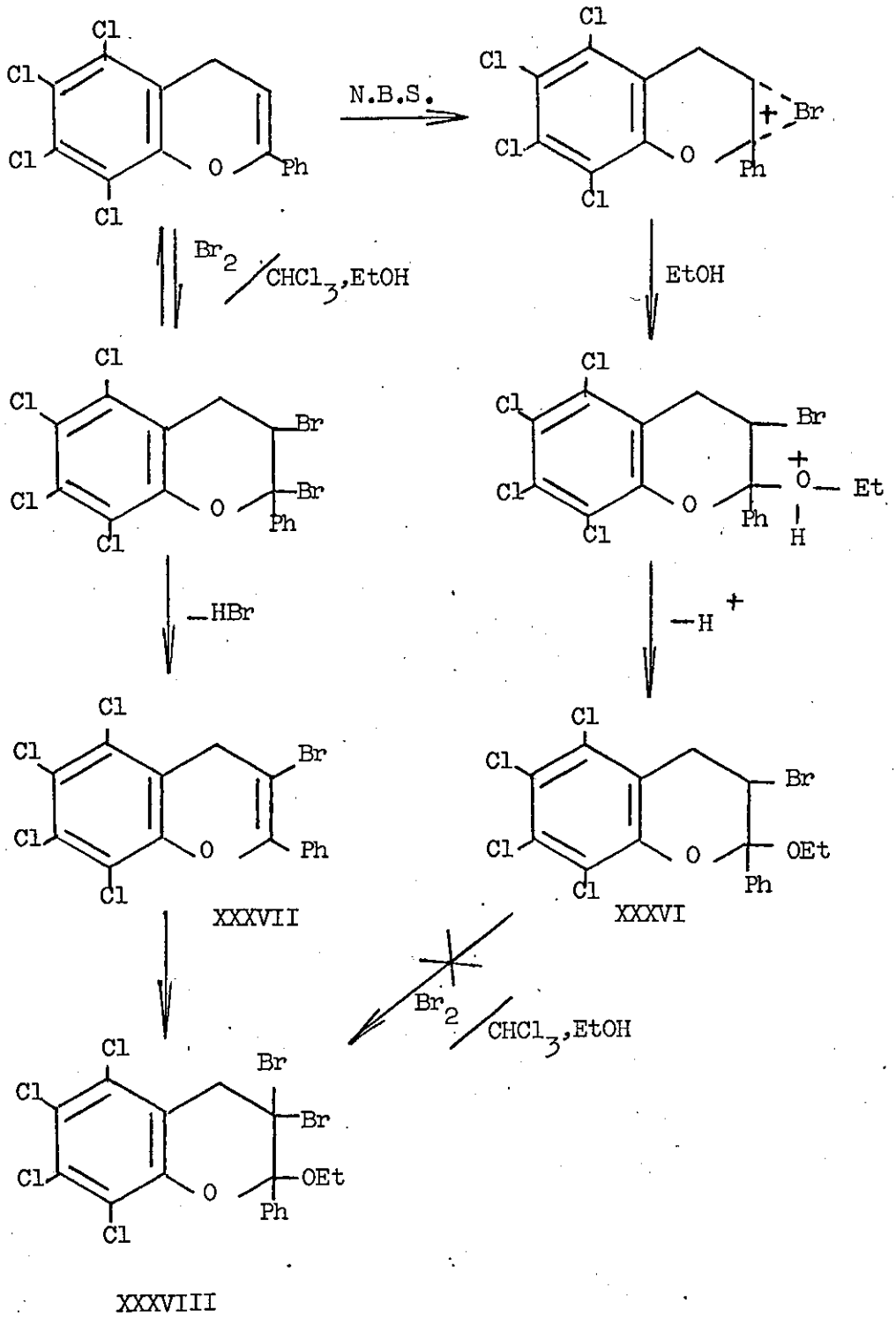
of 3-bromo-5,6-dihydro-4-H-pyran. An adduct (XXXV) formed between the succinimide and the brominated dihydropyran, was also obtained in 7% yield.



XXXV

When the reaction was carried out in ethanol a 58% yield of 2-ethoxy-3-bromotetrahydropyran was isolated.[88b] We treated the compound (XV) with N-bromosuccinimide in chloroform as solvent and obtained an almost quantitative yield of 5,6,7,8-tetrachloro-2-ethoxy-3-bromoflavan (XXXVI) (scheme 3). The structure of this unexpected compound was obtained from the following data. The mass spectrum and elemental analysis confirmed the molecular formula, and the u.v. spectrum was similar to that of the ketal (XXXIII, R=Me). Analysis of the ^{1}H n.m.r. spectrum by first order methods was possible; the methylene protons were in different environments and the spectrum obtained could be analysed as an AMX system with ($J_{gem.}$ = 18.0 Hz., $J_{vic.}$ = 5.0 and 2.5 Hz.). Chemical evidence, which will be presented later, confirmed that the bromine atom was at position-3.

We found no trace of an adduct between the flavan and succinimide; and when the reaction was attempted in dichloroethane only starting material was recovered.


N.B.S.
Br2 / CHCl3, EtOH
EtOH
—HBr
—H+
XXXVII
XXXVI
Br2 / CHCl3, EtOH
XXXVIII

Scheme 3

The mechanism suggested (scheme 3) shows an initial bromonium ion, and we believe that this intermediate is attacked by ethanol (present as a stabiliser in chloroform) to form the product (XXXVI). The alternative mechanism which would involve a carbonium ion at position-2 may be discounted as apparently only one isomer is formed, on the basis of an examination of the ^{1}H n.m.r. spectrum and the sharp melting point of the product.

Scheme 3 also illustrates the reaction which occurred when the 4-H-flaven (XV) was allowed to stand overnight in a solution of chloroform containing bromine. The dibromoketal (XXXVIII) could not be obtained from the bromoketal (XXXVI) under similar conditions. This leads us to speculate that after an initial bromination of the double bond the system is thermally unstable in favour of the unsaturated system. In returning to the unsaturated conjugated state the loss of hydrogen bromide occurs more easily than loss of molecular bromine and hence the intermediate (XXXVII) is formed. Attack on this by electrophilic bromine would generate a bromonium ion which may then be attacked by the ethanol present to yield the dibromoketal (XXXVIII). This should be stable under these faintly acid conditions. We confirmed that this compound contained two bromine atoms by mass spectrometry and elemental analysis gave the molecular formula. The u.v. spectrum was similar to the other ketal spectra with characteristic peaks at 289 and 299 nm. The ^{1}H n.m.r.

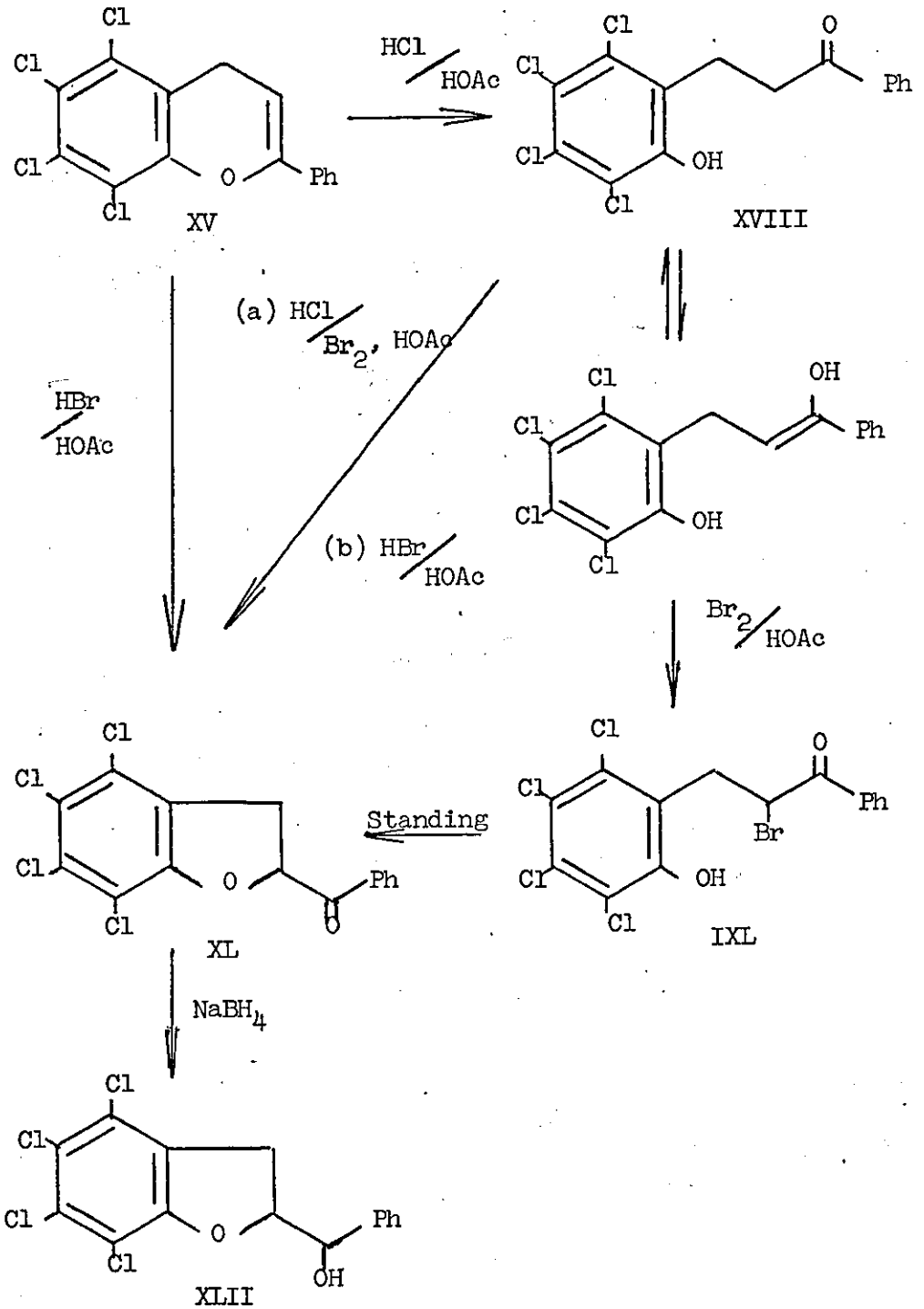
spectrum showed an AB quartet (J = 17.0 Hz., Δ = 0.4 p.p.m.) for the methylene protons.

We also obtained a high yield of the dibromoketal (XXXVIII) when the ketone (XVIII) was allowed to stand in chloroform containing bromine. A possible mechanism for this reaction may be initial dibromination via enol ketone tautomerism and subsequent ring closure to the hemiketal and hence to the ketal. We prefer to discount this mechanism in the light of the reaction of the ketone (XVIII) with bromine in acetic acid. The only product we obtained was the α-bromoketone (IXL) (scheme 4) in 98% yield. No dibromination had occurred as would be expected if the above mechanism were correct. An alternative mechanism involves the initial ring closure to the hemiketal (XXXIV), an equilibrium system is known to exist,[85] and dehydration of this would return us to the 4-H-flaven which could react as exemplified in scheme 3. We have no evidence that this mechanism is operating other than analogy with the formation of 4-H-flaven where sodium sulphate[85a] or acetic anhydride[85b] will dehydrate the hemiketal intermediate.

The structure of the α-bromoketone (IXL) was established from the following data. Elemental analysis and mass spectrometry confirmed the molecular formula. The bromine atom was shown to be α to the carbony group from an examination of the i.r. spectrum, the carbonyl stretching frequency (1682 cm.$^{-1}$) has been shifted to higher energy compared to the non-brominated ketone (XVIII) (C=O, 1770 cm.$^{-1}$). The ^{1}H n.m.r. spectrum showed one

exchangeable proton in the aromatic region, as expected for the phenolic proton, a two proton doublet (τ 6.31), and a methine triplet (τ 4.38). This compound was unstable and was found to dehydrobrominate readily to form a dihydrobenzofuran derivative (XL) (scheme 4). The formation of dihydrobenzofurans is well documented in the literature,[43c] and a method often employed has been an acid catalysed elimination of hydrogen bromide to effect the ring closure.[89] The treatment of the ketone (XVIII) with bromine in acetic acid containing hydrochloric acid, or alternatively with hydrobromic acid in acetic acid, resulted in the formation of the dihydrobenzofuran (XL). Hydrobromomic acid in acetic acid was also found to react with the 4-H-flaven (XV) to give a mixture of the ketone (XVIII) and the dihydrobenzofuran (XL). There is sufficient free bromine in hydrobromic acid to α-brominate the ketone (XVIII).

We established the structure of the dihydrobenzofuran (XL) from the following data. Elemental analysis and the mass spectrum confirmed the molecular formula. The i.r. spectrum showed a carbonyl absorption at 1687 $cm.^{-1}$ characteristic of an aromatic ketone. The ^{1}H n.m.r. spectrum was analysed by first order methods. The methine proton at position-2 appeared as two doublets (J = 8.0 Hz. and 10.0 Hz.) centred at τ 3.90, but the methylene protons did not appear to be geminally coupled, only two overlapping doublets were observed (τ 6.31). When the ketone (XVIII) was heated under reflux with bromine in acetic anhydride containing deuterium chloride a 72% yield of the [2-^{2}H]-dihydrobenzofuran (XLI) was obtained containing 98% [^{2}H] by mass spectrometry. The ^{1}H n.m.r. spectrum of this


Cl
Cl
Cl
Cl
O
Ph
XV
HCl
HOAc
Cl
Cl
Cl
O
Ph
OH
XVIII
(a) HCl
Br2, HOAc
HBr
HOAc
(b) HBr
HOAc
Cl
Cl
Cl
OH
Ph
OH
Br2
HOAc
Cl
Cl
Cl
O
Ph
Br
OH
IXL
Standing
Cl
Cl
Cl
O
Ph
XL
NaBH4
Cl
Cl
Cl
O
Ph
OH
XLII

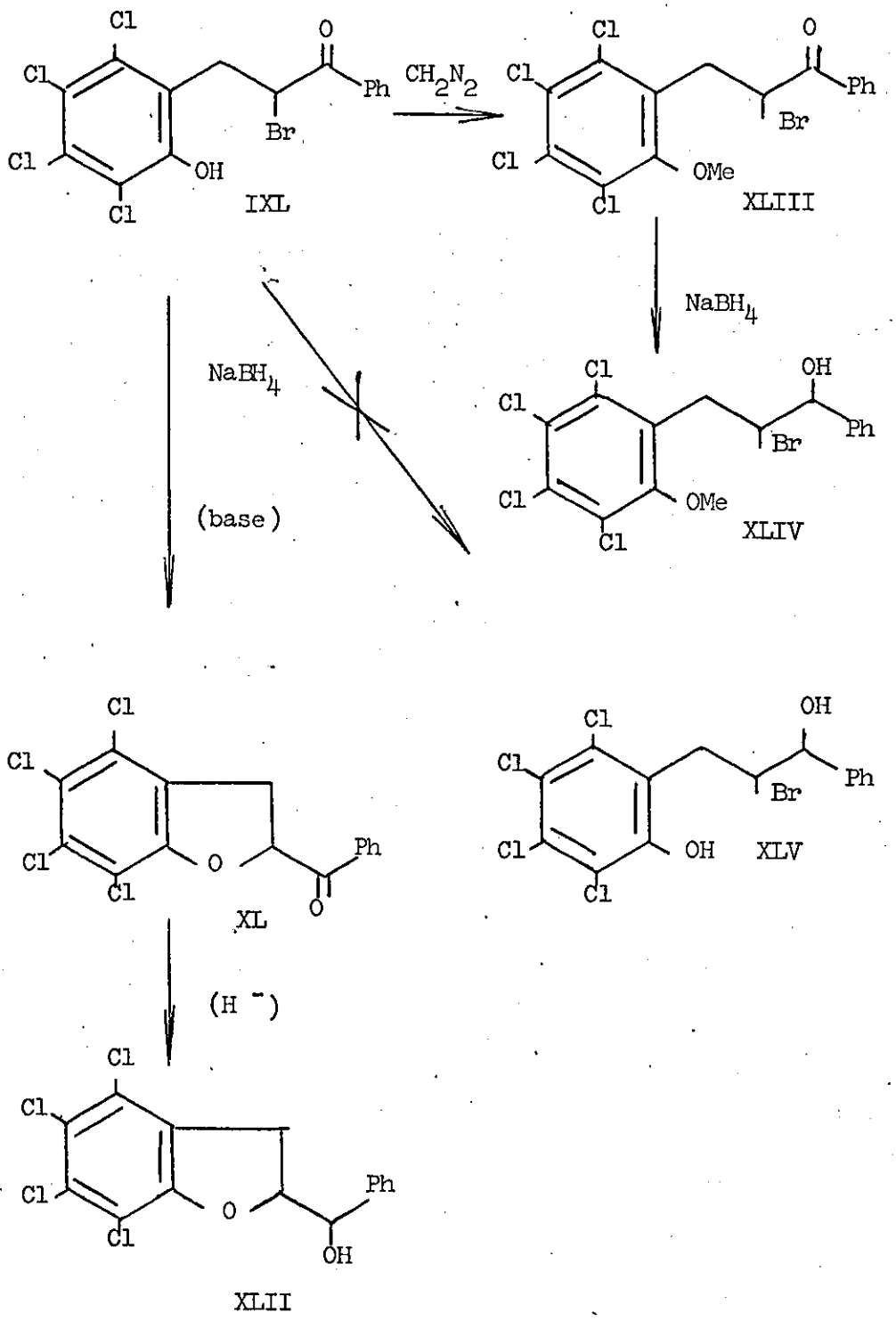
Scheme 4

compound showed five aromatic protons and a singlet (τ 6.33) for the two protons at position-3. Further, spin-spin decoupling experiments on the ^{1}H n.m.r. spectrum of the dihydrobenzofuran (XL) showed that when the methine proton was irradiated the methylene protons appeared as a singlet and not a geminally coupled doublet.

That the dihydrobenzofuran (XL) is formed is further confirmation that the position of bromination of the ketone (XVIII) is α to the carbonyl group. This argument may also be extended to the position of bromination for the reaction involving N-bromosuccinimide. When either the α-bromoketone (IXL) or the bromoketal (XXXVI) were heated under reflux in a solution of acetic anhydride containing concentrated hydrochloric acid high yields of the dihydrobenzofuran (XL) were obtained.

Reduction of the dihydrobenzofuran (XL) with sodium borohydride gave the expected alcohol (XLII).

In the formation of the dihydrobenzofuran (XL) the intermediate α-bromoketone (IXL) which we isolated, was studied further (scheme 5). Methylation of the phenol with diazomethane followed by treatment with sodium borohydride gave the alcohol (XLIV), whose molecular formula was confirmed by accurate mass measurement. The ^{1}H n.m.r. spectra of the alcohol (XLIV) and the intermediate methoxyketone (XLIII), which could be isolated, could not be analysed by first order methods. The i.r. spectrum of the compound (XLIII) showed a carbonyl absorption at 1690 $cm.^{-1}$ which is


Cl
Cl
Cl
Cl
O
Ph
Br
OH
IXL
CH_2N_2
OMe
XLIII
$NaBH_4$
(base)
XLIV
OH
XL
(H^-)
XLII
XLV

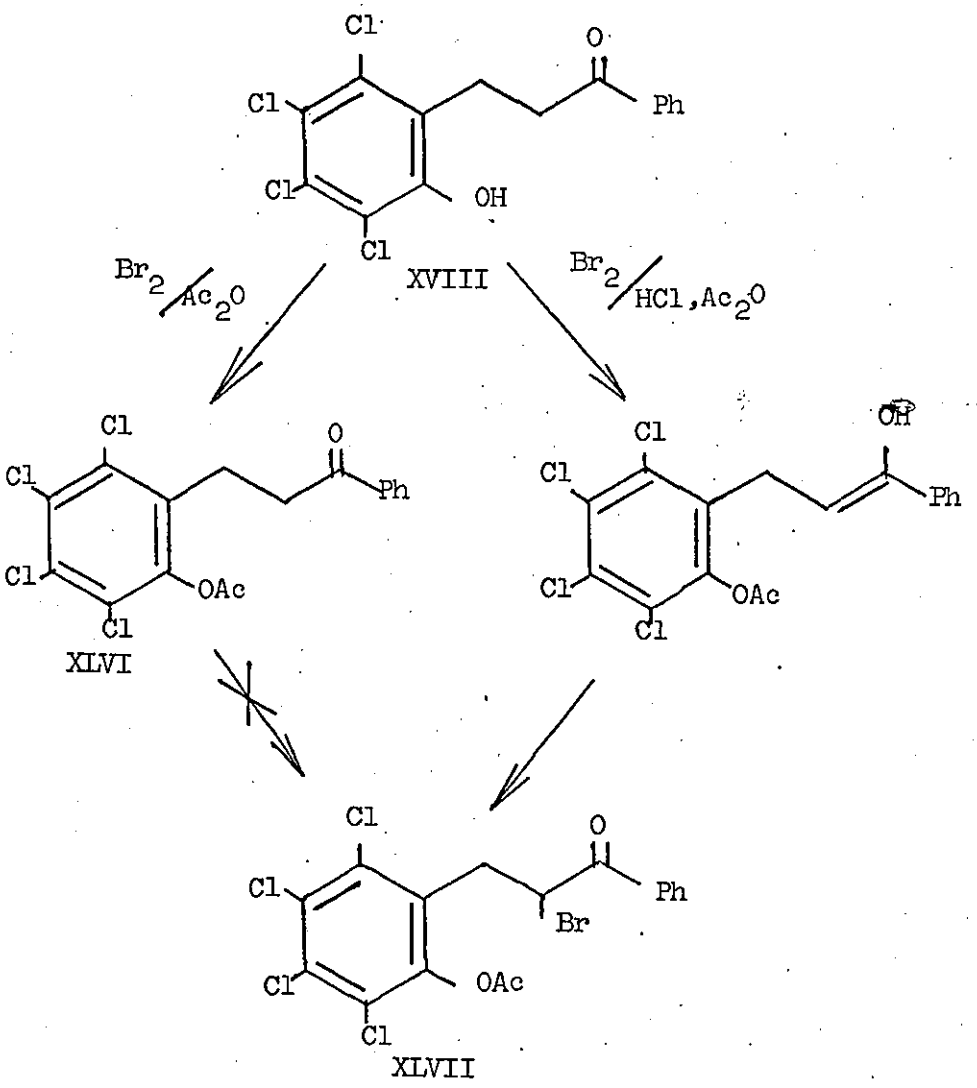
Scheme 5

higher than for the phenolic-α-bromoketone (IXL) (C=O, 1682 cm.$^{-1}$) indicating that there may be some hydrogen bonding from the phenol to the ketone.

The α-bromoketone (IXL) was also treated with sodium boronhydride in an attempt to form a phenolic alcohol (XLV). The mass spectrum of the product showed that bromine was not present. Elemental analysis indicated that the molecular formula was $C_{15}H_{10}Cl_4O_2$ and the i.r. spectrum confirmed that the carbonyl function had been reduced to an alcohol. The ^{1}H n.m.r. could not be analysed by first order methods, but was identical, as was the other data, with that obtained for the alcohol (XLII). The ring closure of the α-bromoketone (IXL) to form the dihydrobenzofuran (XL) is obviously extremely rapid under basic conditions as well as in an acidic medium.

Enol ketone tautomerism may be either base or acid catalysed;[83] we found that α-bromination of the ketone (XVIII) required the presence of acid. We treated the ketone (XVIII) with a solution of acetic anhydride containing bromine and obtained only the acetate (XLVI) in 95% yield (scheme 6), the molecular formula of which was confirmed by mass spectrometry and elemental analysis, and the i.r. spectrum indicated an ester carbonyl (C=O, 1770 cm.$^{-1}$) and an aromatic ketone (C=O, 1680 cm.$^{-1}$). The ^{1}H n.m.r. spectrum showed a four proton singlet (τ 6.84), which has been found with similar compounds (XIX and XX) described in Section 1.

When the reaction was repeated and a small amount of

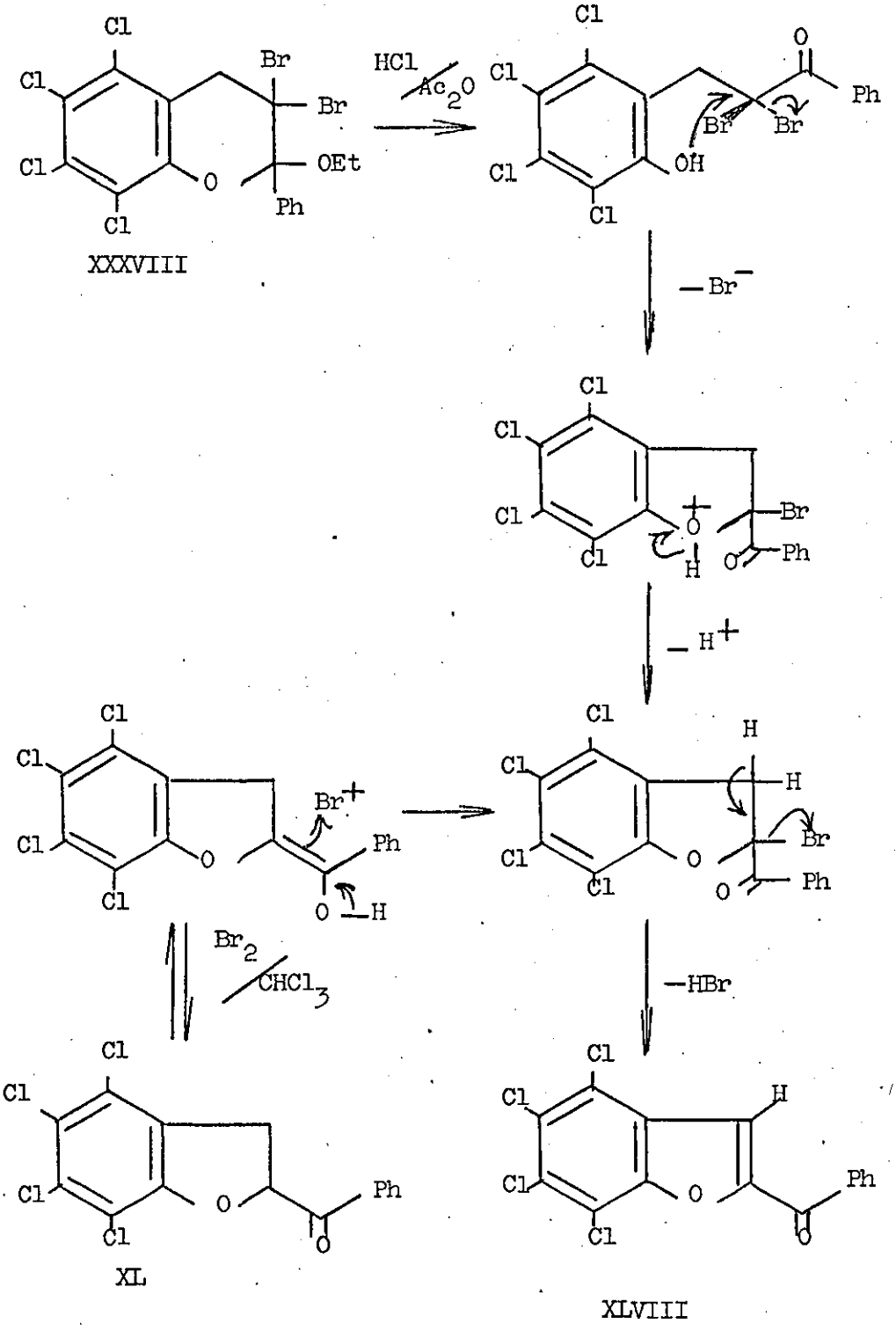

Cl
Cl
Cl
Cl
O
Ph
OH
XVIII
Br_2 / Ac_2O
Br_2 / HCl, Ac_2O
Cl
Cl
Cl
Cl
O
Ph
OAc
XLVI
Cl
Cl
Cl
Cl
OH
Ph
OAc
Cl
Cl
Cl
Cl
O
Ph
Br
OAc
XLVII

Scheme 6

dilute hydrochloric acid was present in the reaction solution, the α-bromoketo-acetate (XLVII) was obtained (scheme 6) together with the dihydrobenzofuran (XL). As expected further treatment of the α-bromoketo-acetate with acetic acid containing hydrochloric acid did not give the dihydrobenzofuran (XL) and unchanged starting material was recovered. The ^{1}H n.m.r. spectrum of compound (XLVII) was analysed by first order methods for an AMX system with (J_{gem} = 15.0 Hz., $J_{vic.}$ = 8.0 Hz. and 6.0 Hz.).

Having examined in some detail the bromination of the ketone (XVIII) and the subsequent cyclisation by loss of hydrogen bromide we turned our attention to the dibromoketal (XXXVIII). This compound, when reacted with a solution of acetic anhydride and hydrochloric acid gave a poor yield of 2-benzoyl-4,5,6,7-tetrachlorobenzofuran (XLVIII). We found however that by allowing the dihydrobenzofuran (XL)to react in a solution of chloroform containing bromine, a high yield of the benzofuran was obtained (scheme 7).

The dibromoketal (XXXVIII) also reacted with methanolic potassium hydroxide and we obtained the expected 2-H-flaven (IL) (scheme 8). As there was now an unsaturated centre present nucleophilic attack by the oxygen lone pair to eliminate bromide to form a benzofuran should not occur. We treated the 2-H-flaven (IL) under the usual acid in acetic anhydride conditions and obtained a mixture of products, the major one of which was isolated and shown to be the hemiketal



XXXVIII

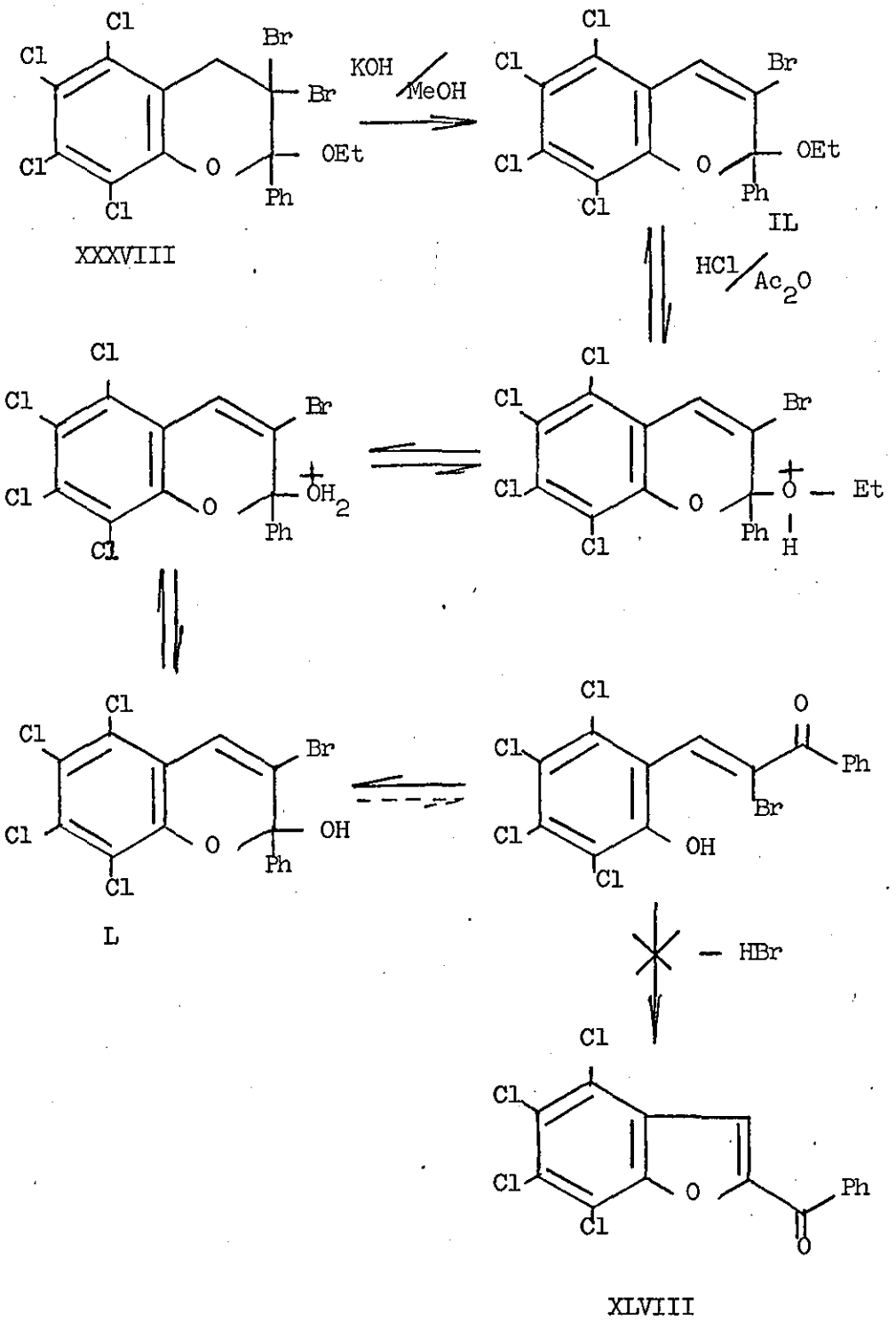
XL

XLVIII

Scheme 7

(L)(scheme 8). The other minor products were not identified. As anticipated the benzofuran (XLVIII) was not formed, and in the absence of this driving force the equilibrium between ketone and hemiketal can be seen to firmly favour the cyclic hemiketal form.

None of these derivatives appeared to be useful intermediates in the degradation of the ketone (XVIII) to a salicylic acid derivative; and as at this time the degradation *via* the oxime (XX) was successful we left this particular aspect of the work.


Cl
Br
Cl
Br
KOH
MeOH
OEt
Cl
O
Ph
Cl
XXXVIII
IL
HCl
Ac2O
OH2
Et
H
L
OH
HBr
XLVIII

Scheme 8

EXPERIMENTAL

General Methods

General methods are as described in section 1 (experimental) with the following exception. U.v. spectra are for methanol solutions.

Reaction of 5,6,7,8-tetrachloro-4-H-flaven (XV) with Methanolic Hydrochloric acid

A solution of the compound (XV) (825 mg.) in methanol (20 ml.) and chloroform (50 ml.) containing concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. The solution gave, after cooling, 5,6,7,8-tetrachloro-2-methoxyflavan (XXXI, R=Me) (717 mg., 80%), m.p. 156-158° (from acetone).

(Found: C, 50.9; H, 3.2%; M[mass spectrometry] 378. $C_{16}H_{12}Cl_4O_2$ requires C, 50.85; H, 3.2%; M 378).

τ 2.25-2.75 (m, 3H), 6.98 (s, 3H), 6.9-8.5 (m, 4H).

$\lambda_{max.}$ 216 ($\log_{10}\varepsilon$ 4.63), 228 (3.95), 290 (3.12), 299 (3.20) nm.

$\nu_{max.}$ 2980, 2950, 2840, 1565, 1545, 1452, 1428, 1400, 1355, 1325, 1270, 1250, 1200, 1175, 1150, 1058, 1045, 1030, 1012, 930, 905, 880, 785, 775, 702 $cm.^{-1}$

Reaction of the Compound (XV) with Ethanolic Hydrochloric acid

A solution of the compound (XV) (160 mg.) in ethanol (20 ml.) and chloroform (30 ml.) containing concentrated hydrochloric acid (2.5 ml.) was heated under reflux for 5 min.

Water (10 ml.) was added to the cold solution, the chloroform layer separated and the aqueous phase further extracted with chloroform (2 x 10 ml.). The combined extracts were washed with water, dried and concentrated to leave an oil, which on examination by thin layer chromatography showed the presence of two products. Separation by preparative layer chromatography gave:

(a) 5,6,7,8-tetrachloro-2-ethoxyflavan (XXXIII, R=Et) (46 mg., 26%), m.p. 124-125° (from benzene:light petroleum 1:1). (Found: C, 52.2; H, 3.5%; M [mass spectrometry] 392. $C_{17}H_{14}Cl_4O_2$ requires C, 52.05; H, 3.6%; M 392).

τ 2.25-2.75 (m, 5H), 6.53 (q [J = 7.0 Hz.], 2H), 6.9 - 8.5 (m, 4H), 8.80 (t[J = 7.0 Hz.], 3H).

$\nu_{max.}$ 2980, 2950, 1550, 1430, 1400, 1352, 1268, 1245, 1200, 1156, 1056, 1020, 970, 930, 885, 770, 705 $cm.^{-1}$

and (b) Phenyl-2'-(2-hydroxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XVIII) (40 mg., 23%).

Reaction of the ketone (XVIII) with Methanolic hydrochloric acid

A solution of the ketone (XVIII) (50 mg.) in methanol (20 ml.) and chloroform (5 ml.) containing concentrated hydrochloric acid (5 ml.) was heated under reflux for 15 min. Water (10 ml.) was added to the cold solution and the chloroform layer separated. The aqueous phase was further extracted with chloroform (2 x 10 ml.). The combined extracts were dried and concentrated to leave an oil which was purified by preparative layer chromatography to give 5,6,7,8-tetrachloro-2-methoxyflavan (XXXIII, R=Me) (40 mg., 78%).

Reaction of the compound (XV) with Hydrogen peroxide

Hydrogen peroxide (0.5 ml., 30%) was added to a warm solution of the compound (XV) in acetic acid (10 ml.) and chloroform (5 ml.), and the solution was allowed to stand for 30 min. The solution was then neutralised by the cautious addition of sodium hydroxide solution (2N.) and extracted with chloroform (2 x 10 ml.). The combined extracts were dried and concentrated to leave a solid which was crystallised from benzene to give the ketone (XVIII) (50 mg., 21%).

Reaction of the Compound (XV) with N-bromosuccinimide

Method I. A solution of the compound (XV) (140 mg.) in chloroform* containing N-bromosuccinimide (72 mg.) was heated under reflux for 1 hr. When cool water (10 ml.) was added, the chloroform layer separated, dried and concentrated. Separation of the product from succinimide by preparative layer chromatography gave: 5,6,7,8-tetrachloro-2-ethoxy-3-bromoflavan (XXXVI) (198 mg. 98%), m.p. 143-144° (from light petroleum).

(Found: C, 43.25; H, 2.85%; M[mass spectrometry] 470 $C_{17}H_{13}Br\,Cl_4O_2$ requires C, 43.60; H, 2.75%; M 470).

τ 2.2-2.7 (m, 5H), 5.52 (AMX q [J_{XM} = 5.0 Hz., J_{XA} = 2.5 Hz],1H) 6.18 (AMX q [J_{MX} = 5.0 Hz., J_{MA} = 18.0 Hz.], 1,H), 6.60 (AMX q [J_{AX} = 2.5 Hz., J_{AM} = 18.0 Hz.], 1H).

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* Chloroform contains approximately 5% ethanol to act as a stabilising agent.

$\lambda_{max.}$ 216 ($\log_{10}\varepsilon$ 4.31), 288 (2.78), 298 (2.89) nm.

$\nu_{max.}$ 2990, 1545, 1450, 1418, 1395, 1335, 1310, 1240, 1187, 1160, 1150, 1055, 1040, 1005, 940, 770, 700 cm.$^{-1}$

Reaction of the Compound (XV) with Bromine in chloroform

A solution of the compound (XV) (201 mg.) in chloroform * (20 ml.) containing bromine (1 ml.) was allowed to stand at room temperature for 2½ days. Removal of solvent and azeotropic distillation with benzene left a pale yellow solid. Crystallisation from light petroleum gave: 5,6,7,8-tetrachloro-2-ethoxy-3,3-dibromoflavan (XXXVIII) (310 mg., 94%), m.p. 173-174°.

(Found: C, 37.2; H, 2.15%; M [mass spectrometry] 548. $C_{17}H_{12}Br_2Cl_4O_2$ requires C, 37.45; H, 2.25 %; M 548).

τ 1.95 -2.65 (m, 5H), 5.77 (AB q. [J = 17.0 Hz., δ = 0.4 p.p.m.], 2H), 6.56 (q [J = 7.0 Hz.], 2H), 8.98 (t [J = 7.0 Hz.], 3H).

$\lambda_{max.}$ 222 ($\log_{10}\varepsilon$ 4.17), 289 (3.12), 299 (3.18) nm.

$\nu_{max.}$ 2990, 2940, 2900, 1550, 1450, 1420, 1390, 1303, 1245, 1198, 1130, 1100, 1080, 1032, 1010, 970, 958, 885, 874, 790, 765, 740, 720, 700, 675, 660 cm.$^{-1}$

Reaction of the ketone (XVIII) with Bromine in Chloroform

A solution of the ketone (XVIII) (142 mg.) in chloroform * (10 ml.) containing bromine (1 ml.) was allowed to stand at room temperature for 16 hr. Removal of the solvent and crystallisation from light petroleum gave the product (XXXVIII)

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* See footnote to page 103

(210 mg., 95%).

Attempted Reaction of the Ketal (XXXVI) with Bromine in Chloroform

A solution of the ketal (XXXVI) (50 mg.) in chloroform (20 ml.) containing bromine (0.5 ml.) was allowed to stand at room temperature for 24 hr. Removal of the solvent gave unchanged starting material (48 mg.).

Reaction of the Ketone (XVIII) with Bromine in Acetic acid

A solution of the ketone (XVIII) (103 mg.) in acetic acid (3 ml.) containing bromine (1 ml.) was allowed to stand at room temperature for 15 hr. Removal of the acetic acid by azeotropic distillation with benzene left an oil which, after crystallisation from light petroleum/diethyl ether gave : phenyl-1'-bromo-2'-(2-hydroxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (IXL) (120 mg., 98%) m.p. 152-153°.

(M [mass spectrometry] 442. $C_{15}H_9BrCl_4O$ requires M 442).

τ 1.9 - 2.6 (m, 6H [one exchangeable by D_2O]), 4.38 (t, [J = 7.0 Hz.], 1H), 6.31 (d, [J = 7.0 Hz.], 2H).

$\lambda_{max.}$ 217 ($\log_{10} \epsilon$ 4.76), 240 (438), 295 (3.63), 304 (3.65) nm.

$\nu_{max.}$ 3450-3350, 1682, 1598, 1565, 1450, 1417, 1390, 1290, 1170, 984, 907, 835, 740, 720, 700, 680, 655 $cm.^{-1}$

Reaction of the Ketone (XVIII) with Bromine in the presence of Mineral acid

Method I. A solution of the ketone (XVIII) (50 mg.), bromine (0.5 ml.) and concentrated hydrochloric acid (5 ml.) in acetic acid (5 ml.) was heated under reflux for 2 min., poured

onto ice (20 g.),and extracted with chloroform (3 x 10 ml.). The combined extracts were washed with water, dried and concentrated to leave an oil which was purified by preparative layer chromatography and gave: 2-benzoyl-4,5,6,7-tetrachloro-2,3-dihydrobenzofuran (XL) (36 mg., 73%), m.p. 145-146° (from light petroleum:diethyl ether, 3:1).

(Found: C, 49.9; H, 2.25%; M [mass spectrometry] 362. $C_{15}H_8Cl_4O_2$ requires C, 49.75; H, 2.25%; M 362).

τ 1.7-2.6 (m, 5H), 3.90 (d x d) [J = 8.0 Hz., J = 10.0 Hz.], 1H), 6.31 (d [J = 8.0 Hz.], 6.34 (d [J = 10.0 Hz.], 1H).

$\lambda_{max.}$ 223 ($\log_{10}\varepsilon$ 4.24), 241 (4.24), 294 (3.55), 304 (358) nm.

$\nu_{max.}$ 1687, 1600, 1450, 1417, 1390, 1255, 1235, 1175, 1015, 984, 915, 785, 687 $cm.^{-1}$

Method II. A solution of the ketone (XVIII) (73 mg.) in acetic acid (10 ml.) containing hydrobromic acid (5 ml., 48%) was heated under reflux for 15 min. Work up as in Method I gave the dihydrobenzofuran (XL) (24 mg., 35%).

Reaction of the Compound (XV) with Hydrobromic acid in Acetic acid

The procedure was as in Method II using the compound (XV) (180 mg.) and gave two products:

(a) the ketone (XVIII) (130 mg., 64%), and

(b) the dihydrobenzofuran (XL) (44 mg., 22%).

Reaction of the α-Bromoketone (IXL) with Hydrochloric acid in Acetic Anhydride

Concentrated hydrochloric acid (5 ml.) was added dropwise to a solution of the α-bromoketone (IXL) (28 mg.) in acetic anhydride (5 ml.) and the solution heated under reflux for 2 min., poured onto ice (20 g.), and extracted with chloroform (3 x 10 ml.). The combined extracts were washed with water and dried. Azeotropic distillation with benzene left an oil which was crystallised from light petroleum/diethyl ether to give the dihydrobenzofuran (XL) (21 mg., 93%).

Reaction of the Bromoketal (XXXVI) with Hydrochloric acid in Acetic Anhydride

The procedure was as described above using the ketal (XXXVI) (218 mg.), and gave the dihydrobenzofuran (XL) (176 mg., 90%).

Reaction of the Ketone (XVIII) with Bromine in the presence of Deuterium Chloride

The procedure was as described above using the ketone (XVIII) (126 mg.) and deuterium chloride (1.8 ml., 20% in D_2O) and gave 2-benzoyl-[2-^{2}H]-4,5,6,7-tetrachloro-2,3-dihydrobenzofuran (XLI), (87 mg., 72%) [^{2}H = 98% by mass spectrometry]

τ 1.85-2.6 (m, 5H), 6.33 (b.s., 2H).

Reduction of the Dihydrobenzofuran (XL) with Sodium Borohydride

A solution of sodium borohydride (90 mg.) in sodium hydroxide (5 ml., 2N) was added to a solution of the dihydrobenzofuran (XL) (150 mg. in warm methanol (50 ml.). The solution was allowed

to stand at room temperature for 3 hr. before neutralisation with hydrochloric acid (2N). The solution was extracted with chloroform (2 x 20 ml.) and the combined extracts washed with water, dried and concentrated to leave an oil, which was purified by preparative layer chromatography and gave :

2-(4,5,6,7-tetrachloro-2,3-dihydrobenzofuryl)phenylcarbinol (XLII) (67 mg., 44%), m.p. 133-134° (from light petroleum: diethyl ether 5:1).

(Found: C, 49.25; H, 2.8%; M [mass spectrometry] 364.

$C_{15}H_{10}Cl_4O_2$ requires C, 49.5; H, 2.8%; M 364).

τ 2.62 (s, 5H) 4.7-5.3 (m, 2H), 6.92 (d [J = 8.5 Hz.], 2H), 7.10 (b.s., 1H [exchangeable with D_2O]).

$\lambda_{max.}$ 216 ($\log_{10}\varepsilon$ 4.47), 239 (4.34), 281 (3.03) nm.

$\nu_{max.}$ 3300-3000, 1593, 1422, 1388, 1180, 1050, 1025, 988, 855, 830, 785, 750, 694 $cm.^{-1}$

Preparation of 1-Phenyl-2-bromo-3-(2'-hydroxy-3',4',5',6'-tetrachlorophenyl)-1-propanol(XLIV)

An excess of an ethereal solution of diazomethane was added to a solution of the α-bromoketone (IXL) (188 mg.) in diethyl ether (10 ml.) and methanol (0.5 ml.). Removal of the solvents left an oil which was crystallised from light petroleum/diethyl ether and gave the methoxy derivative (XLIII) (199 mg. 89%) m.p. 105-106°.

τ 1.9-2.6 (m, 5H), 4.35 (ABX q [$J_{AX} + J_{BX}$ = 8.0 Hz.], 1H), 5.9-6,5 (m, 2H), 6.10 (s, 3H).

$\lambda_{max.}$ 216 ($\log_{10}\varepsilon$ 4.68), 240 (4.27), 294 (3.54), 303 (3.53) nm.

$\nu_{max.}$ 1690, 1600, 1453, 1420, 1390, 1235, 1175, 1015, 985, 910, 785, 690 cm.$^{-1}$

Sodium borohydride (400 mg.) was added to a solution of compound (XLIII) (650 mg.) in chloroform (10 ml.) and methanol (20 ml.). After 30 min. the solution was neutralised by the careful addition of sulphuric acid (2N) and extracted with chloroform (3 x 30 ml.). The combined extracts were washed with water, dried, and concentrated to leave an oil which was purified by preparative layer chromatography and gave: 1-phenyl-2-bromo-3-(2'-hydroxy-3',4',5',6'-tetrachlorophenyl)-1-propanol (XLIV) (200 mg., 31%) m.p. 88-89° (from light petroleum : diethyl ether 2:1).

(Found $^{M}/_{e}$ 455.8863. $C_{16}H_{13}{}^{79}Br^{35}Cl_4O_2$ requires $^{M}/_{e}$ 455.8853).

τ 2.66 (s, 5H), 4.8-5.45 (m, 2H), 6.28 (s, 3H), 6.5 - 7.1 (m, 2H), 7.0 (b.s., 1H [exchangeable by D_2O]).

$\nu_{max.}$ ($CHCl_3$) 3600-3500, 1595, 1450, 1420, 1375, 1170, 1016, 985, 905, 695 cm.$^{-1}$

Attempted Reduction of the α-Bromoketone (IXL) with Sodium Borohydride

Sodium borohydride (6 mg.) was added to a solution of the α-bromoketone (IXL) (130 mg.) in methanol (10 ml.) and the solution was allowed to stand at room temperature for 15 min. The solution was neutralised by the careful addition of hydrochloric acid (0.1N) and concentrated before extracting with chloroform (2 x 10 ml.). The combined extracts were washed with water, dried, and concentrated to leave an oil

which was purified by thin layer chromatography and gave the compound (XLII) (50 mg., 38%), m.p. 133-134° (from light petroleum, diethyl ether).

(Found: C, 49.7; H, 2.8% M [mass spectrometry] 364.

$C_{15}H_{10}Cl_4O_2$ requires C, 49.5; H, 2.75%; M 364).

^1H n.m.r., u.v., and i.r. spectra identical to that of compound (XLII) derived from the dihydrobenzofuran (XL).

Reaction of the Ketone (XVIII) with Bromine in Acetic Anhydride

A solution of the ketone (XVIII) (57 mg.) in acetic anhydride (2 ml.) containing bromine (0.1 ml.) was swirled at room temperature for 10 min. Removal of the co-reactants by azeotropic distillation with benzene left an oil which, upon crystallisation from light petroleum, gave : phenyl-2'-(2-acetoxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XLVI) (60 mg., 95%) m.p. 104-106°.

(Found: C, 50.35; H, 3.2%; M [mass spectrometry] 406.

$C_{17}H_{12}Cl_4O_3$ requires C, 50.3; H, 3.0%; M 406).

τ 1.95-2.6 (m, 5H), 6.84 (s, 4H), 7.66 (s, 3H).

$\nu_{max.}$ 1770, 1680, 1600, 1449, 1392, 1370, 1205, 1271, 1018, 878, 748, 740, 683 $cm.^{-1}$

Reaction of the Ketone (XVIII) with Bromine in Acetic Anhydride containing Hydrochloric acid

Hydrochloric acid (1 ml., 20%) was added to a solution of the ketone (XVIII) (127 mg.) in acetic anhydride (2 ml.) containing bromine (0.1 ml.) and the solution was heated under reflux for 2 min. before ice/water (10 ml.) was added. The aqueous mixture was extracted with chloroform (3 x 10 ml.) and

the combined extracts were washed with water and concentrated. After azeotropic distillation with benzene the oil which was left was separated into two major products by preparative layer chromatography, and gave in order of decreasing R_f value:

(a) Phenyl-1'-bromo-2'-(2-acetoxy-3,4,5,6-tetrachlorophenyl)-ethyl ketone (XLVII) (67 mg., 39%), m.p. 89-90° (from light petroleum).

(Found: C, 42.65;H,2.45%; M [mass spectrometry] 484.

$C_{17}H_{11}Br\ Cl_4O_3$ requires C, 42.1; H, 2.3%; M 484).

τ 1.9-2.65 (m, 5H), 4.49 (AMX q. [J_{XM} = 8.0 Hz., J_{XA} = 6.0 Hz.], 1H), 6.37 (AMX o. [J_{MX} = 8.0 Hz., J_{AX} = 6.0 Hz., J_{AM} = 15.0 Hz.], 2H), 7.60 (s, 3H).

$\nu_{max.}$ 1787, 1693, 1600, 1450, 1435, 1392, 1379, 1358, 1306, 1230, 1198, 1155, 1013, 948, 862, 826, 763, 720, 680 cm.$^{-1}$ and

(b) The dihydrobenzofuran (XL) (20 mg., 15%).

Reaction of the Dibromoketal (XXXVIII) with Hydrochloric acid in Acetic Anhydride

Concentrated hydrochloric acid (2 ml.) was added to a solution of the dibromoketal (XXXVIII) (120 mg.) in acetic anhydride (2 ml.) and the mixture was heated under reflux for 30 min. Water (10 ml.) was added to the cold solution which was then extracted with chloroform (2 x 10 ml.). The combined extracts were washed with water, dried, and concentrated to leave an oil which was shown to contain two compounds by thin layer chromatography. Separation by preparative layer chromatography gave, in order of decreasing R_f :

(a) 2-benzoyl-4,5,6,7-tetrachlorobenzofuran (XLVIII) (17 mg., 22%) m.p. 141-143° (from ethanol).

(Found: C, 50.8; H, 1.85%; M [mass spectrometry] 360.
$C_{15}H_6CL_4O_2$ requires C, 50.05; H, 1.7%; M 360).
τ 1.8-2.6 (m, 6H).
$\lambda_{max.}$ 214 ($\log_{10}\varepsilon$ 4.55), 254 (4.21), 311 (4.37) nm.
$\nu_{max.}$ 3130, 1662, 1600, 1548, 1450, 1418, 1378, 1285, 1275, 1268, 1240, 1186, 970, 870, 798, 710, 680 $cm.^{-1}$ and

(b) unreacted starting material (87 mg.)

Reaction of the Dihydrobenzofuran (XL) with Bromine in Chloroform

A solution of the dihydrobenzofuran (XL) (40 mg.) in chloroform (10 ml.) containing bromine (0.2 ml.) was allowed to stand overnight. Removal of the solvent and bromine left a pale yellow solid. Purification by preparative layer chromatography gave: the benzofuran (XLVIII) (35 mg., 98%).

Reaction of the Dibromoketal (XXXVIII) with Methanolic Potassium Hydroxide

Potassium hydroxide (128 mg.) was added to a solution of the dibromoketal (XXXVIII) (350 mg.) in methanol (10 ml.) and chloroform (10 ml.), and the mixture was heated under reflux for 45 min. The cold solution was made acidic with hydrochloric acid (0.1N) and extracted with chloroform (2 x 10 ml.). The combined extracts were washed with water, dried, and concentrated to leave a pale yellow oil. Purification by preparative layer chromatography gave : 5,6,7,8-tetrachloro-2-ethoxy-3-bromo-2-H-flaven (IL) (188 mg., 42%), m.p. 105-106° (from light petroleum:diethyl ether 3:1).

(Found: C, 43.55; H, 2.5%; M [mass spectrometry] 468.

$C_{17}H_{11}Br\ Cl_4O_2$ requires C, 43.55; H, 2.35%; M 468).

τ 2.4-2.75 (m, 6H), 7.36 (q [J = 7.0 Hz.], 2H),

8.74 (t[J = 7.0 Hz.], 3H).

$\lambda_{max.}$ 237 ($\log_{10}\varepsilon$ 4.49), 250 (4.38), 285 (4.22), 296 (4.22), 330 (3.58) nm.

$\nu_{max.}$ 2980, 2900, 1630, 1560, 1539, 1495, 1451, 1400, 1350, 1308, 1240, 1222, 1130, 1111, 1068, 1055, 1020, 962, 950, 890, 865, 765, 755, 727, 695, 668, 650 cm.$^{-1}$

Reaction of the Flaven (IL) with Hydrochloric acid in Acetic Anhydride

A solution of the flaven (IL) (153 mg.) in acetic anhydride (5 ml.) containing concentrated hydrochloric acid (4 ml.) was heated under reflux for 20 min. The solution was then poured into ice/water (20 ml.) and extracted with chloroform (3 x 10 ml.). The combined extracts were washed with water, concentrated and distilled with benzene to leave an oil. Purification of the major product by preparative layer chromatography gave : 5,6,7,8-tetrachloro-2-hydroxy-3-bromo-2-H-flaven (L) (72 mg., 50%), m.p. 95-96° (from ethanol).

(Found: C, 40.85; H, 1.75%; M [mass spectrometry] 440.

$C_{15}H_7Br\ Cl_4O_2$ requires C, 40.85; 1.6%; M 440).

τ 2.25-2.7 (m, 6H), 5.75 (b.s., 1H [exchangeable by D_2O].

$\lambda_{max.}$ 338 ($\log_{10}\varepsilon$ 4.45), 350 (4.31), 283 (4.18), 294 (4.16), 324 (4.55), 333 (4.54) nm.

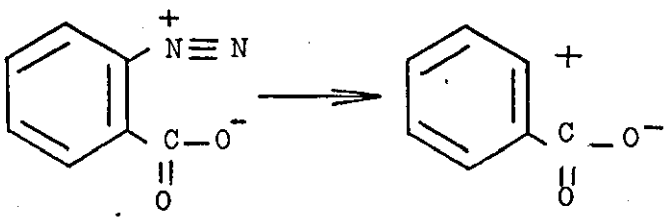
$\nu_{max.}$ 3400-3300, 1450, 1400, 1295, 1216, 1090, 1080, 1010, 970, 950, 910, 870, 765, 730, 700 cm.$^{-1}$

SECTION 3

The Formation and Rearrangement of some 5,6,7,8-Tetrachloro-1,3-benzodioxans.

INTRODUCTION

The diazotisation of anthranilic acid in aqueous acetone has been reported[90] to yield 2,2-dimethyl-1,3-benzodioxan--4-one. The acetone adding to the 1,4-dipolar intermediate generated by the stepwise loss of nitrogen from the benzenediazonium-2-carboxylate intermediate. Similarly, the formation of 2,2-diphenyl-3,1-benzoxathian-4-one[91] from thiobenzophenone and benzenediazonium-2-carboxylate is known.



Other workers[92] have also reported trapping the 1,4-dipolar intermediate.

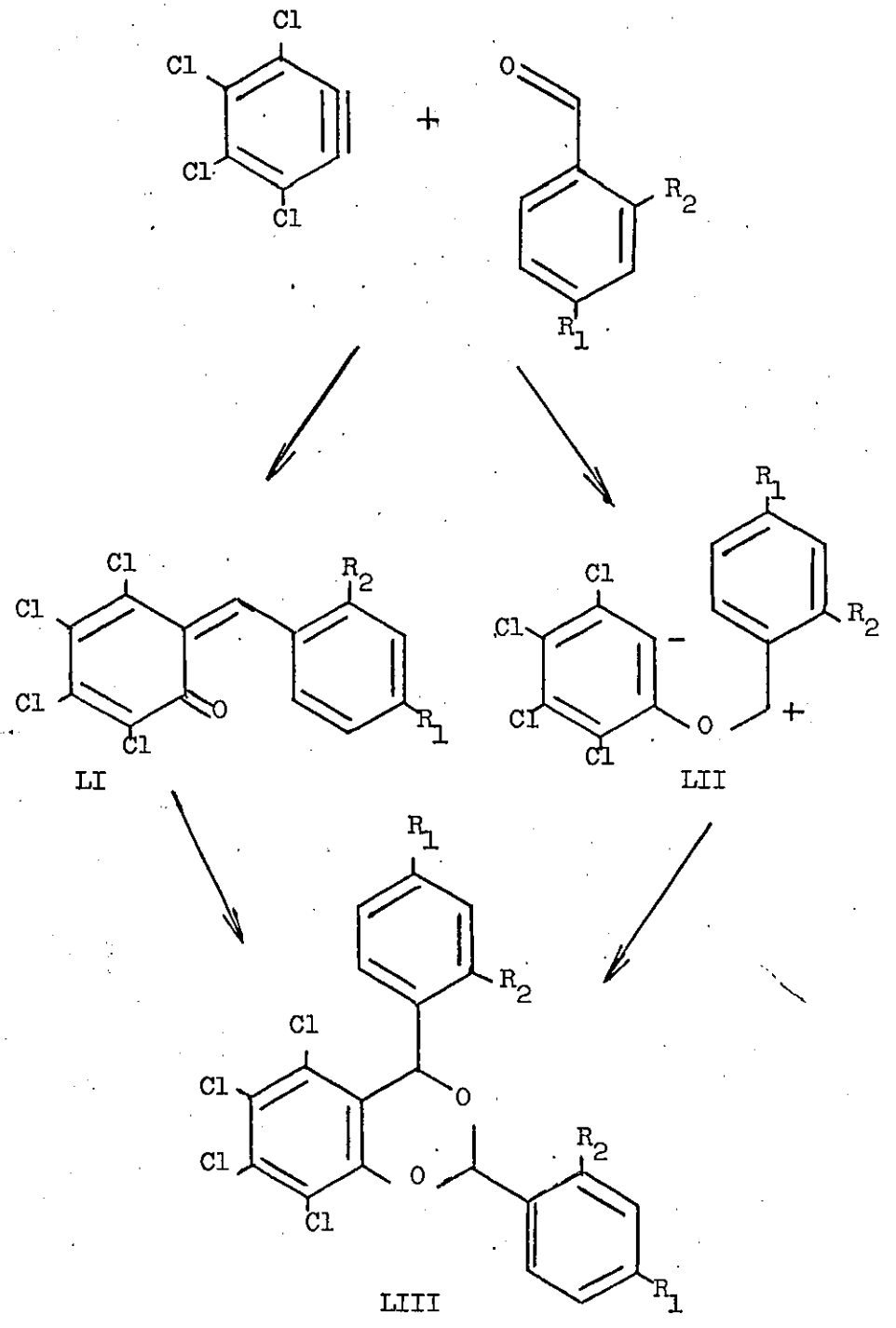
We have found no products analogous to those reported[90,91] when tetrachloroanthranilic acid was aprotically diazotised in the presence of carbonyl compounds. The products obtained and reactions undertaken involving these products are described in this section.

DISCUSSION

To further examine the reaction between tetrachlorobenzyne and carbonyl compounds we used as co-reactants a number of aromatic aldehydes. A. priori predictions from the behaviour of, for example, cinnamaldehyde with tetrachlorobenzyne led us to expect an o-quinone methide intermediate (LI).[93] Alternatively a stepwise addition by the carbonyl to tetrachlorobenzyne should lead to a 1,4-dipolar species (LII) (Scheme 1). Neither of these intermediates would be expected to undergo intramolecular rearrangements; as in the case of the o-quinone methide formed from the reaction of tetrachlorobenzyne with an αβ-unsaturated aldehyde; unless participation of the aromatic ring is considered. Should the latter occur the product expected would be identical to that which would be obtained of a 1,4-cycloaddition reaction analogous to that of tetrachlorobenzyne with styrene.[31]

o-Quinone methide is reported[50] to react with the exocyclic double bond of styrene to yield a flavan; and by analogy one may expect a benzodioxan derivative as the product from the reaction of the intermediate (LI) with a further molecule of aldehyde. The dipolar intermediate (LII) may also react with another molecule of the aldehyde to yield the same benzodioxan (Scheme 1). The only adduct we obtained from the reaction between tetrachlorobenzyne and benzaldehyde was 5,6,7,8-tetrachloro-2,4-diphenyl-1,3-benzodioxan (LIII, R_1=R_2=H).[94]

We established the structures of the adducts (LIII) from the following data. Elemental analyses confirmed their



R_1 = H R_2 = H

R_1 = H R_2 = OMe

R_1 = OMe R_2 = H

Scheme 1

respective molecular formulae. The mass spectra showed extremely weak molecular ions; the favoured breakdown was loss equivalent to one molecule of aldehyde precursor. Analysis of the ^{1}H n.m.r. spectra was possible by first order methods. The methine protons at positions 2 and 4 were seen to resonate at different chemical shifts. They were assigned from a consideration of the Schoolery rules[95] which predict that the dibenzylic methine proton adjacent to an ether linkage at position-4 should be more shielded than the benzylic methine proton at position-2 which is adjacent to two ether links. The phenyl groups also resonate at slightly different chemical shifts, for example, for the adduct (LIII, $R_1 = R_2 = H$) (τ 2.47 and 2.42). The substituted adduct (LIII, R_1 = OH, R_2 = OMe) gave a complex multiplet in the aromatic region; but for the adduct (LIII, R_1 = OMe, R_2 = H) a <u>para</u>-substituted pattern could be distinguished (J_{A-B} = 9.0 Hz, δ = 0.5 p.p.m.) in which the peaks were broadened. The u.v.spectra showed a characteristic peak at 301 nm. ($\log_{10} \varepsilon$ 3.4) in all cases.

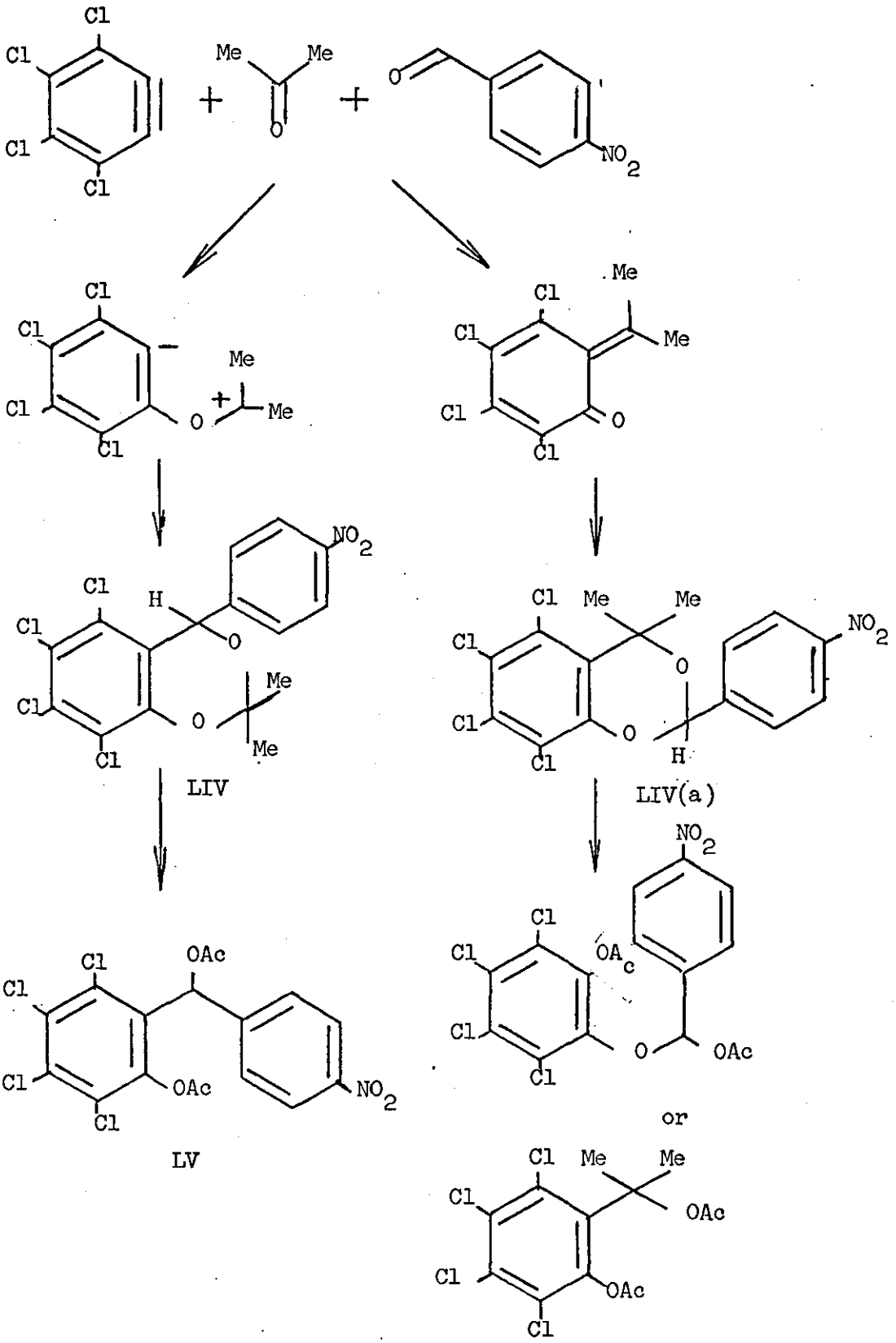
The yield of adduct (LIII), by either mechanism, may be expected to increase if an electron releasing group <u>e.g.</u> methoxyl is present on the aromatic aldehyde ring in either the <u>ortho</u> or <u>para</u> position. This was found when anisaldehyde was used as co-reactant, the yield increased from 13%, for benzaldehyde, to 20%. However, when <u>o</u>-methoxybenzaldehyde was used only a 3% yield was obtained. In this connection it is noteworthy to mention that no product was obtained in an attempted reaction between tetrachlorobenzyne and phenylpropargyl aldehyde (section 1, p. 19).

In all cases the yields were low and we believe this is due to the formation of a dihydro-3,1-benzoxazin-4-one by the reaction of tetrachloroanthranilic acid with the respective aldehyde. Benzaldehyde was found to react readily with tetrachloroanthranilic acid to form 5,6,7,8-tetrachloro--2-phenyl-1,2-dihydro-3,1-benzoxazin-4-one, a compound of low solubility and negligible mobility on thin layer chromatography. However, we generated tetrachlorobenzyne by the thermolysis of 2-carboxytetrachlorobenzenediazonium chloride in boiling chloroform containing benzaldehyde and were able to isolate a 54% yield of the adduct (LIII, R_1 = H, R_2 = H). This confirmed our suspicions that a condensation reaction of tetrachloroanthranilic acid was occurring in competition with diazotisation.

When p-nitrobenzaldehyde was used as co-reactant, as may be expected from the electron withdrawing effect of the nitro group, no aryne adduct was obtained. However, when acetone was present as solvent an adduct (LIV) was obtained albeit in low yield.[96] The ^{1}H n.m.r. spectrum indicated the presence of two methyl groups (τ 8.38 and 8.43), a para di-substituted benzene ring, and a methine singlet (τ 4.08). The infra-red spectrum confirmed the absence of a carbonyl group and the u.v. spectrum was similar to adducts (LIII). The mass spectrum and an elemental analysis confirmed that the adduct (LIV) contained a molecule of p-nitrobenzaldehyde, one of acetone, and one of tetrachlorobenzyne. Two isomeric structures may be considered and the actual structure of the product might be expected to

depend on precise mechanistic details (Scheme 2). Alkaline hydrolysis[97] or a reductive cleavage[98] had been reported to open the 1,3-dioxan ring but we found them to be unsatisfactory in this case. A satisfactory degradation was achieved by treating the adduct (LIV) in acetic anhydride with concentrated sulphuric acid. The structure of the diacetate (LV) obtained was confirmed from the following data. A low voltage mass spectrum (20 e.v.) indicated a $M^{+\cdot}$ ion of 467, whereas a $M^{+\cdot}$ ion of 483 would have been anticipated if the diacetate was obtained from the alternative isomer (LIVa). In any case one might have anticipated that an acidic cleavage of the compound (LIVa) under acetylating conditions would have resulted in the loss of the p-nitrobenzaldehyde residue (Scheme 2). The ^1H n.m.r. spectrum confirmed that the para-disubstituted benzene residue was still present together with two acetate groups (τ 7.74 and 7.84) and a methine singlet (τ 2.45). In the adduct (LIV) this methine proton was at τ 4.08 which is comparable to the chemical shift values obtained for the methine protons at position-4 in the adducts (LIII). The infra-red spectrum indicated that the two acetate groups were in different molecular environments (C = O 1793 $cm.^{-1}$ and 1747 $cm.^{-1}$) as would be expected for a benzylic and a phenyl acetate respectively. Finally elemental analysis confirmed the molecular formula.

Since we had shown that para-nitrobenzaldehyde does not react with tetrachlorobenzyne, these results suggest that the mechanism of the above reaction involves initial attack by acetone.



Scheme 2

To obtain the product (LIV) a 1,4-dipolar species must have been formed which could then attack the para-nitrobenzaldehyde to yield the product isolated. We cannot however comment on the mechanism of formation of the adducts (LIII) where two molecules of aldehyde are present in the product, except to say that the presence of acetone does not affect the yield of these products, and neither does the presence of 2,3-butandione.

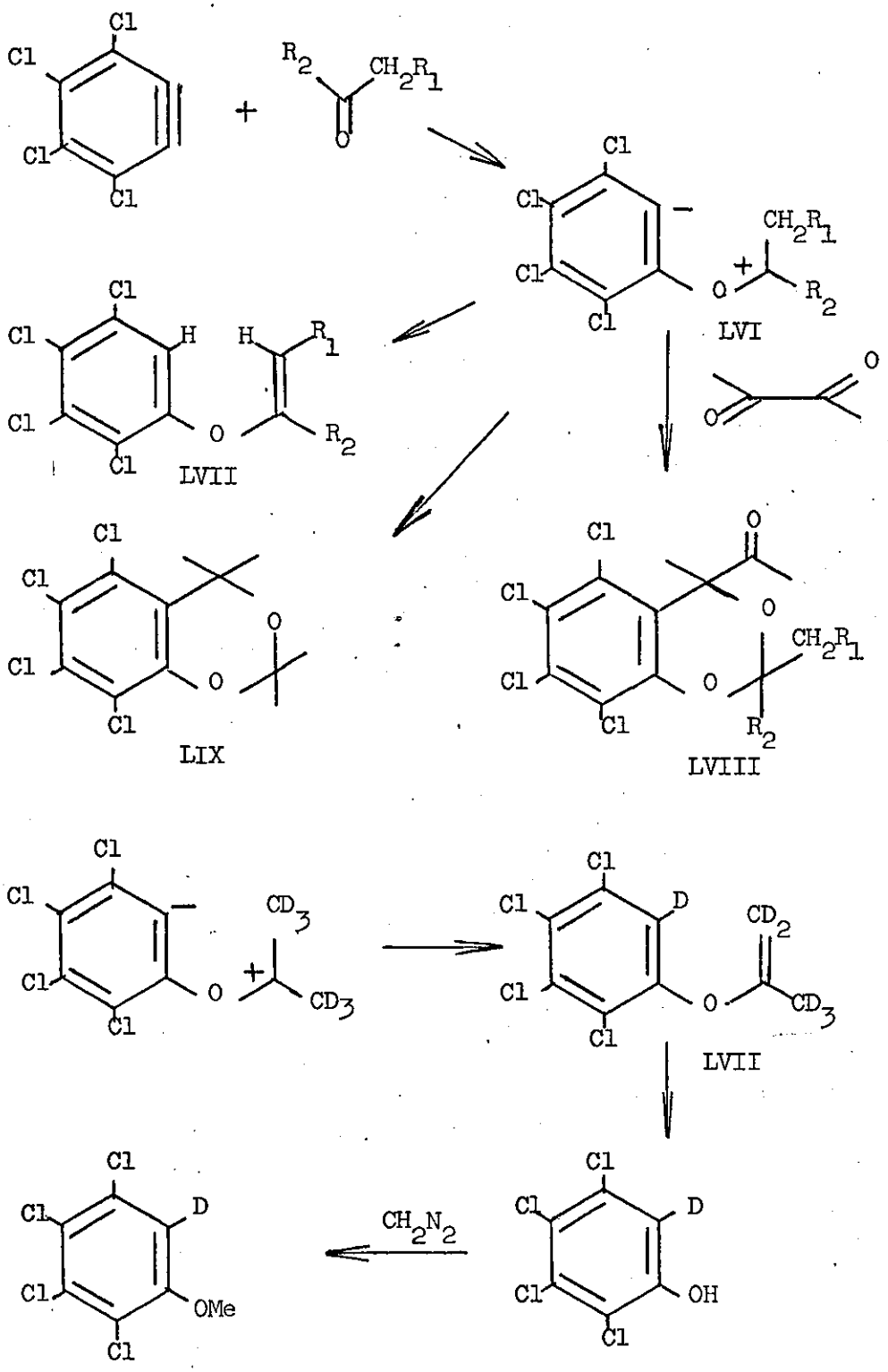
It was known[99] that tetrachlorobenzyne would react with 2,3-butandione in the presence of simple ketones to give two products (Scheme 3), one of which was possibly an enol ether, and the other had been shown to contain a carbonyl group. We reinvestigated the reaction in order to establish the structure of the unknown product (LVIII), and to confirm the structures of the enol ethers (LVII). We have also shown that the acetone and diethyl ketone will react with tetrachloroanthranilic acid to form 2,2-disubstituted-1,2-dihydro-3,1-benzoxazin-4-ones, as previously discussed (section 1 p. 19 and this section p. 117).

The enol ethers (LVII) were unstable and rapidly hydrolysed to tetrachlorophenol.[100] Also their behaviour on thin layer chromatography was extremely similar to 2,3,4,5-tetrachloro--(3'-methyl)-butyl ether, formed by the attack of either 3-methylbutyl nitrite or 3-methylbutyl alcohol on tetrachlorobenzyne.[66] To isolate them more easily tetrachloroanthranilic acid was diazotised by the concurrent addition of 3-methylbutyl nitrite and tetrachloroanthranilic acid to a large excess of the

ketone. The molecular formulae of the enol ethers were established by accurate mass measurements. The ^{1}H n.m.r. of all three enol ethers showed a methine singlet (τ ca. 2.8) for the aromatic proton. Both compounds (LVII(a) and LVII(b)) could be analysed by first order methods and showed two olefinic protons (τ 5.75 and 6.13) which are coupled (2.5 Hz). The compound (LVII(c)) derived from diethyl ketone showed a methine quartet (τ 5.23, J = 7.5 Hz) coupled to a methyl doublet.

We have also been able to obtain in very low yield (1.5%) an adduct containing two molecules of acetone and one molecule of tetrachlorobenzyne. The structure of this tetramethyl adduct (LIX) was established from an accurate mass measurement of the molecular ion. The ^{1}H n.m.r. spectrum showed the presence of two equal intensity singlets (τ 7.27 and 7.48). The mechanism of the reaction most probably goes by the 1,4-dipolar intermediate (LVI) but the nature of the product does not allow us to be more certain of the mechanism.

We have mentioned that the enol ethers are easily hydrolysed to tetrachlorophenol, and when tetrachlorobenzyne was generated by the thermolysis of 2-carboxytetrachlorobenzenediazonium chloride (XIII)in warm dry acetone, we obtained a 98% yield of the phenol. We confirmed that the proton present on the aromatic ring in the enol ethers (LVII) came from the ketone, and was not picked up from extraneous sources,



LVII, LVIII (a) R_1 = H R_2 = Me

LVII, LVIII (b) R_1 = H R_2 = Et

LVII, LVIII (c) R_1 = Me R_2 = Et

Scheme 3

by using hexadeuterio-acetone. Thermolysis of the aryne precursor (XIII) in deuterio-acetone and methylation of the product with ethereal diazomethane gave tetrachloroanisole containing less than 10% [^{1}H] by mass spectrometry and ^{1}H n.m.r. The deuterio-acetone was shown by mass spectrometry to contain 8% [^{1}H] before reaction and 14% [^{1}H] after reaction. Hence in the formation of the enol ethers (LVII) the aromatic proton is obtained solely from the ketone; most probably by an intramolecular proton migration. Alternatively, a thermally allowed concerted 'ene-like' $2\pi s + 2\pi s + 2\sigma s$ reaction may be involved.

The other adducts (LVIII) which we obtained from the aprotic diazotisation of tetrachloroanthranilic acid in the presence of simple ketones and 2,3-butandione and which were known[99] to contain a carbonyl group, could, by analogy with our other results, have the structure (LIV) (Scheme 3) or be an isomer with the functions at positions 2 and 4 interchanged. Treatment of the adduct (LVIII(a)) with sodium methoxide resulted only in the cleavage of the acetyl group to leave 5,6,7,8-tetrachloro-trimethyl-1,3-benzodioxan.

Treatment of the adduct (LVIII(a)) in acetic anhydride with concentrated sulphuric acid gave a monoacetate (LX) (ν C = O 1740 cm.$^{-1}$). When the reaction was repeated using acetic acid and hydrobromic acid a monobromo-compound was obtained. By bubbling a stream of nitrogen through the former reaction mixture and the effluent gas through a solution of

2,4-dinitrophenylhydrazine we were able to isolate the 2,4-dinitrophenylhydrazone of acetone. Treatment of the other adducts (LVIII(b) and LVIII(c)) in acetic anhydride with concentrated sulphuric acid also gave the identical monoacetate (LX). The ^{1}H n.m.r. of the compounds (LX) and (LXI) were similar, both showed the presence of methyl singlets (τ7.45 and τ7.50), and also methylene singlets (τ4.75 and τ5.30) respectively. Compound (LX) also showed the presence of an acetyl group (τ7.95).

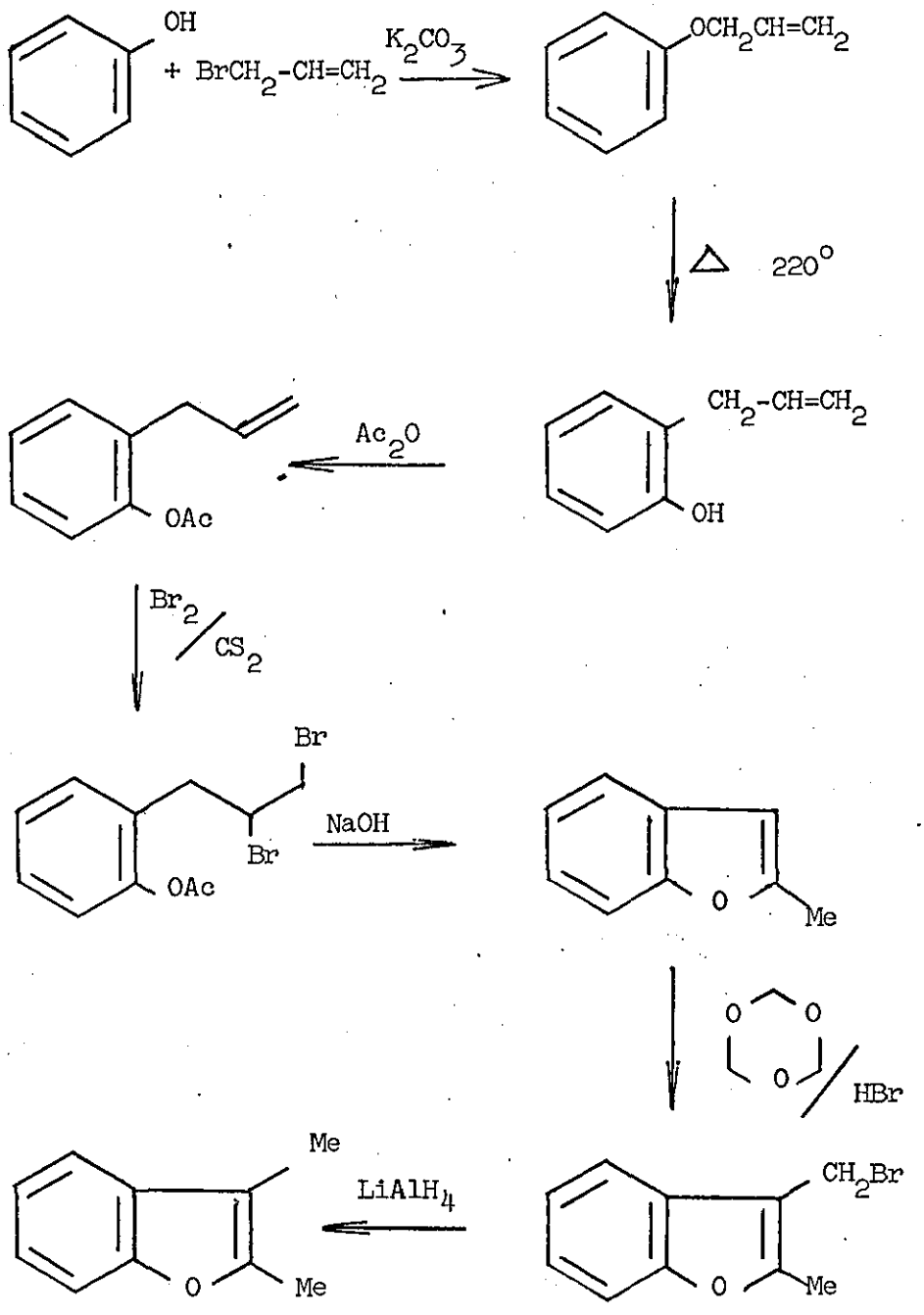
The adduct (LVIII(a)) could be reduced with sodium borohydride to give a pair of diastereoisomeric alcohols (LXII) which were separable by thin layer chromatography. Treatment of these, or the acetates (LXIII) derived from them, in acetic anhydride with concentrated sulphuric acid gave 4,5,6,7-tetrachloro-2,3-dimethyl-benzofuran (LXIV), the structure of which was established from the following data. The mass spectrum and elemental analysis confirmed the molecular formula, and the expected extended styrene chromophore[101] was found in the u.v. spectrum. This was also present in the u.v. spectra of the compounds (LX) and (LXI). The ^{1}H n.m.r. spectrum showed two methyl singlets (τ7.62 and 7.71) which were assigned by analogy with known data. The methyl resonance in 3-methybenzofuran occurs at higher field than does the methyl of the 2-isomer.[102] We were also able to confirm this by synthesis. 2-Methyl-3-bromomethylbenzofuran (scheme 4), was prepared and the ^{1}H n.m.r. spectrum showed the presence of a methyl and a methylene singlet at

τ 7.73 and 5.62 respectively. Reaction of this compound with lithium aluminium hydride gave a partial conversion to 2,3-dimethylbenzofuran, the ^{1}H n.m.r. spectrum of which showed the presence of the second methyl resonance at τ 7.80.

Comparison of the ^{1}H n.m.r. spectra of 2-methyl-3-bromomethylbenzofuran and the tetrachloro analogue (LXI) also showed close agreement. To conclusively establish the structures of the adducts (LX) and (LXI) we converted the acetate (LX) into the bromo compound (LXI) with hydrobromic acid. Reaction of the bromo compound with lithium aluminium deuteride gave the benzofuran (LXIV) in which the singlet in the ^{1}H n.m.r. spectrum at τ7.71 for the methyl group at position-3, was replaced by the expected two proton multiplet.

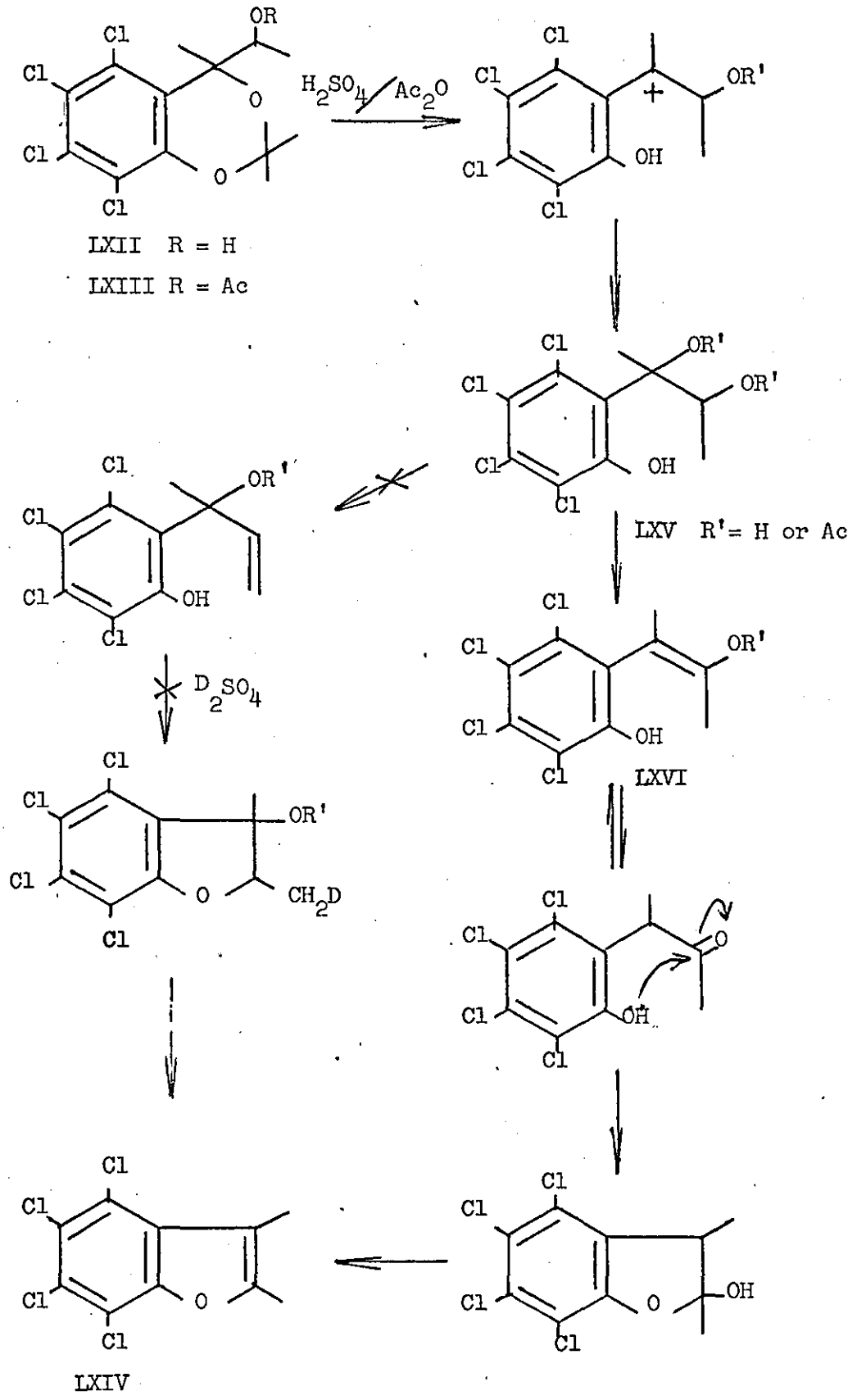
The mechanism of these rearrangements to benzofuran derivatives was investigated. Scheme 5 illustrates two possible mechanisms for the formation of the 2,3-dimethylbenzofuran (LXIV). There is the possibility that intermediate (LXV) may dehydrate (or de-acetylate) in a number of ways. Loss of the secondary oxygen function, however, is unlikely as there is a tertiary function present. This was confirmed by using deuterio sulphuric acid to effect the rearrangement; no deuterium incorporation was found. Should the enol (LXVI) be formed, rearrangement would lead to a ketone which can then cyclise and dehydrate to give the product (LXIV).

To rationalise the formation of either the acetate (LX) or the bromocompound (LXI) (Scheme 6) we again suggest

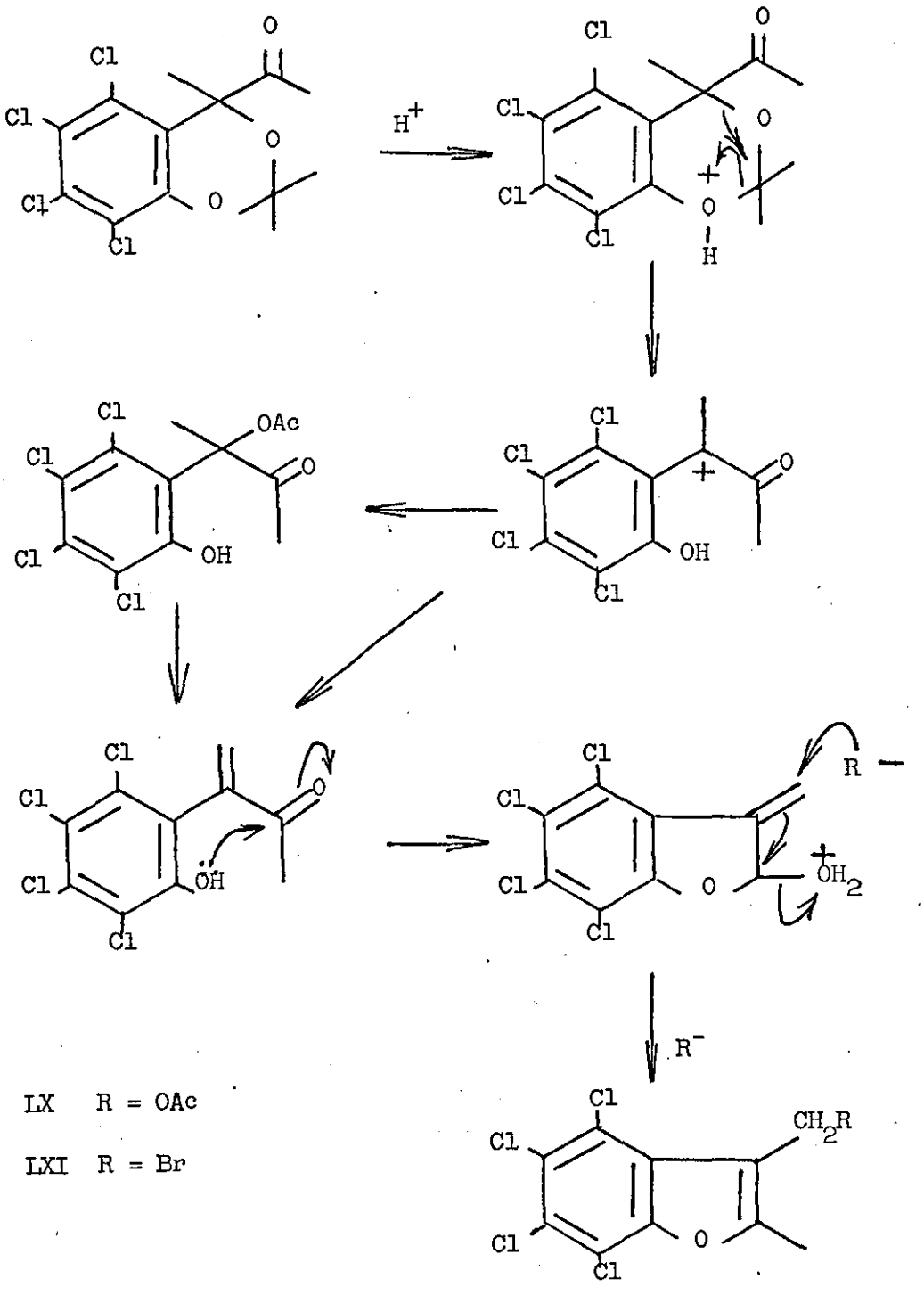

OH
+ BrCH2-CH=CH2
K2CO3
OCH2CH=CH2
△ 220°
CH2-CH=CH2
OH
Ac2O
OAc
Br2
CS2
Br
Br
OAc
NaOH
O
Me
O
O
O
HBr
CH2Br
O
Me
LiAlH4
Me
O
Me

Scheme 4

initial loss of, for example, acetone, to form a carbonium ion (LXVII). The unsaturated intermediate (LXVIII) may then be formed by loss of proton or by deacetylation of the tertiary acetate, which would lead to the same intermediate (LXVIII). Cyclisation could then occur, and a nucleophilic addition of either acetate or bromide ion at the vinyl double bond, accompanied by the loss of water, would afford the respective benzofuran derivatives.


OR
Cl
Cl
Cl
Cl
O
O
H_2SO_4 / Ac_2O
OR'
OH
LXII R = H
LXIII R = Ac
OR'
OR'
OH
LXV R'= H or Ac
OR'
OH
LXVI
D_2SO_4
OR'
CH_2D
O
OH
OH
O
LXIV

Scheme 5



LX R = OAc

LXI R = Br

Scheme 6

EXPERIMENTAL

General methods

General methods are as described in Section 1 (experimental).

Reaction of Tetrachlorobenzyne with Benzaldehyde

A solution of tetrachloroanthranilic acid (2.75 g., 0.01 mol.) in diethyl ether (10 ml.) and dichloromethane (30 ml.) was added dropwise to a stirred solution of benzaldehyde (30 g., 0.3 mol.) and 3-methylbutyl nitrite (3 ml.) in dichloromethane (10 ml.) maintained at 40°. After the addition was complete stirring was continued for a further 15 min. Removal of solvent and excess of co-reactant left a red oil which was eluted from a column of active alumina (Brockman grade 1) in light petroleum and gave, (a) 2,3,4,5-tetrachlorophenyl-ethyl ether[64] (440 mg., 17%) and (b) 5,6,7,8-tetrachloro-2,4--diphenyl-1,3-benzodioxan (LIII, $R_1 = R_2 = H$) (571 mg., 13.4%), m.p. 222-224° (from chloroform).

(Found: C, 56.6; H, 3.0%; M [mass spectrometry] 426. $C_{20}H_{12}Cl_4O_2$ requires C, 56.4; H, 2.85%; M 426).

τ 2.48 (s, 5H), 2.53 (s, 5H), 3.63 (s, 1H), 4.02 (s,1H).

$\lambda_{max.}$ 220 ($\log_{10} \varepsilon$ 4.26), 291 (3.03), 301 (3.13) nm.

$\nu_{max.}$ 1572, 1548, 1455, 1415, 1400, 1348, 1315, 1265, 1202, 1058, 1040, 1025, 995, 795, 770, 750, 735, 710 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with Anisaldehyde

The procedure described for benzaldehyde was followed using anisaldehyde (13.6 g., 0.1 mol.) and gave, (a) 2,3,4,5-tetrachlorophenyl ethyl ether[64] (202 mg., 7.8%), and

(b) 5,6,7,8-tetrachloro-2,4-di-(4'-methoxyphenyl)-1,3-benzodioxan (LIII R_1 = OMe, R_2 =H) (1.0 g., 20%), m.p. 171-173° (from chloroform).

(Found: C, 54.3; H, 3.35%; M [mass spectrometry] 486. $C_{22}H_{16}Cl_4O_4$ requires C, 54.4; H, 3.3%; M 486).

τ 2.88 (p. sub. pattern [J_{AB} = 8.0 Hz, $\sigma_{AA'}$ 0.5 p.p.m.], 4H), 3.92 (s, 1H), 4.17 (s, 1H), 6.21 (s, 3H), 6.23 (s,3H).

$\lambda_{max.}$ 237 ($\log_{10}\varepsilon$ 4.41), 273 (3.55), 276 (3.54), 279 (3.53), 282 (3.52), 292 (3.40), 301 (3.47) nm.

$\nu_{max.}$ 1615, 1515, 1415, 1395, 1326, 1306, 1254, 1203, 1175, 1114, 1058, 1030, 998, 965, 960, 915, 908, 840, 815, 780, 764 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with o-Methoxybenzaldehyde

The procedure described for benzaldehyde was followed using o-methoxybenzaldehyde (12 g., 0.1 mol.) and gave, 5,6,7,8-tetrachloro-2,4-di-(2'-methoxyphenyl)-1,3-benzodioxan (LIII R_1 = H, R_2 = OMe) (160 mg., 3%), m.p. 208-209° (from chloroform).

(Found: C, 54.6; H, 3.45%; M [mass spectrometry, 20 e.v.] 486. $C_{22}H_{16}Cl_4O_2$ requires C, 54.4; H, 3.3%; M 486).

τ 50° 2.2-3.2 (m, 8H), 3.45 (s, 1H), 3.63 (s, 1H), 6.14 (s, 3H), 6.50 (s, 3H).

$\lambda_{max.}$ 228 ($\log_{10}\varepsilon$ 4.28), 275 (3.77), 281 (3.75), 301 (3.41) nm.

$\nu_{max.}$ 1610, 1592, 1497, 1470, 1395, 1383, 1350, 1305, 1291, 1255, 1075, 1035, 1025, 958, 918, 767, 758, 750 $cm.^{-1}$

Reaction of Tetrachloroanthranilic acid with Benzaldehyde

A solution of tetrachloroanthranilic acid (1.5 g.) and benzaldehyde (0.7 g.) in diethyl ether (20 ml.) was heated under reflux for 16 hr. Removal of solvent left a red oil which crystallised to give 5,6,7,8-tetrachloro-2-phenyl-2,3-dihydro-3,1-benzoxazin-4-one (1.7 g., 89%), m.p. 180-181 (from chloroform:benzene, 1:1).

(Found: C, 46.25; H, 2.05; N, 3.85%; M [mass spectrometry] 363. $C_{14}H_7Cl_4NO_2$ requires C, 46.3; H, 2.0; N, 3.86%; M 363).

$\nu_{max.}$ 3410, 1735, 1580, 1462, 1450, 1350, 1330, 1270, 1250, 1200, 1023, 1010, 990, 784, 697 $cm.^{-1}$

Thermolysis of 2-Carboxytetrachlorobenzenediazoniumchloride (XIII) in the presence of Benzaldehyde

Compound (XIII) (1.1 g.) was added to a solution of benzaldehyde (5.0 g.) in chloroform (50 ml.), which was then heated under reflux for 15 min. Removal of the solvent left a red oil, elution of which from a column of silica gave the adduct (LIII, $R_1 = R_2 = H$) (0.8 g., 54%).

Attempted Reaction of Tetrachlorobenzyne with p-Nitrobenzaldehyde

The procedure described for benzaldehyde was followed using p-nitrobenzaldehyde (15.1 g., 0.1 mol.) and gave only 5,6,7,8-tetrachlorophenyl ethyl ether[64] (842 mg., 32.5%).

Reaction of Tetrachlorobenzyne with p-Nitrobenzaldehyde in Acetone

A solution of tetrachloroanthranilic acid (5.5 g., 0.02 mol.) in dry acetone (50 ml.) was added dropwise to a stirred solution of p-nitrobenzaldehyde (15.1 g., 0.1 mol.) and 3-methylbutyl

nitrite (6 ml.) in dry acetone (50 ml.) maintained at 50°. Stirring was continued for 1 hr. after the complete addition of tetrachloroanthranilic acid solution. Removal of solvent left a red solid which was eluted from a column of deactivated alumina with light petroleum:benzene (1:1). The yellow oil which was obtained was purified by preparative layer chromatography and gave,

(a) 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether[65] (378 mg., 6%), and

(b) 5,6,7,8-tetrachloro-2,2-dimethyl-4-(4'-nitrophenyl)--1,3-benzodioxan (LIV) (389 mg., 4.8%, m.p. 178-179° (from benzene).

(Found: C, 45.2; H, 2.6; N, 3.4%; M [mass spectrometry] 423. $C_{16}H_{11}Cl_4NO_4$ requires C, 45.5; H, 2.6; N, 3.3%; M 423).

τ 2.16 (p.disub.pattern [J_{AB} = 9.0 Hz., $d_{AA'}$ = 0.77 p.p.m.], 4H), 4.08 (s, 1H), 8.39 (s, 3H), 8.44 (s,3H).

$\lambda_{max.}$ 222 ($\log_{10}\epsilon$ 4.26), 255 (4.12), 284 (3.65), 302 (3.85) nm.

$\nu_{max.}$ 1610, 1568, 1540, 1533, 1404, 1375, 1358, 1350, 1290, 1205, 1140, 1053, 883, 870, 854, 838, 790, 748, 695, 660 $cm.^{-1}$

Reaction of the Adduct (LIV) with Sulphuric acid in Acetic Anhydride

Concentrated sulphuric acid (2.5 ml.) was added to a solution of the adduct (LIV) (98 mg.)in acetic anhydride (10 ml.). The solution became hot and rapidly darkened

and after 3 min. was poured onto ice (20 g.). The aqueous mixture was extracted with ether (3 x 25 ml.) and the combined extracts washed with water and concentrated to leave an acetic acid solution from which crystallised (2-acetoxy-3,4,5,6-tetrachlorophenyl)-4'-nitrophenyl-methyl--acetate, (LV) (53 mg., 48%), m.p. 158-160° (from ethanol: benzene, 1:1).

(Found: C, 43.5; H, 2.25; N, 3.1%; M [mass spectrometry, 20 e.v.] 467. $C_{17}H_{11}Cl_4NO_6$ requires C, 43.7; H, 2.35; N, 3.0%; M 467).

τ 2.13 (p. disub. pattern [J_{AB} = 9.0 Hz, $d_{AA'}$ = 0.8 p.p.m.], 4H), 2.44 (s, 1H), 7.73 (s, 3H), 7.84 (s, 3H).

$\nu_{max.}$ 3130, 3100, 1793, 1746, 1612, 1604, 1530, 1394, 1370, 1350, 1223, 1182, 1163, 1040, 1010, 945, 876, 863, 854, 782, 743, 693 cm.$^{-1}$

Reaction of Tetrachloroanthranilic acid with Diethyl ketone

A solution of tetrachloroanthranilic acid (0.5 g.) in diethyl ketone (20 ml.) was heated under reflux for 24 hr. Removal of solvent left a red oil which crystallised to give 5,6,7,8-tetrachloro-2,2-diethyl-1,2-dihydro-3,1--benzoxazin-4-one (0.6 g., 95%), m.p. 185-187° (from benzene).

(Found: C, 41.85; H, 3.1; N, 4.1%; M [mass spectrometry] 343. $C_{12}H_{11}Cl_4NO_2$ requires C, 42.0; H, 3.25; N, 4.1%; M 343).

$\nu_{max.}$ 3320, 2980, 2950, 1718, 1580, 1480, 1465, 1330, 1290, 1230, 1180, 1105, 1015, 995, 785, 690 cm.$^{-1}$

Reaction of Tetrachloroanthranilic acid with Acetone

The procedure described for diethyl ketone was followed using dry acetone (20 ml.) and gave 5,6,7,8-tetrachloro-2,2-dimethyl-1,2-dihydro-3,1-benzoxazin-4-one (0.5 g., 87%), m.p. 208-210°(from benzene).

M [mass spectrometry] 315.

$\nu_{max.}$ 3400, 1725, 1680, 1480, 1450, 1393, 1370, 1270, 1220, 1190, 1090, 880, 800, 785, 690, 678 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with 2,3-butandione in Acetone

A solution of tetrachloroanthranilic acid (5.5 g., 0.02 mol.) in dry acetone (50 ml.) was added dropwise to a stirred solution of 2,3-butandione (8.6 g., 0.1 mol.) and 3-methylbutyl nitrite (2.5 ml.) in dry acetone (30 ml.) maintained at 40°. Stirring was continued for a further 30 min. after the addition was complete. Removal of the co-reactants left a red oil, examination of which by thin layer chromatography indicated the presence of four products. The oil was eluted from a column of silica in light petroleum and gave in order of decreasing R_f value,

(a) a mixture of two products which was separated by preparative layer chromatography into

(i) 2,3,4,5-tetrachlorophenyl-1'-methylvinyl ether (LVII(a)) (415 mg., 7.5%), oil.

(Found M/e 269.9180. $C_9H_6{}^{35}Cl_4O$ requires M/e 269.9175).

τ 2.88 (s, 1H), 5.80 (m, 1H), 6.13 (d [J_{gem} = 2.5 Hz], 1H), 8.01 (d [J_{allyl} = 1.0 Hz], 3H).

$\lambda_{max.}$ 214 ($\log_{10} \epsilon$ 4.38), 293 (3.06), 300 (2.85) nm., and

(ii) 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether[65] (300 mg. 4%).

(b) 5,6,7,8-tetrachloro-2,2,4-trimethyl-4-acetyl-1,3-benzodioxan (LVIII(a)) (1.7 g., 23%), m.p. 75-76° (from light petroleum).

(Found: C, 43.8; H, 3.35; Cl, 39.6; M [mass spectrometry] 358. $C_{13}H_{12}Cl_4O_3$ requires C, 43.8; H, 3.38; Cl, 39.9%; M 358).

τ 7.90 (s, 3H), 8.10 (s, 3H), 8.40 (s, 3H), 8.47 (s, 3H).

$\lambda_{max.}$ 234 ($\log_{10} \epsilon$ 4.03), 294 (3.36), 302 (3.45) nm.

$\nu_{max.}$ 3020, 2960, 1728, 1563, 1539, 1400, 1375, 1280, 1200, 1162, 1103, 1020, 1000, 980, 873, 793, 675 cm.$^{-1}$

Further elution of the column with benzene gave

(c) 2,3,4,5-tetrachlorophenol[100] (1.1 g., 23%)

Reaction of Tetrachlorobenzyne with 2,3-Butandione in Methyl ethyl ketone

The procedure described for acetone was followed using methyl ethyl ketone and gave

(a) 2,3,4,5-tetrachlorophenyl-2'-ethylvinyl ether (LVII(b)) (347 mg., 14%) oil.

(Found: M/e 283.9333. $C_{10}H_8{}^{35}Cl_4O$ requires M/e 283.9329).

τ 2.84 (s, 1H), 5.77 (d [J_{gem} = 2.5 Hz.], 1H), 6.12 (d [J_{gem} = 2.5 Hz.], 1H), 7.68 (q [J = 7.0 Hz.], 2H), 7.80 (t [J = 7.0 Hz.], 3H).

$\nu_{max.}$ oil 2990, 1650, 1570, 1535, 1420, 1355, 1265, 1220, 1157, 1103, 1065, 1000, 915, 840, 745, 703 cm.$^{-1}$

(b) 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether[65] (426 mg., 5%).

(c) 5,6,7,8-tetrachloro-2,4-dimethyl-2-ethyl-4-acetyl-1,3--benzodioxan (LVIII (b)) (1.2 g., 17%) m.p. 102-103° (from light petroleum).

(Found:C, 45.15; H, 3.95; Cl, 37.9%; M [mass spectrometry] 372. $C_{14}H_{14}Cl_4O_3$ requires C, 45.15; H, 3.75; Cl, 38.2%; M 372).

τ 7.95 (s, 3H), 7.99 (q, [J = 7.5 Hz], 2H), 8.08 (s, 3H), 8.47 (s, 3H), 9.00 (t, 3H).

$\lambda_{max.}$ 230 ($\log_{10}\epsilon$ 4.07), 295 (3.28), 303 (3.39) nm.

$\nu_{max.}$ 2990, 2950, 1740, 1558, 1537, 1400, 1385, 1352, 1250, 1216, 1166, 1150, 1100, 1055, 1032, 1003, 985, 890, 880, 790 cm.$^{-1}$

and (c) 2,3,4,5-tetrachlorophenol (0.8 g., 17%)

Reaction of Tetrachlorobenzyne with 2,3-Butandione in Diethyl ketone

The procedure described for acetone was followed using diethyl ketone and gave

(a) 2,3,4,5-tetrachlorophenyl-2-ethyl-2-propenyl ether (LVII) (c)) (828 mg., 14%) oil.

(Found: $^{M}/_{e}$ 297.9486. $C_{11}H_{10}{}^{35}Cl_4O$ requires $^{M}/_{e}$ 297.9486).

τ 2.96 (s, 1H), 5.24 (q [J = 7.5 Hz], 1H), 7.71 (q [J = 7.0 Hz], 2H), 8.36 (d [J = 7.5 Hz.], 3H), 8.87 (t [J = 7.0 Hz.], 3H).

(b) 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether[65] (430 mg., 7%)

(c) 5,6,7,8-tetrachloro-2,2-diethyl-4-methyl-4-acetyl-1,3-benzodioxan (LVIII(c)) (0.9 g., 12%) m.p. 123-124° (from light petroleum)

(Found: C, 46.7; H, 4.2; Cl, 36.7%; M [mass spectrometry] 386. $C_{15}H_{16}Cl_4O_3$ C, 46.65; H, 4.15; Cl, 36.8%; M 386).

τ 7.88 (s, 3H), 8.10 (s, 3H), 8.3 (m, 4H), 9.05 (m, 6H).

$\lambda_{max.}$ 230 ($\log_{10}\varepsilon$ 4.06), 295 (3.25), 303 (3.39) nm.

$\nu_{max.}$ 3000, 2960, 1740, 1407, 1310, 1065, 915, 790, 680 $cm.^{-1}$

Reaction of Tetrachlorobenzyne with Acetone

A solution of 3-methylbutyl nitrite (2.5 ml.) in dry acetone (10 ml.) was added dropwise to a stirred solution of tetrachloroanthranilic acid (5.5 g.) in dry acetone (50 ml.) maintained at 40°. Removal of the solvent left a red oil which was eluted from a silica column to give an oil. Separation of the products present in the oil by preparative layer chromatography gave, in order of decreasing R_f value,

(a) the enol ether (LVII(a)) (400 mg., 7%)

(b) 2,3,4,5-tetrachlorophenyl-(3'-methylbutyl) ether[65] (300 mg., 4%), and

(c) 5,6,7,8-tetrachloro-2,2,4,4-tetramethyl-1,3-benzodioxan (LIX) (110 mg., 1.5%), m.p. 173-176° (from light petromeul). (Found $^{M}/_{e}$ 327.9596. $C_{12}H_{12}{}^{35}Cl_4O_2$ requires $^{M}/_{e}$ 327.9591).

τ 8.26 (s, 6H), 8.48 (s, 6H).

$\lambda_{max.}$ 220 ($\log_{10}\varepsilon$ 4.64), 240 (4.00), 293 (4.26), 304 (4.39), 318 (4.41) nm.

Thermolysis of 2-Carboxytetrachlorobenzenediazonium chloride (XIII) in Acetone

The compound (XIII) (1.8 g.) was warmed in dry acetone (20 ml.) until complete solution occurred (5 min.). Removal of the solvent left a solid which was purified by preparative layer chromatography and gave 2,3,4,5-tetrachlorophenol (1.12 g., 98%), m.p. 116°, (lit.[100] m.p. 116°).

Thermolysis of the Compound (XIII) in Hexadueterio-acetone

The compound (XIII) (153 mg.) was warmed in hexadeuterio--acetone (2 ml.), containing 8% [^{1}H] [by mass spectrometry], for 5 min. The hexadeuterio-acetone was then distilled off and found to contain 14% [^{1}H] [by mass spectrometry]. The oil remaining was treated with excess of ethereal diazomethane. Removal of the solvent left an oil which was purified by preparative layer chromatography and gave 1-methoxy-[2-^{2}H]--3,4,5,6-tetrachlorobenzene[65] containing 90% [^{2}H] [by mass spectrometry].

Reaction of the Adduct (LVIII(a)) with Sodium Methoxide

The adduct (LVIII (a)) (400 mg.) was added to a solution of methanol (50 ml.) in which sodium (2.5 g.) had been dissolved. The solution was heated under reflux for 2 days. When cool the solution was neutralised with hydrochloric acid (2N) and extracted with chloroform (3 x 50 ml.). The combined extracts were washed with water, dried, and concentrated to leave an oil. Separation of the major fraction from this oil by preparative layer chromatography gave 5,6,7,8-tetrachloro-2,2,4-trimethyl-1,3--benzodioxan (90 mg., 20%) m.p. 68-70° (from light petroleum). (Found: C, 41.75; H, 3.25%; M [mass spectrometry] 316. $C_{11}H_{10}Cl_4O_2$ requires C, 41.8; H, 3.2%; M 316).

τ 4.98 (q [J = 6.0 Hz], 1H), 8.39 (s, 3H), 8.41 (d [J = 6.0 Hz], 1H), 8.63 (s, 3H).

$\lambda_{max.}$ 222 ($\log_{10}\varepsilon$ 4.22), 284 (3.26), 302 (3.37) nm.

$\nu_{max.}$ 3000, 1568, 1407, 1380, 1278, 1215, 1150, 1004, 975, 854, 795, 665 cm.$^{-1}$

Reaction of the Adduct (LVIII(a)) with Sulphuric acid in Acetic Anhydride

Concentrated sulphuric acid (2 ml.) was added to a solution of the adduct (LVIII(a)) (372 mg.) in acetic anhydride (15 ml.). After 2 min. the brown solution was poured onto ice and extracted with chloroform (3 x 20 ml.). Removal of solvent and azeotropic distillation with benzene left an oil which was purified by preparative layer chromatography and gave 4,5,6,7-tetrachloro-3-acetoxymethyl-2-methylbenzofuran (LX) (174 mg., 50%), m.p. 131-132 (from light petroleum:diethyl ether, 3:1).

(Found: C, 42.0; H, 2.55%; M [mass spectrometry] 342. $C_{12}H_8Cl_4O_3$ requires C, 42.15; H, 2.35%; M 342).

τ 4.75 (s, 2H), 7.45 (s, 3H), 7.95 (s, 3H).

$\lambda_{max.}$ 229 ($\log_{10}\varepsilon$ 4.35), 267 (4.14), 272 (4.11), 292 (3.38), 303 (3.23).

$\nu_{max.}$ 2980, 1740, 1625, 1430, 1495, 1485, 1300, 1232, 1193, 1025, 855, 805 $cm.^{-1}$

Reaction of the Adduct (LVIII (b)) with Sulphuric acid in Acetic Anhydride

The procedure described for the adduct (LVIII(a)) was followed using the adduct (LVIII(b)) (327 mg.) and gave the compound (LX) (108 mg. 39%).

Reaction of the Adduct (LVIII(c)) with Sulphuric acid in Acetic Anhydride

The procedure described for the adduct (LVIII(a)) was followed using the adduct (LVIII(b)) (205 mg.) and gave the compound (LX) (60 mg., 29%).

Identification of Acetone Formation in the Reaction of the Adduct (LVIII(a)) with Sulphuric acid and Acetic Anhydride

The procedure described for the above reactions was followed using the adduct (LVIII(a)) (480 mg.). Nitrogen was bubbled through the reaction solution for 10 min., and the effluent gas passed through a hot solution of 2,4-dinitrophenylhydrazine (0.25 g.) in ethanol (5 ml.) containing hydrochloric acid (0.5 ml.). Removal of the solvent and separation by preparative layer chromatography gave acetone--2,4-dinitrophenylhydrazone m.p. 126-128° (lit.[103] m.p. 128°). A control experiment indicated that the acetone did not come from the reaction of concentrated sulphuric acid upon acetic anhydride.

Reaction of the Adduct (LVIII(a)) with Hydrobromic acid in Acetic acid

Hydrobromic acid (10 ml., 48%) was added to a solution of the adduct (LVIII(a)) (700 mg.) in acetic acid (25 ml.) and the mixture heated under reflux for 2 hr. Water (50 ml.) was added to the cooled solution and extracted with chloroform (3 x 25 ml.). The combined extracts were washed with water, dried, and concentrated. Acetic acid was removed by azeotropic distillation to leave, 4,5,6,7-tetrachloro-3-bromomethyl-2-methylbenzofuran (LXI) (500 mg., 71%), m.p. 140-142° (from benzene: light petroleum, 1:1).

(Found: C, 33.25; H, 1.45%; M [mass spectrometry] 362. $C_{10}H_5Br\ Cl_4O$ requires C, 33.1; H, 1.4%; M 362).

τ 5.30 (s, 2H), 7.50 (s, 3H).

$\nu_{max.}$ 2950, 1615, 1417, 1395, 1380, 1295, 1208, 1000, 837, 805, 670 cm.$^{-1}$

Reduction of the Adduct (LVIII(a)) with Sodium Borohydride

A solution of sodium borohydride (310 mg.) in sodium hydroxide (2 ml., 2N.) was added to a solution of the adduct (LVIII(a)) (450 mg.) in methanol (20 ml.) and stirred at room temperature for 3 hr. After neutralisation with hydrochloric acid (2N.) the solution was extracted with chloroform (2 x 25 ml.). The combined extracts were washed with water, dried, and concentrated to give 5,6,7,8-tetrachloro-4-(1'-hydroxyethyl)-2,2,4-trimethyl-1,3-benzodioxan (LXII) (400 mg., 89%), m.p. 118-119° (from benzene).

(Found: C, 43.3; H, 3.95; Cl, 39.15%.

$C_{13}H_{14}Cl_4O_3$ requires C, 43.3; H, 3.9; Cl, 39.45%).

Separation of the diastereoisomers by preparative layer chromatography on silica, with benzene as eluant gave,

(a) R_f 0.215 (300 mg.) τ 5.58 (q [J = 6.5 Hz.], 1H), 8.0 (b.s., 1H [exchangeable by D_2O]), 8.18 (s, 3H), 8.30 (s, 3H), 8.51 (s, 3H) 8.71 (d [J = 6.5 Hz.], 3H).

$\nu_{max.}$ 3580, 3000, 1560, 1534, 1400, 1277, 1215, 1173, 1115, 1082, 1025, 973, 870, 785 cm.$^{-1}$, and

(b) R_f 0.10 (100 mg.) τ 5.49 (q [J = 6.5 Hz.], 1H), 7.8 (b.s., 1H [exchangeable by D_2O]), 7.99 (s, 3H), 8.28 (s, 3H), 8.49 (s, 3H), 9.11 (d [J = 6.5 Hz.], 3H).

$\nu_{max.}$ 3610, 3500-3300, 3010, 1555, 1400, 1280, 1215, 1170, 1030, 975, 895, 870, 785 cm.$^{-1}$

Acetylation of the Alcohol (LXII)

A solution of the alcohol (LXII) (115 mg.) in acetic acid (10 ml.) and acetic anhydride (10 ml.) was heated under reflux for 30 min. The solvent was removed by azeotropic distillation with benzene to leave 5,6,7,8-tetrachloro-4-(1'-acetoxyethyl)-2,2,4-trimethyl-1,3-benzodioxan (LXIII) (120 mg., 90%) m.p. 185-187° (from light petroleum).

(Found: C, 44.8; H, 4.05%; M [mass spectrometry] 402.

$C_{15}H_{16}Cl_4O_4$ requires C, 44.8; H, 4.0%; M 402).

Separation of the diastereoisomers by preparative layer chromatography on silica, with benzene as eluant gave,

(a) R_f 0.445 (95 mg.) τ 4.30 (q [J = 6.5 Hz.], 1H), 8.15 (s, 3H), 8.27 (s, 3H), 8.30 (s, 3H), 8.50 (s, 3H), 8.65 (d [J = 6.5 Hz.], 3H), and

(b) R_f 0.33 (25 mg.) τ 4.10 (q [J = 6.5 Hz.], 1H), 7.85 (s, 3H), 8.12 (s, 3H), 8.26 (s, 3H), 8.52 (s, 3H), 9.05 (d [J = 6.5 Hz], 3H).

$\nu_{max.}$ 3000, 1743, 1555, 1400, 1375, 1252, 1053, 875, 785 $cm.^{-1}$

Reaction of the Alcohol (LXII) with Sulphuric acid in Acetic Anhydride

The procedure described for the adduct (LVIII(a)) was followed using the alcohol (LXII) (165 mg.) and gave, 4,5,6,7-tetrachloro-2,3-dimethylbenzofuran (LXIV) (38 mg. 30%) m.p. 182-184° (from light petroleum).

(Found: C, 42.5; H, 2.35%; M [mass spectrometry] 284.

$C_{10}H_6Cl_4O$ requires C, 42.6; H, 2.15%; M 284).

τ 7.62 (s, 3H), 7.71 (s, 3H).

$\lambda_{max.}$ 228 ($\log_{10} \varepsilon$ 4.42), 233 (4.38), 272 (4.12), 293 (3.54), 305 (3.19) nm.

$\nu_{max.}$ 2980, 2940, 1630, 1415, 1400, 1380, 1293, 1188, 1095, 835, 810 $cm.^{-1}$

Reaction of the Acetate (LXIII) with Sulphuric acid in Acetic Anhydride

The procedure described for the adduct (LXIII(a)) was followed using the acetate (LXIII) (70 mg.) and gave the benzofuran (LXIV) (17 mg., 24%).

Reaction of the Alcohol (LXII) with Deuteriosulphuric acid in Acetic Anhydride

The procedure described for the adduct (LVIII(a)) was followed using the alcohol (LXII) (175 mg.) and deuterio-sulphuric acid (3 ml.) to give the benzofuran (LXIV) (35 mg. 11%) containing no deuterium [by mass spectrometry and ^1H n.m.r.].

Reaction of the acetate (LX) with Hydrobromic acid

Hydrobromic acid (10 ml, 48%) was added to a solution of the acetate (LX) (50 mg.) in acetic acid (5 ml.). The mixture was stirred at room temperature for 5 min., poured onto ice (20 g.) and extracted with chloroform (2 x 20 ml.). The combined extracts were washed with water, dried, and concentrated to leave the bromo compound (LXI) (29 mg. 56%). The i.r. spectrum was identical to that of the product obtained by treating adduct (LVIII(a)) with hydrobromic acid in acetic acid.

Reaction of the Bromo compound (LXI) with Lithium aluminium hydride

Lithium aluminium hydride (0.1 g.) was added to a solution of the bromo compound (LXI) (363 mg.) in dry diethyl ether (10 ml.). The mixture was stirred at room temperature for 1 hr. before water (10 ml.) was added. The ether layer was separated, dried, and concentrated to leave a mixture of two compounds. Separation by preparative layer chromatography gave,

(a) the benzofuran (LXIV) (180 mg.) and

(b) unreacted starting material (120 mg.)

Reaction of the Bromo compound (LXI) with Lithium aluminium deuteride

The procedure described above was followed using the bromo compound (200 mg.) and lithium aluminium deuteride (5 mg.) and gave,

(a) 4,5,6,7-tetrachloro-2-methyl-3-[1-^{2}H] methylbenzofuran. (89 mg.) containing 98% [1-^{2}H] [by mass spectrometry], τ 7.63 (s, 3H), 7.71 (m, 2H), and

(b) unreacted starting material (53 mg.).

Preparation of 3-Bromomethyl-2-methylbenzofuran

Potassium carbonate (100 g.) was added to a solution of phenol (47 g., 0.5 mol.) and allylbromide (60.5 g., 0.5 mol.) in acetone (200 ml.), and the mixture heated under reflux for 2½ hr. The cooled solution was filtered and concentrated, dissolved in diethyl ether (200 ml.) and extracted with sodium hydroxide (2N) The organic phase

was washed with water, dried, concentrated and distilled to give phenyl allyl ether[104] (26 g., 40%) b.p. 80-82°, 20 mm. Hg.

The ether was heated at 220-230° for 5 hr. to form o-allylphenol.[104] The cold mixture was dissolved in sodium hydroxide (200 ml., 2N) and extracted with diethyl ether (2 x 100 ml.). The alkaline phase was acidified with hydrochloric acid (2N) and extracted with diethyl ether (2 x 100 ml.). The combined extracts were washed with water, dried, and concentrated to leave a brown liquid (17.3 g.), which was heated under reflux in acetic anhydride (25 g.) for 4½ hr. Distillation of the reaction mixture gave o-allyl phenyl acetate (18.4 g.) b.p. 73-76°, 0.4 mm. Hg. The acetate was dissolved in carbon disulphide (80 ml.) and the solution cooled to 0°. Bromine (168 g.) was added dropwise to the stirred solution, which was stirred for a further ½ hr. after addition was complete. The brown oil left after removal of the solvent was extracted with hot light petroleum (3 x 100 ml.). The dibromide (24 g.) crystallised from the light petroleum, and was added to a solution of potassium hydroxide (20 g.) in ethanol (200 ml.) and heated under reflux for 1 hr. Water (150 ml.) was added to the concentrated solution and the mixture extracted with chloroform (2 x 100 ml.). The combined extracts were washed with water, dried, concentrated and distilled to give 2-methylbenzofuran[105] (3 g., 32%), b.p. 56-60° 2.5 mm. Hg.

Stirring the 2-methylbenzofuran (2.9 g.) with trioxane (2 g.) in hydrobromic acid (40 ml.) at room temperature for 1½ hr. gave a pale yellow solution.[106] This was extracted with diethyl ether (2 x 25 ml.) and the combined extracts washed with water, dried, concentrated and distilled to give 3-bromomethyl-2-methylbenzofuran (1.35 g., 30%) b.p. 102-103° 0.8 mm. Hg.

(Found: C, 55.75; H, 4.05%; M [mass spectrometry] 224. $C_{10}H_9BrO$ requires C, 53.35; H, 4.05%; M 224).

τ 2.5-3.0 (m, 4H) 5.62 (s, 2H), 7.73 (s, 3H).

Reaction of 3-Bromomethyl-2-methylbenzofuran with Lithium aluminium hydride

Lithium aluminium hydride (80 mg.) was added to a solution of 3-bromomethyl-2-methylbenzofuran (1.35 g.) in dry diethyl ether (25 ml.) and the mixture heated under reflux for 2 hr. Water (10 ml.) was added to the cooled solution and the organic phase separated, dried, and concentrated to leave a mixture of starting material and 2,3-dimethylbenzofuran.[107] τ 2.5-3.1 (m), 5.62 (s), 7.73 (s), 7.80 (s).

REFERENCES

1. R.W.Hoffmann, "Dehydrobenzene and Cycloalkynes", Verlag Chemie, G.m.b.h., Weinheim; Academic Press, New York, 1967.

2. A.Wurtz, Compt.rend., 1867, 64, 749; A.Kekule, ibid., 1867, 64, 752.

3. J.D.Roberts, H.E.Simmons, L.A.Carlsmith, and C.W. Vaughan, J.Amer.Chem.Soc., 1953, 75, 3290.

4. E.W.Gowling, S.F.A.Kettle, and G.M.Sharples, Chem.Comm., 1968, 21.

5. E.K.Fields and S.Meyerson, Chem.Comm., 1965,474.

6. I.P.Fischer and F.P.Lossing, J.Amer.Chem.Soc., 1963, 85, 1018; R.S.Berry, J.Clardy, and M.E.Schafer, ibid., 1964, 86, 2738. idem., Tetrahedron Letters, 1965, 15, 1003.

7. R.S.Berry, G.N.Spokes, and R.M.Stiles, J.Amer.Chem.Soc., 1960, 82, 5240; idem., ibid., 1962, 84, 3570; M.E.Schafer and R.S.Berry, ibid., 1965, 87, 4497.

8. G.Porter and J.I.Steinfeld, J.Chem.Soc.(A), 1968, 877.

9. J.D.Roberts, D.A.Semenow, H.E.Simmons, and L.A. Carlsmith, J.Amer.Chem.Soc., 1956, 78, 601; C.A.Coulson, Chemical Society Symposium, Bristol, 1958, Chem.Soc.Special.Publ. No.12, p.85.

10. R.Hoffmann, A.Imamura, and W.J.Hehre, J.Amer.Chem.Soc., 1968, 90, 1499.

11. R.B.Woodward and R.Hoffmann, Angew.Chem.Internat.Edn., 1969, 8, 781.

12. R.W.Atkin and C.W.Rees, Chem.Comm., 1969, 152.

13. M.Jones and R.M.Levin, J.Amer.Chem.Soc., 1969, 91, 6411.

14. H.Heaney, Fortschr.Chem.Forsch., 1970, 16 (1), 35.

15. B.H.Klandermann and T.R.Criswell, J.Amer.Chem.Soc., 1969, 91, 510.

R.Huisgen and R.Knorr, Tetrahedron Letters, 1963, 1017.

16. C.D.Campbell and C.W.Rees, Proc.Chem.Soc., 1964, 296; idem., Chem.Comm., 1965, 192.

17. M.Stiles and R.G.Miller, J.Amer.Chem.Soc., 1960, 82, 3802;

M.Stiles, R.G.Miller, and W.Burckhardt, ibid., 1963, 85, 1792.

18. G.Wittig and R.W.Hoffmann, Angew.Chem., 1961, 73, 435; idem., Chem.Ber., 1962, 95, 2718.

19. L.Friedman, personal communication.

20. E. Le Goff, J.Amer.Chem.Soc., 1962, 84, 3786.

21. L.Friedman and F.M.Logullo, J.Amer.Chem.Soc., 1963, 85, 1549.

22. V.Villiger, Ber., 1909, 42, 3529; and references cited therein.

23. V.Villiger and L.Blangey, Ber., 1909, 42, 3549.

24. D.G.O'Sullivan and P.W.Sadler, J.Chem.Soc., 1957, 2916.

25. H.Heaney and T.J.Ward, personal communication.

L.Friedman, personal communication, has also prepared tetrachlorobenzenediazonium-2-carboxylate hydrochloride.

26. J.Nakayama, O.Simamura, and M.Yoshida, Chem.Comm., 1970, 1222.

27. B.Gething, C.R.Patrick, and J.C.Tatlow, J.Chem.Soc., 1961, 1574;
L.J.Belf, M.W.Buxton, and J.F.Tilney-Bassett, Tetrahedron, 1967, 23, 4719.

28. R.Lesser and R.Weiss, Ber., 1913, 46, 3937.

29. B.P.860, 292, 1961; J.M.Chapman, W.Graham, and R.H.Evans, to Glaxo Laboratories Ltd.

30. H.Heaney, K.G.Mason, and J.M.Sketchley, J.Chem.Soc.(C), 1971, 567.

31. R.Harrison, H.Heaney, J.M.Jablonski, K.G.Mason, and J.M.Sketchley, J.Chem.Soc.(C), 1969, 1684.

32. H.Heaney, K.G.Mason, and J.M.Sketchley, Tetrahedron Letters, 1970, 485.

33. V.Franzen, H.-I.Joschek, and C.Mertz, Annalen, 1962, 654, 82;
H.Hellmann and D.Eberle, ibid., 1963, 662, 188.

34. J.P.N.Brewer, H.Heaney, and T.J.Ward, J.Chem.Soc.(C), 1969, 355.

35. F.M.Logullo, Ph.D.Thesis, Case Institute of Technology, quoted in reference 1, p. 178.

36. J.P.N.Brewer, H.Heaney, and J.M.Jablonski, Tetrahedron Letters, 1968, 4455.

37. H.E.Simmons, J.Amer.Chem.Soc., 1961, 83, 1657.

38. H.Heaney and J.M.Jablonski, Tetrahedron Letters, 1967, 2733.

39. H.H.Wasserman and J.Solodar, J.Amer.Chem.Soc., 1965, 87, 4002;
I.Tabushi, R.Oda, K.Okazaki, Tetrahedron Letters, 1968, 3743;
H.H.Wasserman, A.J.Solodar, and L.S.Keller, ibid., 1968, 5597;
L.Friedman, R.J.Osiewicz and P.W.Rabideau, ibid., 1968, 5735;
M.Jones and R.H.Levin, ibid., 1968, 5593.

40. H.Heaney, J.M.Jablonski, K.G.Mason, and J.M.Sketchley, J.Chem.Soc.(C), in press.

41. H.Heaney and J.M.Jablonski, Chem.Comm., 1968, 1139.

42. A.S.Onischenko, "Diene Synthesis", Israel Program for Scientific Translations, Jerusalem, 1964, p. 535;
J.Colonge and G.Descotes, in "1,4-Cycloaddition Reactions", ed. J.Hamer, Academic Press, New York, 1967, p.217.

43. e.g. (a) F.M.Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworth, London, 1963;
(b) T.A.Geissman, "The Chemistry of Flavonoid Compounds", Pergamon Press, New York, 1962;
(c) R.C.Elderfield, "Heterocyclic Compounds", Vol.2, Wiley, London, 1951.

44. e.g. F.Bergel, A.Jacob, A.R.Todd, and T.S.Work, J.Chem.Soc., 1938, 1375.

45. J.W.Clark-Lewis and R.W.Jemison, Aust.J.Chem., 1970, 23, 315; and references cited therein.

46. W.D.Ollis and I.O.Sutherland, "Chemistry of Natural Phenolic Compounds", Pergamon Press, Oxford, 1961, p.84; A.B.Turner, Quart.Rev., 1964, 18, 347.

47. G.Cardillo, R.Cricchio, and L.Merlini, Tetrahedron Letters, 1969, 907.

48. E.E.Schweizer, D.M.Crouse, and D.L. Dalrymple, Chem.Comm., 1969, 354.

49. P.D.Gardner, H.Sanafizadeh R., and R.L.Brandon, J.Amer.Chem.Soc., 1959, 81, 5515.

50. D.A.Bolon, J.Org.Chem., 1970, 35, 3666.

51. S.B.Cavitt, H.Sanafizadeh R., and P.D.Gardner, J.Org.Chem., 1962, 27, 1211; A.Merijan, B.A.Shoulders, and P.D.Gardner, ibid., 1963, 28, 2148.

52. E.N.Marvell, G.Caple, T.A.Gosink, and G.Zimmer, J.Amer. Chem.Soc., 1966, 88, 619.

53. G.W.Kirby, S.L.Tan, and B.C.Uff, Chem.Comm.,1970, 1138.

54. J.A.Elvidge and R.G.Foster, J.Chem.Soc., 1964, 981.

55. W.E.Parnham and L.D.Huestis, J.Amer.Chem.Soc., 1962, 84, 813.

56. J.W.Clark-Lewis, L.M.Jackman and T.M.Spotswood, Aust.J.Chem., 1964, 17, 632.

57. e.g. H.Heaney and J.M.Jablonski, J.Chem.Soc. (C), 1969, 1895.

58. J.W.Clark-Lewis, Aust.J.Chem., 1968, 21, 2059.

59. J.A.Van Allan, G.A.Reynolds, and T.H.Regan, J.Org.Chem., 1967, 32, 1897.

60. S.Yaraslavsky, Tetrahedron Letters, 1965, 1503.

61. A.I.Vogel, "Practical Organic Chemistry", Longman Green, London, 1956.

62. R.L.Shriner and A.G.Sharp, J.Org.Chem., 1939, 4, 579.

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

64. J.P.N.Brewer, H.Heaney and J.M.Jablonski, Tetrahedron Letters, 1968, 4455.

65. J.M.Jablonski, Ph.D.Thesis, Loughborough University of Technology, 1968.

66. J.M.Sketchley, Ph.D.Thesis, Loughborough University of Technology, 1970.

67. V.J.B.Ekeley, E.C.Rogers, and M.Swisher, J.Amer. Chem.Soc., 1922, 44, 1756; and references cited therein.

68. G.Casivaghi and G.Casnati, Chem.Comm., 1970, 321.

69. D.J.Bennett, G.W.Kirby, and V.A.Moss, J.Chem.Soc. (C), 1970, 2049.

70. R.Gompper, G.Seybold, and B.Schmolke, Angew.Chem. Internat.Edn., 1968, 7, 389.

71. S.V.Ley, personal communication.

72. W.Borsche and A.Geyer, Ber., 1914, 47, 1160.

73. e.g. (a) M.Greenwood and M.Nierenstein, J.Chem.Soc., 1920, 117, 1594;

(b) P.Karrer, R.Widmer, A.Helfenstein, W.Hürliman, O.Nievergelt, and P. Monsarrat-Thoms, Helv.Chim.Acta., 1927, 10, 729;

73. (c) R.L.Shriner and R.B.Moffett, J.Amer.Chem.Soc., 1940, 62, 2711;

(d) F.E.King, T.J.King, and L.C.Manning, J.Chem.Soc., 1953, 3932;

(e) A.R.Alertsen, Acta.Chem.Scand.,1955, 9, 1725.

74. K.Freudenberg, H.Fikentscher, and W.Werner, Ann., 1925, 309, 442.

75. E.J.Tillmanns and J.J.Ritter, J.Org.Chem., 1957, 22, 839.

76. A.I.Meyers, A.Nabeya, H.W.Adickes, J.M.Fitzpatrick, G.R.Malone, and I.R.Politzer, J.Amer.Chem.Soc., 1969, 91, 764.

77. S.J.Cristol and W.P.Norris, J.Amer.Chem.Soc., 1953, 75, 2645.

78. G.Saucy, R.Marbet, H.Lindlar, and O.Isler, Helv.Chim.Acta., 1959, 42, 1945.

79. K.N.Campbell, B.K.Campbell, and L.T.Eby, J.Amer.Chem.Soc., 1938, 60, 2882.

80. M.B.Green and W.J.Hickingbottom. J.Chem.Soc., 1957, 3262.

81. C.F.H.Allen and C.O.Edens, Org.Syn.Coll. Vol.III, p. 731.

82. A.Scipioni, Ann.Chim.(Rome), 1951, 41, 697; Chem.Abs., 1952, 46, 8635.

83. J.D.Roberts and M.C.Caserio, "Basic Principles of Organic Chemistry", Benjamin, New York, 1965, p. 443.

84. P.Maitte, Ann. Chim., 1954, 9, 431.

85. (a) W.Baker and J.Walker, J.Chem.Soc., 1935, 646;
(b) L.I.Smith and R.B.Carlin, J.Amer.Chem.Soc., 1942, 64, 435.

86. e.g. M.S.Karasch, R.Malec, and N.C.Yang, J.Org.Chem., 1957, 22, 1443.

87. W.J.Bailey and J.Bello, J.Org.Chem., 1955, 20, 525;
E.A.Braude and E.S.Waight, J.Chem.Soc., 1952, 116.

88. J.R.Shelton and C. Cialdella, J.Org.Chem., 1958, 23, 1128;
R.Paul and S.Tchelitcheff, Compt.rend., 1953, 236, 1968.

89. C.D.Hurd and W.A.Hoffman, J.Org.Chem., 1940, 5, 212.

90. G.P.Chuisoli and C.Venturello, Chem.Comm., 1969, 771.

91. D.C.Dittmer and E.S.Whitman, J.Org.Chem., 1969, 34, 2004.

92. S.F.Dyke, A.J.Floyd, and S.Ward, Tetrahedron Letters, 1969, 2837;
idem., Tetrahedron, 1970, 26, 4005.

93. H.Heaney, J.M.Jablonski, and C.T.McCarty, submitted to J.Chem.Soc.(C).

94. H.Heaney and C.T.McCarty, Chem.Comm., 1970, 123.

95. L.M.Jackman and S.Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon, Oxford, 1969, p. 181.

96. H.Heaney and C.T.McCarty, Chem.Comm., 1970, 123.

97. H.Irving and E.G.Curtis, J.Chem.Soc., 1943, 319.

98. R.L.Alimchandani and A.N.Meldrum, J.Chem.Soc., 1921, 201.

99. H.Heaney and J.M.Jablonski, personal communication.

100. R.Howe, J.Chem.Soc.(C), 1966, 478.

101. A.I.Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon, Oxford, 1964, p. 138.

102. Prof.J.A.Elvidge, personal communication.

103. I.Heilbron and H.M.Bunbury, "Dictionary of Organic Compounds", Eyre and Spottiswoode, London, 1953, p.14.

104. L.Claisen and G.Eisleb, Ann., 1913, 401, 21.

105. J.A.Elvidge and R.G.Foster, J.Chem.Soc., 1964, 981.
R.Adams and R.E.Rindfusz, J.Amer.Chem.Soc., 1919, 41, 648.

106. R.Gaertner, J.Amer.Chem.Soc., 1952, 74, 5319.

107. E.Bisagni and R.Royer, Bull.Soc.chim.France, 1962, 925.